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MANN'S

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# PHARMACOVIGILANCE

THIRD EDITION

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EDITED BY ELIZABETH B. ANDREWS AND NICHOLAS MOORE

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WILEY Blackwell



# MANN'S PHARMACOVIGILANCE



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Third edition

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# Foreword

The publication of a third edition of this book in twelve years bear's ample testimony to the continuing importance of pharmacovigilance, the study of the safety of marketed medicines.

It is also a memorial to the founding editor, Professor Ronald Mann, who sadly died in December 2013, shortly before the new edition appeared. It had already been decided by the new editors to rename the book Mann's Pharmacovigilance, made more prescient by recent events. Ron Mann, as he was universally known, had spent a professional lifetime in the field of drug safety as a regulator, as an educator and as a physician. I had the privilege of working with him at the (then) UK Medicines Control Agency some twenty years ago when the word pharmacovigilance had not even been invented. Ron's quest to instil scientific rigour into the then disorganised field of drug safety represented a great step forward in the regulation of medicines, and the three editions of this book clearly demonstrate this achievement. The title Mann's Pharmacovigilance is richly deserved.

Over the lifetime of the book, several trends in drug safety have become more evident. We have seen advances in the science of pharmacovigilance and with this, progress in the technology to allow them. Examples such as the electronic submission of case reports and the invention of automated data mining techniques have been matched by greater attention to benefit-risk assessment rather than mere considerations of drug safety, and by emphasis on proactive risk management planning. The

frameworks of medicines regulation – the scientific, the legal and the public health – are increasingly accepted not only by major regulatory authorities but by those in the developing world. The role of the patient has become more insistent and that of the health care professional more important.

Drug safety is no longer the preserve of the regulator and the pharmaceutical industry. These trends are clearly reflected in the changes in the structure of this third edition of Mann's Pharmacovigilance. Three major changes can be seen. First there is evidence of greater global reach, with descriptions of spontaneous reporting systems in many more countries than covered in previous editions. Second, there is more focus on active surveillance using multiple population based databases. There are new chapters on collaborative efforts to enhance signal detection and evaluation. Thirdly, the scope of the book has broadened beyond drugs and medical devices with new chapters on vaccine surveillance and the evaluation of the safety of biologics. In many respects, vaccine safety practice is more effective than that of medicines; we should also question whether the techniques of medicines surveillance as currently applied are appropriate for biopharmaceutical products, or whether a new approach is needed.

Ron Mann would have approved of these changes.

Alasdair Breckenridge  
January 2014



# 1

## Introduction: Updated from Second Edition

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### BACKGROUND

Pharmacovigilance – the study of the safety of marketed drugs under the practical conditions of clinical use in large communities – involves the paradox that what is probably the most highly regulated industry in the world is, from time to time, forced to remove approved and licensed products from the market because of clinical toxicity. Why is such close regulation not effective in preventing the withdrawal of licensed products? The question has been with us from the very early days of the 1960s and remains with us today, and its consideration tells us a great deal about pharmacovigilance.

The greatest of all drug disasters was the thalidomide tragedy of 1961–1962. Thalidomide had been introduced, and welcomed, as a safe and effective hypnotic and anti-emetic. It rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth

defects in an estimated 10 000 children in the countries in which it was widely used in pregnant women. The story of this disaster has been reviewed elsewhere (Mann, 1984).

The thalidomide disaster led, in Europe and elsewhere, to the establishment of the drug regulatory mechanisms of today. These mechanisms require that new drugs shall be licensed by well-established regulatory authorities before being introduced into clinical use. This, it might be thought, would have made medicines safe – or, at least, acceptably safe. But Table 1.1 summarizes a list of 46 licensed medicines withdrawn, after marketing, for drug safety reasons since the mid 1970s in the UK.

Why should the highly regulated pharmaceutical industry need, or be compelled, to withdraw licensed medicines for drug safety reasons? Why do these problems of licensed products being found toxic continue despite the accumulated experience of more than 50 years since the thalidomide tragedy?

Table 1.1 Drugs withdrawn in the UK by the marketing authorization holder or suspended or revoked by the Licensing Authority, 1975–2010.

Brand name (drug substance)	Year action taken	Major safety concern
Secholex (polidexide)	1975	Safety concerns because of impurities
Eraldin (practolol)	1975	Oculomucocutaneous syndrome
Opren (benoxaprofen)	1982	Hepatotoxicity, serious skin reactions
Devryl (clomacran phosphate)	1982	Hepatotoxicity
Flosint (indoprofen)	1982	Gastrointestinal toxicity
Zomax (zomepirac)	1983	Anaphylaxis
Osmosin (indomethacin-modified release)	1983	Small-intestine perforations
Zelmid (zimeldine)	1983	Neurotoxicity
Flenac (fenclofenac)	1984	Lyell's syndrome
Methrazone (feprazone)	1984	Serious skin reactions, multisystem toxicity
Althesin (alphaxalone plus alphadolone)	1984	Anaphylaxis
Pexid (perhexilene)	1985	Hepatotoxicity, neurotoxicity
Suprol (suprofen)	1986	Nephrotoxicity
Merital (nomifensine)	1986	Hemolytic anemia
Unicard (dilevalol)	1990	Hepatotoxicity
Glauline eye drops 0.6% (metipranolol)	1990	Uveitis
Halcion (triazolam)	1991	Psychiatric reactions
Micturin (terodiline)	1991	Arrhythmias
Teflox (temafloxacin)	1992	Multisystem toxicity
Centoxin (nebacumab)	1993	Mortality
Roxiam (remoxipride)	1994	Aplastic anemia
Volital (pemolin)	1997	Hepatotoxicity
Romazin (troglitazone)	1997	Hepatotoxicity
Serdolect (sertindole)	1998	Arrhythmias
Tasmar (tolcapone)	1998	Hepatotoxicity
Ponderax (fenfluramine)	1998	Cardiac valvular disease
Adifax (dexfenfluramine)	1998	Cardiac valvular disease
Posicor (mibepradil)	1998	Drug interactions
Trovan (trovafloxacin)	1999	Hepatotoxicity
Grepafloxacin (Raxar)	1999	QT interval prolongation
Prepulsid (cisapide)	2000	QT interval prolongation
Alec (pumactant)	2000	Adverse comparative trial results
Droleptan (droperidol)	2001	Increased cardiac risks
Lipobay (cerivastatin)	2001	Rhabdomyolysis
Kava-Kava	2001	Liver toxicity
Anorectic agents (amfepramone, phentermine)	2000	Heart valve disorders
Vioxx (rofecoxib)	2004	Increased cardiovascular event risks
Non-proprietary (co-proxamol)	2005	Use in suicide
Bextra (valdecoxib)	2005	Stevens–Johnson syndrome
Prexige (lumiracoxib)	2007	Hepatotoxicity
Carisoma (carisoprodol)	2007	Abuse potential
Trasylol (aprotinin)	2007	Death following cardiac surgery
Accomplia (rimonabant)	2008	Depression, Suicide
Raptiva (efalizumab)	2009	Progressive Multifocal Leukoencephalopathy
Reductil (sibutramine)	2010	Cardiovascular mortality
Avandia (rosiglitazone)	2010	Increased cardiovascular event risk

Partly, the problem is one of numbers. For example, the median number of patients contributing data to the clinical safety section of new drug licensing applications in the UK is only just over 1500 (Rawlins and Jefferys, 1991). Increasing regulatory demands for additional information before approval have presumably increased the average numbers of patients in applications, especially for new chemical entities; nevertheless, the numbers remain far too small to detect uncommon or rare adverse drug reactions (ADRs), even if these are serious.

The size of the licensing applications for important new drugs cannot be materially increased without delaying the marketing of new drugs to an extent damaging to diseased patients. Thus, because of this problem with numbers, drug safety depends very largely on the surveillance of medicines once they have been marketed.

A second reason for difficulty is that the kinds of patients who receive licensed medicines are very different from the kinds of volunteers and patients in whom premarketing clinical trials are undertaken. The patients in formal clinical trials almost always have only one disease being treated with one drug. The drug, once licensed, is likely to be used in an older group of patients, many of whom will have more than one disease and be treated by polypharmacy. The drug may also be used in pediatric patients, who are generally excluded from initial clinical trials. The formal clinical trials may be a better test of efficacy than they are of safety under the practical conditions of everyday clinical usage.

A third problem is that doctors may be slow or ineffective in detecting and reporting adverse drug effects. Many of the drugs summarized in Table 1.1 were in widespread, long-term use before adverse reactions were detected, and even now hospital admissions due to ADRs have shown an incidence of between 2.4% and 3.6% of all admissions in Australia, with similar or greater figures in France and the USA (Pouyanne *et al.*, 2000). Even physicians astute in detecting adverse drug effects are unlikely to identify effects of delayed onset.

A fourth reason for difficulty is that drugs are often withdrawn from the market for what may be very rare adverse effects – too infrequent by far to have shown up in the pre-licensing studies – and we

do not yet have effective means in place for monitoring total postmarketing safety experience. This situation may well change as large comprehensive databases such as the Clinical Practice Research Datalink (CPRD, formerly the GPRD) in the UK and the Mini-Sentinel Network of databases in the USA become more widely used for signal detection and evaluation. These databases record, in quite large and representative populations, all usage of many specific medicines and clinical outcomes and can be used to systematically screen for and evaluate serious adverse events. Because they contain comprehensive information on some important data, such as age, sex, dose, and clinical events on all patients in the represented population, they are systematic compared with spontaneous reporting systems. They may offer a better chance of detecting long-latency adverse reactions, effects on growth and development, and other such forms of adverse experience.

Some of the difficulties due to numbers, patient populations, and so on were recognized quite early. The Committee on Safety of Drugs in the United Kingdom (established after the thalidomide disaster, originally under the chairmanship of Sir Derrick Dunlop, to consider drug safety whilst the Medicines Act of 1968 was being written) said – quite remarkably – in its last report (for 1969 and 1970) that “no drug which is pharmacologically effective is without hazard. Furthermore, not all hazards can be known before a drug is marketed.” This then has been known for over 40 years. Even so, many prescribers still seem to think that licensed drugs are “safe,” and they are surprised when a very small proportion of licensed drugs have to be withdrawn because of unexpected drug toxicity. Patients themselves may have expectations that licensed drugs are “completely safe” rather than having a safety profile that is acceptably safe in the context of the expected benefit and nature of the underlying health condition.

The methodological problems have been long recognized. The Committee on Safety of Medicines, the successor in the UK to the Dunlop Committee, investigating this and related problems, established a Working Party on Adverse Reactions. This group, under the chairmanship of Professor David Grahame-Smith, published its second report

in July 1985. The report supported the continuation of methods of spontaneous reporting by professionals but recommended that postmarketing surveillance studies should be undertaken on “newly-marketed drugs intended for widespread long-term use”; the report also mentioned record-linkage methods and prescription-based methods of drug safety surveillance as representing areas of possible progress (Mann, 1987).

Similar reviews and conclusions have emerged from the USA since the mid 1970s. A series of events in the USA recently created a resurgence of interest in drug safety evaluation and management. The Prescription Drug User Fee Act (PDUFA) of 1992 provided additional resources at the Food and Drug Administration (FDA) for drug reviews through user fees and established target time-lines for FDA reviews. The shorter approval times led to some medications being approved sooner in the USA than in Europe, in contrast to the pre-PDUFA experience. A few highly visible drug withdrawals led to a perception that perhaps drugs were being approved too quickly. Lazarou *et al.* (1998) published the results of a meta-analysis that estimated that 106 000 fatal adverse reactions occurred in the USA in 1994. This and other articles (Wood *et al.*, 1998) stimulated considerable public, congressional, and regulatory attention on reducing the societal burden of drug reactions and medication errors (FDA, 1999; Institute of Medicine, 1999; United States General Accounting Office, 2000). As a result, greater attention and resources are currently being devoted to signal generation and evaluation by the FDA, industry, and academic centers. Moreover, efforts are underway to develop better tools to manage recognized risks through a variety of interventions, such as communications with healthcare providers and patients, restricted product distribution systems, and other mechanisms. Additional effort is being focused on measuring the success of these risk-management interventions. This new initiative represents a fundamental shift in the safety paradigm in the USA and offers new challenges to pharmacovigilance professionals. In fact, the shift is not restricted to the USA, as both the FDA and the European Medicines Agency (EMEA) in 2005 issued guidance documents for industry on signal detection, evaluation,

good pharmacovigilance practice and recommendations for managing risks after the approval (FDA, 2005a–c).

Even more recently, in December 2010, new pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84) was adopted by the European Parliament and European Council bringing sweeping changes to the European pharmacovigilance system ([http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000492.jsp&mid=WC0b01ac058033e8ad](http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&mid=WC0b01ac058033e8ad)). Changes were aimed at strengthening the safety monitoring process, clarifying and simplifying roles, improving safety decision-making, and enhancing transparency. The legislation also strengthened the legal basis for requiring post-approval safety studies. The new legislation is being implemented through a series of good pharmacovigilance practices guidances ([http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document\\_listing/document\\_listing\\_000345.jsp&mid=WC0b01ac058058f32c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c)).

We have long recognized then that the safety of patients depends not only on drug licensing by regulatory bodies, but also on postmarketing drug safety surveillance, pharmacovigilance. It is also important to note that the same postmarketing information needed to confirm new safety signals is also needed to refute signals and protect the ability of patients to benefit from needed medicines that may be under suspicion due to spurious signals.

## DIAGNOSING ADVERSE DRUG REACTIONS

There are two types of ADRs. Type A reactions are common, predictable, usually dose-dependent, and appear as excessive manifestations of the normal pharmacology/toxicology of the drug; they are seldom fatal. Type B reactions are uncommon, unpredictable, often independent of dose, and usually represent abnormal manifestations of the drug's pharmacology/toxicology; they involve relatively high rates of serious morbidity and mortality.

ADRs frequently mimic ordinary diseases and, if they are uncommon, may easily be overlooked. They

tend to affect the skin, hematopoietic system, and lining of the gut (situations in which there is rapid cell multiplication) or the liver or kidneys (where drugs are detoxified and excreted). These special sites are frequently involved in iatrogenic (doctor-induced), type B illnesses, such as toxic epidermal necrolysis, aplastic anemia, pseudomembranous colitis, drug-induced hepatitis, or nephritis.

A high index of suspicion is needed if ADRs are to be successfully diagnosed. The clinician always has to think: "Could this be drug-induced – is this an ADR?" The question is important, for withdrawal of the cause of an ADR is usually essential.

Iatrogenic ADRs are usually uncommon or rare, and this adds to the difficulty of diagnosis. Some are avoidable, such as skin rashes in patients with glandular fever given ampicillin. Some are accidental, such as the non-iatrogenic disaster of an asthmatic given a beta-adrenergic blocking agent by another member of the family. It is a truism that the detection of common or uncommon ADRs requires vigilance. Many of the known serious ADRs have been recognized by astute clinicians with a high level of awareness, and such awareness is likely to be just as important as new methods of pharmacovigilance are developed as it has been in the past.

Linked with this problem of diagnosing ADRs is the problem of understanding them. Why does one patient in 10 000 get some bizarre type B reaction and the rest of this population not get it? Clearly, our increasing knowledge of clinical pharmacology, drug metabolism, and genetics will contribute to our understanding of these things, and these subjects are explored in many of the chapters in this book.

## CURRENT METHODS OF PHARMACOVIGILANCE

Pharmacoepidemiology is the study of the use of, and effects of, drugs in large numbers of people. As the term implies, this form of enquiry uses the methods of epidemiology; it is concerned with all aspects of the benefit/risk ratio of drugs in populations. Pharmacovigilance is a branch of pharma-

coepidemiology but is restricted to the study, on an epidemiological scale, of drug events or adverse reactions.

"Events," in this context, are happenings recorded in the patient's notes during a period of drug monitoring; they may be because of the disease for which the drug is being given, some other intercurrent disease or infection, an adverse reaction to the drug being monitored, or the activity of a drug being given concomitantly. They can also be because of drug–drug interactions.

Public health surveillance methods are used to identify new signals of possible ADRs. Studies in pharmacoepidemiology are intended to be either "hypothesis generating" or "hypothesis testing," or to share these objectives. Hypothesis-generating studies, with a recently marketed drug, aim to detect unexpected ADRs; hypothesis-testing studies aim to prove whether any suspicions that may have been raised are justified.

## HYPOTHESIS-GENERATING METHODS

### SPONTANEOUS ADVERSE DRUG REACTION REPORTING

Doctors (in some countries, other healthcare professionals, and patients as well) are provided with forms upon which they can notify a central authority of any suspected ADRs that they detect. In the UK, the "yellow card" has been used for this purpose since 1964. Similar forms are provided in the FP10 prescriptions pads, the British National Formulary, and other sources. In the USA, the MedWatch form is used and is made broadly available to health professionals to encourage reporting.

The great strength of spontaneous reporting is that it operates for all drugs throughout the whole of their lifetime; it is the only affordable method of detecting really rare ADRs. The data may represent merely the suspicions of the reporter, but they provide the opinion of a doctor or health professional attending a real-life patient. The main weaknesses are that there is gross underreporting, and the data provide a "numerator" (the number of reports of each suspected reaction) only. Moreover,

some case reports are described in the medical literature but may not be reported by the clinician; such published case reports are subsequently reported by industry sponsors through the spontaneous reporting system. Nevertheless, the scheme is invaluable, and it is essential that health professionals should be provided with the means of reporting their suspicions.

Spontaneous reporting has led to the identification and verification of many unexpected and serious ADRs. These findings have resulted in many marketed drugs being withdrawn or additional information being provided to guide safer use of the product.

A variety of formal epidemiological studies can be undertaken to generate or test hypotheses.

### PREScription-EVENT MONITORING

Prescription–event monitoring (PEM), as conducted in the UK and New Zealand, represents a “hybrid” method, combining aspects of public health surveillance and spontaneous reporting with aspects of formal epidemiological studies. In the UK, this important technique takes advantage of many features of the British National Health Service (NHS). Within the NHS, prescriptions written by general practitioners are sent, once they have been dispensed, to a central Prescription Pricing Authority (PPA). The PPA provides confidential copies of certain prescriptions for newly introduced drugs that are being monitored to the Drug Safety Research Unit (DSRU) at Southampton. At 6 or 12 months after the first prescription for an individual drug in an individual patient, the DSRU sends a “green form” questionnaire to the general practitioner who wrote the original prescription. Changing requirements regarding confidentiality and the effect that these have had on PEM are discussed in the appropriate chapter of this volume.

Thus, the prescriptions provide the “exposure data” showing which patients have been exposed to the drug being monitored, and the green forms provide the “outcome data” showing any events noted during the period of monitoring. Pregnancies, deaths, or events of special interest can be followed up by contact between the DSRU and the

prescribing doctor who holds, within the NHS, the lifetime medical record of all of their registered patients.

The great strengths of this method are that it provides a numerator (the number of reports) and a denominator (the number of patients exposed), both being collected over a precisely known period of observation. Furthermore, nothing happens to interfere with the doctor’s decision regarding which drug to prescribe for each individual patient, and this avoids selection biases, which can make data interpretation difficult. The main weakness of PEM is that only 50–70% of the green forms are returned, and the experience of the patients whose forms are not returned may differ from those returned. In addition, because PEM limits follow-up to 6 or 12 months, it cannot identify events of long latency. Thus, it is of great importance that doctors should continue to support the scheme by returning those green forms that they receive.

So far, some 100 drugs have been studied by PEM, and the average number of patients included in each study (the cohort size) has been over 10 000. This is a substantial achievement and a tribute to the general practitioners who have participated. PEM in the UK and a similar program in New Zealand are unique in providing a monitored-release program that can detect or help refute new signals in the early life of a medicine.

Considerable interest centers around those patients who produce major ADRs that are too rare to be detected in cohorts of around 10 000 patients. How many of these patients have inborn errors of metabolism or other rarities that reflect features of the patient rather than the drug? We do not have adequate facilities to investigate the genetic and metabolic features of those patients who produce these very rare type B adverse reactions.

### OTHER HYPOTHESIS-GENERATING METHODS

Other systematic methods are used in signal generation. In some cases, data being collected for general public health surveillance, such as cause-of-death files, cancer registries, and birth defect registries are used to identify patterns of events that might be associated with medication use. Other programs, such as case-control surveillance of birth defects,

conducted by the Slone Epidemiology Center, screen for potential associations between birth defects and prescription and over-the-counter medications. Analytic methods – data mining techniques – that allow screening of enormous amounts of data for patterns that might deviate from expected are being applied to spontaneous reporting databases, databases on potential drug abuse and diversion, and large population-based health records. Considerable advances are being made in the development and refinement of analytic methods for identification and exploration of potential safety signals in large databases as well as in the aggregation of information across many data sources. Several chapters are devoted to these methods.

## HYPOTHESIS-TESTING METHODS

### Case-Control and Case-Crossover Studies

Studies of this type compare cases with a disease with controls susceptible to the disease but free of it. Using this method, the research compares the exposure rate in the cases with the exposure rate in the controls, adjusting statistically for factors that may confound the association. As with any formal epidemiological or clinical study, great care has to be taken in the design. Special attention is needed in case definition so that the cases truly represent the specific outcome of interest (e.g., Stevens-Johnson syndrome, not all cases of rash). It is also important to select an appropriate control group that represents the population that gave rise to the cases. Careful design can minimize the amount of bias in a study; adequate control in the analysis is also important. Case-control studies have provided a substantial body of evidence for major drug safety questions. Two notable examples are studies that demonstrated the association between aspirin and Reye's syndrome (Hurwitz *et al.*, 1987) and the evaluation of diethylstilbestrol (DES) and vaginal cancer in the offspring of mothers who took DES in pregnancy (Herbst *et al.*, 1974, 1975). Moreover, a case-control study established the protective effects of prenatal vitamin supplementation on the development of neural tube defects (Werler *et al.*, 1993). The final results of these studies present a measure

of the risk of the outcome associated with the exposure under study – expressed as the odds ratio. Only in very special circumstances can the absolute risk be determined. Clearly, a fairly small increase in the risk of a common, serious condition (such as breast cancer) may be of far greater public health importance than a relatively large increase in a small risk (such as primary hepatic carcinoma).

Case-control studies are more efficient than cohort studies, because intensive data need only be collected on the cases and controls of interest. Case-control studies can often be nested within existing cohort or large clinical trial studies. A nested case-control study affords the ability to quantify absolute risk while taking advantage of the inherent efficiency of the case-control design.

The case-crossover design is a design very useful for the evaluation of events with onset shortly after treatment initiation. In this design, cases, but not controls, are identified. A drug association is evaluated through comparing frequency of exposure at the time of the event with frequency of exposure at a different time for the same individuals. This design is less subject to bias than case-control studies because individuals serve as their own controls. As with case-control studies, unless the experience is nested within a larger cohort, it is not possible to estimate the absolute rate of events. For special circumstances, the case-crossover design is a very powerful design in pharmacoepidemiology.

### Cohort Studies

These studies involve a large body of patients followed up for long enough to detect the outcome of interest. Cohort studies generally include an exposed and unexposed group, but there are also single-exposure, disease or general population follow-up studies and registries. Studies must be designed to minimize potential biases. An advantage of the cohort study is its ability to quantify both an absolute risk and a relative risk. Cohort studies can be conducted prospectively, but such studies are usually expensive and time consuming. Retrospective cohort studies can be conducted within large existing databases, providing the advantage of the cohort study design and the efficiencies inherent in studies using existing records.

Case-control studies are particularly useful to confirm a safety signal relating to a rare event (less than 1/1000). Cohort studies are useful when the outcome has not already been identified or when multiple outcomes are of interest. Both case-control and cohort studies can be conducted within large existing databases, assuming the required information is available.

An example of methodologies can be found in the Medicines Evaluation and Monitoring Organization (MEMO). MEMO achieves “record linkage” by joining together general practitioner prescription data (the exposure data) with hospital discharge summaries (the outcome data). This activity takes place in Tayside, Scotland, where (uniquely in the UK) all patients have a personal Community Health Number (CHNo), which is widely used by NHS facilities of all types. Advantages include completeness, freedom from study-introduced bias in data collection, and timely availability of data for analysis. MEMO is an example of the types of databases that have been established since the mid 1970s that utilize data collected for other purposes. These databases have been used to detect and quantitatively evaluate hypotheses regarding safety signals.

Data resources now exist in many countries, especially in North America and western Europe. Some examples of these data resources and application of these databases to answer important safety questions will be described in further chapters.

It has been recognized that single databases, such as those available to MEMO or CPRD, even if they include information on several million individuals in their base population, have limited numbers of patients on specific medications to fully identify or characterize some important risks. Initiatives in western Europe and the USA have encouraged the development of collaborative studies across databases. The EMA coordinates the European Network of Centres of Excellence in Pharmacoepidemiology (ENCePP), which includes over 150 research organizations, special networks, and providers. ENCePP facilitates high-quality research across multiple research sites and multiple large databases. Through the Sentinel initiative in the USA, the FDA has created a network of researchers and databases in its “mini-sentinel” project that includes

17 data partners and data from nearly 100 million individuals (FDA, 2013). The aim of the project is to improve the FDA's ability to monitor the safety of drugs, biologicals, and devices, initially facilitating rapid response to safety signals with robust epidemiologic evaluations.

### Randomized Controlled Trials

In this method of study, a group of patients is divided into two in strictly random order; one group is then exposed and the other not exposed, so that the outcomes can be compared. The method is of great importance because random assignment of treatment removes some of the biases possible in observational studies. It is, however, of only limited (but important) use as a pharmacoepidemiological tool because most serious ADRs are relatively uncommon; randomized controlled trials used in such contexts can, therefore, become unmanageably large and expensive. Large, simple trials have become more common over the last decade in evaluating safety and efficacy in special circumstances, such as vaccine development, hormone replacement therapy, and treatments for common cardiovascular conditions. The availability of large healthcare databases containing information on health outcomes could enable the conduct of randomized naturalistic studies through randomization of marketed treatments across different healthcare sites. This hybrid approach combines the advantages of randomization with the noninterventional follow-up for short- and long-term outcomes through the databases.

### CONCLUSION

Current progress in pharmacovigilance is marked by increasing use of databases and by attempts to make the process more proactive and organized. Attempts are being made to augment the spontaneous, random nature of the generation of pharmacovigilance data and to make the process more systematic and structured. These changes are emphasized by the recent guidance documents for industry by both the EMA and FDA on pharmacovigilance planning and risk management, as well

as new research initiatives. This emphasis on planning a pharmacovigilance program for a drug and trying thoughtfully to minimize risk appears constructive and, to some of us, long overdue. It is notable that the emphasis on proactive safety planning is linked with an expectation that the suspicions arising from spontaneous reporting will rapidly be tested by formal pharmacoepidemiological studies conducted in organized and validated databases or prospective studies.

It is in everyone's interest to develop safe and effective medicines and provide access to patients for whom benefits will outweigh harms. Post-approval surprises, such as drug withdrawals, are not innocent of harm for the drug is precipitously denied to large numbers of patients who found it safe and effective. There has been a coming together of academic, regulatory, and industrial interests across many countries to produce the guidance documents mentioned above, as well as good practice guidelines for the conduct of pharmacopepidemiology studies (International Society for Pharmacoepidemiology, 2004).

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# 2

## History of Pharmacovigilance

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### EARLY HISTORY OF DRUG SAFETY

If Hippocrates' warning from the 4th century BC not to use medicines during early pregnancy had been heeded, the thalidomide tragedy over two millennia later might have been avoided, and our system of pharmacovigilance might be very different than it is today. In reality, though, thalidomide and the birth defects it caused when given to pregnant women in their first trimester was a major tragic event that transformed how we look at the safety and efficacy of our medicines.

Hippocrates was not alone in observing the impacts of medicines on humans. The knowledge that medicines may cause harm dates back to ancient times. Instances of warnings and consequences are recorded in historic documents, as are suggested practice and "regulatory" measures to avoid them.

Homer, Ovid, and Horace in the centuries BC refer to the effects of medicinal plants as both ben-

eficial and harmful. In Eastern lore, the *Yellow Emperor's Book of Medicine*, thought to be compiled between 800 and 200 BC, says that "there are toxic herbs and non-toxic ones" and suggests proper uses. In the early Middle Ages, Persian apothecaries knowledgeable about the risks and benefits of opium and henbane and many remedies compiled the 23-volume *Continens Medicinae*, wherein Abu Bakr Muhammad Ibn Zakariya al-Razi recommended animal testing. Around 1200 AD, Holy Roman Emperor Frederick II established regulations on prescribers and medicines. These included university education and passage of a public examination by physicians before practicing medicine; certification of apothecaries by a physician; regular inspection of apothecaries' drugs and mixtures; and having medical plant farmers pledge to prepare materials carefully. Apothecaries whose treatment caused a patient's death were executed (Stephens, 2010).

## RECENT HISTORY

### PRE-1962

More recently (the 1800s to the mid 1900s) drug safety was defined by crises and legislative reactions. Unproven treatments could be given by physicians or sold directly to patients and potentially result in serious or fatal injuries. News of patients suffering permanent injuries or dying created uproars. Lawmakers and regulators responded with new laws and increasing levels of drug product regulation to protect public health by preventing and/or reducing harm with their use. This task continues today.

Determining true safety and efficacy of medicines has historically been confounded by lack of uniform regulations to define criteria for efficacy of medicines. While safety regulations have progressed, firm reproducible criteria for demonstrating safety are still works in progress, as are criteria for effectiveness and benefit/risk of medicines.

Our understanding of what is safe has also evolved. Arsenic and mercury were used in the 19th century to treat a variety of illnesses from syphilis to leukemia. Medical experts recommended “treating through” side effects, believing the adverse events (AEs) were a sign that the therapeutic dose had been reached and the drug was working (Avorn, 2012).

Serious drug scandals that occurred from 1848 until the mid 1900s focused the need for laws to protect patients from unsafe medicines and spurred establishment of governmental agencies and regulations to oversee drug manufacture, distribution, and prescribing practices. Tragedies involving children were particularly emotionally charged and provoked action. In 1848, a 15-year-old girl in England died from chloroform anesthesia during treatment for an ingrown toenail (Routledge, 1998). *The Lancet* then established a commission inviting physicians in Britain and its colonies to submit reports of anesthesia-related deaths – the forerunner of current spontaneous reporting systems.

In the USA in 1901, 13 children died from contaminated diphtheria antitoxin. Passage of the Biological Control Act in 1902 followed quickly. Its goal was to ensure purity and safety of serums, vaccines, and other products (Lilienfeld, 2008).

Soon thereafter, public outcry about medicines quickly followed a series of 10 articles on the pharmaceutical industry in the widely read *Colliers Magazine* in 1905. Publication of Upton Sinclair's book *The Jungle* on the meatpacking and pharmaceutical industries the following year further increased public concern. The result was the Pure Food and Drugs Act of 1906 (P.L. 59-384, June 30, 1906), which prohibited interstate commerce of adulterated food and drugs and regulated labeling. It contained no safety or efficacy requirements, but did give the Food and Drug Administration (FDA) some authority to withdraw drugs from the marketplace.

Tragedy struck in 1937 when 105 people, including 34 children, died after a new liquid formulation of sulfanilamide was distributed in the USA (Ballestine, 1981; Wax, 1995). Anti-infective sulfanilamide tablets and powders had been used for years to treat streptococcal infections, but it was reformulated into a raspberry-flavored “elixir” when the manufacturer envisioned a more palatable form especially for children. Patient deaths from kidney failure were reported to the American Medical Association (AMA) by physicians within a month. The AMA laboratory isolated the toxin used – ethylene glycol – antifreeze – and issued a warning to physicians. Only then was the FDA alerted and dispatched to collect unused product. A charge of “mislabeling” was the only then-available legal recourse against the manufacturer, as labeling it an “Elixir” falsely implied it contained alcohol. At that time, selling poisonous drugs was not illegal, but misbranding was. It was noted at the time that lack of physician knowledge and education in medical schools in pharmacology contributed to the problem (Avorn, 2012); this shortcoming continues to contribute to drug safety problems today.

### TURNING POINT: THE FEDERAL FOOD, DRUG AND COSMETICS ACT

The sulfanilamide incident prompted an abrupt realization of the need for a change in the FDA's focus from that of a “watchdog” agency concerned primarily with confiscating misbranded products. A new role envisioned an FDA responsible for regulating potentially hazardous medical products. The

Federal Food, Drug, and Cosmetics Act (FDCA) was enacted in 1938. Its passage was a major turning point. Prior to the FDCA, there was little regulation of safety or efficacy of drug products, no oversight of their manufacture, and few penalties for perpetrators of fraud and tragedy. The FDCA began the government's attempt to examine the risk–benefit profile of medical products.

The FDCA required proof of safety through a new drug application (NDA) and gave FDA authority over cosmetics and therapeutic devices. “Adequate directions for use” and “warnings” were to be on the labeling. Penalties, including injunctions, seizures, and prosecution in cases of negligence and willful misconduct on the part of manufacturers were specified. Prior to enactment, the FDA was required to prove that manufacturers intended to defraud; but the FDCA empowered the FDA to pursue manufacturers when deemed appropriate. However, the law did not require proof of efficacy, nor did it specifically restrict distribution and use of investigational drugs. This last omission became important in the USA two decades later when pregnant women were treated with an investigational drug with then unknown severe adverse effects.

Each step toward regulating drugs brought new levels of government oversight and rules that industry saw as intrusive, restrictive, and damaging to profits. Nonetheless, government involvement and oversight increased; with new drug safety problems, laws were enacted and regulations became more clearly defined. In concert, physicians disseminated information when a safety issue became apparent.

#### GRADUAL INCREASE IN REGULATORY AUTHORITY

Gradually, the realization that increased drug safety regulation could help protect public health became clear. Congress found ways to expand the FDA's authority in the late 1940s and early 1950s. An important step was the Durham–Humphrey Amendment of 1951 (Food, Drug and Cosmetics Act Amendments of 1951 (P.L. 82-215, October 26, 1951)). These amendments authorized separation of drugs into two types – drugs that could be used

safely without the assistance of a physician and drugs needing a physician's prescription. Drugs sold without prescriptions became known as “over-the-counter” (OTC) drugs.

During WWII, the need for treatment of battlefield infections spurred antibiotic development, which accelerated in the 1950s. These drugs brought about a revolution in effective treatments for once-fatal infections.

But safety issues developed, too, including allergic reactions and other adverse effects, such as those associated with chloramphenicol, a broad-spectrum antibiotic. One year after its 1949 approval, reports of bone marrow hypoplasia and death from aplastic anemia (blood dyscrasia) were reported in patients (Rich *et al.*, 1950; Claudon and Holbrook, 1952; Wilson *et al.*, 1952). In 1952, the FDA authored a paper that recommended (1) changes to the label and (2) that the drug should not be used for minor infections. However, no formal regulatory action was taken. In response to the FDA's modest action, the AMA together with the American Hospital Association and the American Pharmacists Association set up a blood dyscrasia registry to better track patients with this reaction. Shortly thereafter, in 1955, the FDA began requiring that an NDA include safety reports detailing each individual treated with the drug (Stephens, 2010).

#### TECTONIC SHIFT: THALIDOMIDE

The thalidomide disaster of the late 1950s and early 1960s caused the single biggest change to regulation of drugs worldwide. Thalidomide's AEs shifted the focus of drug safety worldwide from *reactive* to *proactive*. It led to development of regulations mandating specific safety surveillance before marketing, as well as postmarketing pharmacovigilance activities, including reporting requirements, collection of information into reviewable databases, and establishment of pregnancy registries. These requirements represented a concerted effort to identify drug safety signals early and to begin to better understand drug-associated disorders.

Thalidomide was marketed as a sleeping pill and anti-emetic in over 20 countries between 1956 and 1961. Reports of various types of severe limb

defects (phocomelia), peripheral nephritis, and a host of other severe birth defects in babies began to surface in Europe beginning in late 1961 and early 1962. Phocomelia was particularly devastating, as it affects limb development. Thousands of infants were born with shortened or severely misshapen arms, legs, and hands, as well as abnormalities of the digestive, heart, and genitourinary tracts. Unlike many AEs, defects associated with thalidomide were dramatic and clearly visible. It was observed that these birth defects occurred in the children of mothers who had taken thalidomide during their second month of pregnancy. The occurrence of such defects in the absence of exposure to thalidomide was unknown. However, beginning in about 1957, there was a significant spike in the number of cases; a few doctors reported personally seeing dozens. Dr Donald C. Graham of the *Canadian Medical Association Journal* summed up the problem in a 1962 editorial that stated that, “[T]he incidence of such malformations increased so strikingly and so suddenly it appears logical to assume that some recently introduced teratogenic agent was implicated.” He believed, based on the fetal development timeline, that ingestion of that agent would necessarily fall between the sixth to eighth week *in utero*. Using retrospective investigation of the drug use by the mothers during pregnancy, studies provided “strong suggestive evidence that thalidomide was the teratogenic agent involved.” Other causes of the birth defects were examined and ruled out, and thalidomide became the likely suspect (Graham and Routley, 1962).

Thalidomide was not approved for use in the USA because its NDA was delayed. Dr Frances Kelsey, the FDA's reviewer with a particular interest in teratogenicity, requested additional information and determined that, among other shortcomings, the drug's chronic toxicity studies were not long enough and contained inadequate absorption/excretion data. The delay prevented FDA approval of the drug, and thus wider usage in the USA. Dr Kelsey was later awarded the President's Award for Distinguished Federal Civilian Service by President John F. Kennedy (Bren, 2001). However, an intriguing footnote to this story is described below.

## POST-THALIDOMIDE EVOLUTION OF REGULATION

Following this tragedy, understanding of the necessity to monitor drug products for efficacy and safety grew. The result was increased surveillance of drug usage worldwide. However, different countries developed different regulatory mechanisms.

### UNITED STATES OF AMERICA

While thalidomide was not approved in the USA, approximately 20 000 patients, including 624 pregnant women, were exposed to it as part of then-unregulated “clinical investigations.”

Congress reacted by unanimously passing the Drug Amendments of 1962 to the FDCA (P.L. 87-781, October 10, 1962), commonly referred to as the Kefauver–Harris Amendments. This law set up the framework for the US FDA's current drug regulatory system from discovery through development, testing, and marketing until the product is no longer marketed (see Box 2.1).

### Drug Testing

#### *Pre-Clinical Trials*

Early testing of new molecular entities can lead to early identification of potential major drug safety issues. It is often during *in vitro* and animal testing that potential carcinogenesis is detected, although findings in animals do not necessarily lead to discontinuation of the drug or to ultimate findings of carcinogenesis in humans. However, some safety signals can be identified early – prior to exposure of human subjects.

#### *Clinical Trials*

Clinical trials (CTs) are conducted initially in a few healthy individuals. Phase 1 trials develop information on a tolerable, apparently safe dose and assess pharmacodynamics and pharmacokinetics. In Phase 2 trials, efficacy is evaluated in a slightly larger number of subjects with the condition to be treated. Finally, Phase 3 trials study the drug in a

### **Box 2.1 Regulatory Changes following the Thalidomide Tragedy**

Key provisions of The Kefauver–Harris Amendments (P.L. 87-781, October 10, 1962)

- Required *affirmative approval from the FDA* before a product could be marketed 21 Code of Federal Regulations (CFR) § 314).
- Instituted a mandatory investigational new drug process permitting FDA monitoring of testing, transportation, and distribution (21 CFR § 312).
- Mandated registration of subjects exposed during pre-clinical and clinical testing (21 CFR § 50).
- Established three separate phases of clinical trials to prove efficacy (21 CFR § 312).
- Required uniformly formatted drug labeling (21 CFR § 201.57). Labeling must contain:
  - a summary of all information learned about the drug testing;
  - pharmacology;
  - contraindications;
  - warnings;
  - precautions;
  - AEs seen;
  - dosing and administration.
- Established good manufacturing practices (21 CFR § 210).
- Mandatory safety monitoring and reporting requirements for reports received by manufacturers (21 CFR § 314.80).
- Regular postmarketing communication with FDA on experience with the drug (21 CFR § 314.81), including:
  - sales;
  - all spontaneous reports;
  - analysis of medical literature on product.

few hundred to a few thousand subjects with the condition. CTs are primarily designed to assess the *efficacy* of the drug product; safety is examined, but it is not the primary focus. Furthermore, CTs are conducted under well-controlled conditions. Elderly, pediatric and female patients of childbear-

ing years, and those who are pregnant or nursing, and women planning pregnancies are generally excluded. Patients taking multiple medications or suffering from multiple morbidities and those with known psychiatric conditions are also usually excluded.

Yet CTs are vital to determine a drug's safety profile. They generally reveal major problems (e.g., syncope, seizures or hepatotoxicity) as well as minor problems (e.g., headache, nausea, fatigue). They can only identify the more common events, but there is insufficient statistical power to detect important but rare serious events or those that develop after a latency period outside the time-frame of the CT. All AEs found in CTs are collected and the serious AEs (SAEs) are carefully examined and analyzed: Is the SAE likely drug-related? Dose dependent? Unrelated? Manageable? Does the AE impact the risk–benefit profile of the subject drug?

AEs discovered during CTs become part of the approved labeling for the drug and often become the focus of postmarketing pharmacoepidemiology studies to determine if the drug's benefits continue to outweigh its risks. Some of these safety problems have also led to risk management programs.

#### *Postmarketing Surveillance*

These new regulations were just the beginning. In the late 1960s, the AMA provided the FDA with their monitoring “system” and data (primarily on chloramphenicol-associated hematological affects). This spurred refinement of the “1639 form” used to report suspected AEs. Further, exploring a possible linkage of the FDA and the World Health Organization (WHO) in the late 1960s, Professor Jan Venulet met with drug safety representatives in the FDA and collaborated on development of the first coding thesaurus for AEs, drug adverse reaction terms (DART), enabling the same AE to be described by different coders using the same terms. Recreational drug use as well as prescription drug problems in the late 1960s and 1970s spurred a careful look at drug safety. A more rigorous system of AE surveillance was developed at the urging of Senator Edward Kennedy in a 1973 speech to the Pharmaceuticals Manufacturing Association; he

suggested the need for a better system of monitoring post-approval use and effects of prescriptions drugs. At about the same time, in 1974, Milton Silverman (a pharmacologist/medical writer) and Dr Phillip R. Lee (Chancellor at the University of California San Francisco and Assistant Secretary for Health under both the Johnson and Clinton Administrations) authored *Pills, Profits, and Politics*, a book that critically examined the need to evaluate the impact of pharmaceuticals on the public health (Silverman and Lee, 1974). In 1976, the Joint Commission on Prescription Drug Use was established with the mandate to improve the situation. Its recommendations, which included shortening the drug approval process, were largely ignored.

Since CTs cannot fully assess the effects of a drug taken for chronic indications, or, in excluded populations, it is only after the drug is approved and more widely used that these AEs can be seen. The profile of AEs becomes more apparent, but still not necessarily complete. Some AEs are recognized only after prolonged use or only long after market approval is granted.

Often, a drug's true profile of events becomes clear only through postmarketing surveillance. For example, amiodarone, a cardiac drug approved in Europe in 1980 and in the USA in 1985, was found to cause pulmonary fibrosis (Marchlinski *et al.*, 1982), as well as hepatic disorders and other chronic disorders after long use (Podrid, 1987). Acetaminophen came on world markets in the 1950s but its liver effects in overdose were not recognized until 1966 (Boyd and Bereczky, 1966; Thomson and Prescott, 1966). Cumulative effects of multiple doses of acetaminophen were not realized until the 1970s (Wright and Prescott, 1973).

A comprehensive profile of AEs can also become more difficult if the AEs resemble conditions that are often found concomitantly in patients with the disease being treated (e.g., worsening of more serious and life-threatening arrhythmias when taking anti-arrhythmic drugs such as encainide, flecainide (CAST I, Capone *et al.*, 1991), and moricizine (CAST II, Brooks *et al.*, 1994). Then, it may be difficult to distinguish between a disease-related cause and a drug-associated one.

More recently, genetics have explained an AE appearing more frequently in one ethnic group.

Realization of the connection may not be perceptible for many years. In the case of carbamazepine-induced Stephens-Johnson syndrome in Han Chinese possessing a certain allele, this association was discovered nearly 40 years after the drug was approved by the FDA (Chung *et al.*, 2004).

Drug sponsors bear primary responsibility to monitor, examine, and report AEs. Reports are also sent directly to the FDA (and to other regulatory bodies, as well as to the WHO). Regulatory bodies also monitor reports, and they are compiled into the US FDA's adverse event reporting system (AERS) database. In parallel, other regulatory agencies require AE reports, as detailed below.

But pharmacovigilance does not end with reporting of AEs. Signals of potential safety hazards generated by those reports must be investigated. It is the primary responsibility of the drug's sponsor to conduct follow-up pharmacoepidemiological studies to determine whether in fact, a signal generated by spontaneous reports, case reports or other mechanisms is a true signal or the result of chance. See Table 2.1.

#### *The US FDA Adverse Event Reporting System*

The US voluntary AERS is the primary source used by the FDA to identify drug safety problems in postmarketed drugs (Fung *et al.*, 2001). Spontaneous reports of AEs are sent to manufacturers and to the FDA by healthcare professionals, consumers, and attorneys, among others. Manufacturers are required to submit all reports of AEs received. Serious, unlabeled reports must be submitted to the FDA within 15 calendar days; other reports are submitted to the FDA via periodic reports. Serious AEs are death, life threatening, disability, birth defects, hospitalization (or prolongation of hospitalization).

AERS, called FAERS as of late 2013, is the primary source used by the FDA to identify drug safety problems in postmarketing. AERS is analyzed by regulators, manufacturers, researchers, and attorneys in an effort to detect, examine, quantify, and publicize potential drug safety concerns. A finding of a possible safety issue in AERS generally represents a signal that there may be a problem. AERS is not designed to (nor can it) effectively examine the validity of a signal, since any report or

Table 2.1 Differences in detecting, attributing and recording AEs: CTs versus postmarket use.

Type of data collection	Setting of observation	Patient factors	Data analysis
CTs	Randomized and double-blinded controlled conditions Limited number of patients Short-term observation	Specially selected cases and diseases Healthier patients with fewer risk factors Concomitant drugs often excluded Many populations excluded (elderly, pediatric, many women)	Only efficacy amenable to analysis (sparse AE data) AEs not usually defined endpoints, variably analyzed
Postmarketing setting	Not usually controlled and never randomized Highly variable subjects Long-term use	Multiple comorbidities Variations in lifestyle and demographic factors Concomitant drugs, including OTC Off-label use	Spontaneous reports of AEs not quantifiable Events may be over- or under-detected, -attributed, -reported Potentially subject to media bias Efficacy seldom quantified

Source: Adapted from Jones JK, Idanpaan-Heikkila J. Adverse reactions, postmarketing surveillance and pharmacoepidemiology. In: Burley DM, Clarke JM, Lasagna L, editors. Pharmaceutical Medicine. 2 ed. London: Edward Arnold; 1993. p. 145–180.

group of reports represent an unknown fraction of the total events. Signals generated through AERS (or indeed through case reports or other avenues) must be examined through comprehensive pharmacoepidemiological studies to determine whether the signal represents a true safety issue or results from other factors.

## UNITED KINGDOM

In the UK, the Committee on the Safety of Drugs (CSD) was established in 1964; in 1968 it became the Committee on Safety of Medicines (CSM). In May 1964 the chairman wrote to physicians and dentists asking that they report any suspected adverse drug reactions (ADRs). Each was sent a supply of yellow postage-paid cards to use in reporting ADRs. The system became known as the “yellow card system,” and it continues to the present. Other healthcare practitioners were added over the years: pharmacists in 1997, nurses in 2002, and consumers in 2005.

The yellow card system was designed to detect signals of potential problems that require further investigation. It is a voluntary system, and there was/is uncertainty regarding which ADRs should be reported (e.g., new, unlabeled versus known and

labeled). Like all voluntary reporting systems, the yellow card system suffers from the problem of underreporting. The incidence of ADRs cannot be determined from the number of reports received because there is no denominator.

The limitations of the yellow card system became apparent when it failed to detect problems with practolol in the mid 1970s. Practolol was a selective beta-blocker that was found to cause oculomucocutaneous syndrome, a serious AE with symptoms of severe psoriasisiform rashes, otitis, sclerosing serositis, and conjunctivitis sicca. The association with practolol was likely overlooked by practitioners because early manifestations of the syndrome resembled common ailments, including psoriasis, conjunctivitis, and dry eye conditions. Minor eye AEs found in CTs of practolol included were discovered retrospectively. Had *all AEs*, instead of just *suspected ADRs* from CTs been examined, the more serious ADRs from the drug might have been prevented. Approximately 100 000 patients were treated with practolol, some for up to 2 years, and many hundreds were affected (Amos *et al.*, 1978; Inman, 1986). Practolol, only marketed in the UK, was withdrawn in 1976.

Benoxyprofen, also a non-steroidal anti-inflammatory drug (NSAID), was marketed in

Europe beginning in 1980 and in the USA beginning in May 1982. The drug, renally excreted and with a long half-life, was targeted to elderly patients, who often have limited renal function. The CSM received reports first of photosensitivity, followed in 1982 with reports of fatal hepatic and renal damage believed to be associated with the drug. The *British Medical Journal* published reports of at least 12 deaths in May 1982, mostly due to liver and kidney failure. In early August, the CSM stopped sales of the drug and communicated the risk to other health agencies (Inman, 1986).

Following the ibuprofen withdrawal, the CSM formed the Grahame-Smith Working Party. In 1983 it made recommendations, primarily to address underreporting of suspected ADRs (Routledge, 1998). These recommendations included:

- increased publicity of yellow card system;
- easier availability of yellow cards to potential reporters;
- improving pre-marketing safety studies;
- encourage postmarketing studies on all new drugs marketed for widespread long-term use.

## GERMANY

In 1958, the German Drug Commission asked physicians to begin voluntary reporting of all suspected ADRs. However, it was not until after the thalidomide tragedy that the system really began to function as intended. In 1963, the German Society for Internal Medicine published the first ADR report forms; and Germany was one of the earlier contributors to the WHO Collaborative Drug Monitoring Center.

## SCANDINAVIA

Norway and Sweden began pilot programs for reporting ADRs to national monitoring centers in 1965; Denmark followed in 1968. Norwegian doctors and dentists were required to report suspected fatal or life-threatening AEs starting in 1973. In 1979 this requirement was expanded to include AEs leading to serious sequelae and new or unexpected ADRs. Sweden's similar mandatory

reporting program began in 1975. Denmark's ADR reporting program is similar to those of Norway and Sweden, but the Norwegian program is not mandatory.

## JAPAN

Japan's drug safety system began in 1967 as a voluntary reporting system operated by the Japanese Government under the Ministry of Health and Welfare. In 1979, the government's revision of laws governing pharmaceuticals expanded the country's pharmacovigilance program and established the "Reexamination System for New Drugs" to ensure quality, safety, and efficacy of drug products.

One hundred and ninety-two Japanese hospitals were originally designated as "monitoring hospitals," where physicians were expected to report "novel" or serious ADRs to the National Drug Monitoring Center. The number of Japanese monitoring hospitals has multiplied since the system's inception. While it is not mandatory, the following ADRs are expected to be reported:

- unforeseen reactions to drugs;
- undesirable reactions that are serious or abnormal; and
- other undesirable reactions that doctors consider important or worth reporting.

In addition to reports from industry, AE information was collected by three systems:

- prescription drugs via the National Drug Monitoring System;
- OTC drugs via the National Pharmacy Monitoring System;
- new drugs via the Reexamination System for New Drugs.

Reports were followed up if additional information was necessary. ADRs were then examined and potential associations with suspected drugs assessed.

Interestingly, when they thought too few case reports were received, the National Drug Monitoring Center would ask its monitoring hospitals to report all AEs encountered with specific designated old and new drugs (Inman, 1986).

Unlike many other systems, the Japanese system rewarded reporting doctors with a small amount of cash and a subscription to *ADR Information*; the US FDA also briefly had such a reward system in the early 1970s (Inman, 1986).

## WORLD HEALTH ORGANIZATION

Under the auspices of 10 countries, a 3-year feasibility study of a collaborative international program of pharmacovigilance was begun by Professor Jan Venulet in 1968 (Venulet and Helling-Borda, 2010). Funded by the USA and located near the FDA, Professor Venulet and the FDA's drug safety group developed, among other things, a standard thesaurus, DART, to describe spontaneous reports in a uniform body-system-based terminology. At the FDA, DART evolved into COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms), which was used until MedDRA (Medical Terminology for Drug Regulatory Authorities) was adopted in the later 1990s by the European Commission as part of the International Conference on Harmonization. The feasibility study was successful; Venulet developed a program agreed to by member states for recording, storing, and retrieving incoming spontaneous reports into a database, as well as methodologies for analyzing the data received. This effort became the International Drug Monitoring Programme, which was then moved to WHO headquarters in Geneva, Switzerland. In 1978, the program was moved to Uppsala, Sweden. Today, the Uppsala Monitoring Centre's mission ([www.who-umc.org/DynPage.aspx?id=96990&mn1=7347&mn2=7469&mn3=7470](http://www.who-umc.org/DynPage.aspx?id=96990&mn1=7347&mn2=7469&mn3=7470)) is to "safeguard patients" and to:

- lead the research and development of tools and methodologies for pharmacovigilance and patient safety;
- lead and support global pharmacovigilance activities;
- develop effective networks and sustainable pharmacovigilance systems;
- apply best practice in communication and networking with stakeholders;
- provide high-quality and cost-effective tools, services, and international dictionaries, classifi-

cations, and terminologies for pharmacovigilance and patient safety;

- build an effective organization for the future with open, impartial, and ethical values and performance.

This monitoring program has been very effective and now serves over 80 countries with annual meetings to exchange practices, provide training, and serve as a database of AEs from member countries.

## FRANCE

France's pharmacovigilance program evolved quite differently from those of other countries; it began with pharmacologists, toxicologists, physicians, and pharmacists establishing methods to evaluate AEs and to warn others about them. It has been active and used since 1977 (Begaud, 1984). They worked together to set up three regional units where ADRs could be reported and where risks could be examined and communicated. The original three regional centers were in Paris, Lyon, and Marseilles (Moore *et al.*, 2002), but over the years they have expanded to more than 31 centers nationwide. All are located at university hospitals; they examine AEs within individual defined geographical regions. The regional centers collect and record suspected ADRs, provide information to healthcare practitioners and facilities, and conduct research on potential drug risks.

At about the same time in the early 1970s, the national order of physicians and the French pharmaceutical manufacturers' association began working together to set up a national center that became the Pharmacovigilance Unit, a part of Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS). This unit coordinates the work of the regional centers and is coordinated through a national network. This unit has more recently come to be administered by the French National Agency for the Safety of Medicines and Health Products (ANSM), the new regulatory body that replaced AFSSAPS in 2012.

One of the primary differences between the French system and others is that AEs reported to the French system are evaluated as to causality and

use a specific “French method” developed and refined in the 1980s (Begaud, 1984).

## SPECIAL ISSUES IN PHARMACOVIGILANCE

There is no question that the practice of pharmacovigilance by manufacturers and regulators has saved lives and limited injuries that may otherwise have occurred. Many drug products have been taken off the market as a result of drug-related safety concerns communicated by reports of suspected AEs (see Table 2.2).

### EXAMPLES OF DRUGS THAT WERE WITHDRAWN FROM THE MARKET

This section highlights selective examples of drugs that often achieved wide use, but were later found to have an unacceptable risk–benefit profile, or, in the case of Bendectin, withdrawn by the company independent of regulatory actions. Some of these events contributed to the awareness and development of the current risk management programs.

Diethylstilbestrol (DES), an early synthetic estrogen that was given to pregnant women from about 1940 through 1970 to reduce the potential for miscarriage, was withdrawn from the market in 1971 when safety concerns arose over the appearance of rare vaginal tumors in girls and young women exposed to DES prenatally. This AE was validated by an epidemiological study that linked the exposure to DES to the risk in the offspring generation (Fowler and Edelman, 1978).

In 1982, another NSAID, zomepirac, a non-narcotic analgesic, was rapidly adopted by emergency-room physicians and dentists for treatment of acute pain. Although the label cautioned against use if a history of aspirin allergy was known, this instruction was often ignored; within several months reports of acute allergic reactions and anaphylaxis were made. The sponsor updated its label and the FDA reported some cases in the *New England Journal of Medicine*. However, a series of cases of acute allergy and anaphylaxis were reported, and after an emergency-room physician appeared on television to warn about the drug, it was with-

drawn at the FDA's request. Interestingly, this product had been marketed in the UK as a chronic NSAID and had only been rarely associated with these reactions; thus, one risk factor appeared related to intermittent use as an analgesic.

In the 1990s, three drugs were discovered to be associated with life-threatening arrhythmias when drug levels rose due to interaction with other common drugs sharing the same liver-metabolizing enzyme, cytochrome P450 3A4. Terfenadine, a widely used non-sedating antihistamine, was reported to cause Torsade de Pointes, an arrhythmia sometimes leading to ventricular fibrillation and death. The risk was deemed unacceptable because of the wide exposure and the commonness of the interacting drugs – including erythromycin (Monahan *et al.*, 1990). In the late 1990s, cisapride (Propulsid), a remedy for diabetic gastroparesis and severe gastroesophageal reflux, was found to also interact with the same common medications as terfenadine, causing drug concentration levels to rise and resulting in adverse cardiac effects. Interacting medications included erythromycin and clarithromycin. These contraindications were first added to cisapride's label, but concomitant prescribing of interacting drugs continued until cisapride was removed from the market 7 years after its approval (Jones *et al.*, 2001). A third drug, astemizole, an antihistamine, followed this pattern and was also removed (Staffa *et al.*, 1995).

Troglitazone (Rezulin), an antidiabetic drug, was approved in 1997. Soon, several cases of hepatotoxicity were reported to the FDA, and the FDA requested a label change advising physicians to monitor liver function. Additional cases reported, plus the finding that physicians were not routinely monitoring liver function, led to troglitazone's examination at FDA advisory committee meetings. Troglitazone was taken off the US market in 2000 (Gitlin *et al.*, 1998) and from the UK market more quickly.

An example of a drug with known AEs including death from overdose due to a low therapeutic index of therapeutic dose to toxic dose was propoxyphene (Darvocet/Darvon), a pain reliever. Potential abuse and abuse-related deaths were the subject of a special FDA, National Institutes of Health, and Alcohol, Drug Abuse, and Mental Health

Table 2.2 Sample of drugs removed from the market for safety reasons, 1978 to 2012.

Year removed	Drug (generic name)	Reason removed
1978	Phenformin (DBI)	Lactic acidosis
1980	Ticrynafen (Selacryn)	Hepatotoxicity
1982	Benozaprofen (Oraflex)	Hepatotoxicity
1983	Zomepirac sodium (Zomax)	Anaphylaxis
1985	Pituitary growth hormone (IND)	Creutzfeldt–Jakob disease
1986	Nomifensine (Merital)	Hemolytic anemia
1987	Suprofen (Suprol)	Flank pain syndrome
1991	Guar gum (Calban)	Esophageal obstruction
	Encainide (Encaid)	Excess mortality <sup>a</sup>
1992	Temafloxacin (Omniflox)	Hemolytic anemia (often accompanied by renal or hepatic dysfunction and/or coagulopathy)
1993	Flosequinan (Manoplax)	Excess mortality
1997	Phenolphthalein (Ex-Lax)	Carcinogenicity <sup>b</sup>
1997	Fenfluramine (Pondimin)	Cardiac valvulopathy
1997	Dexfenfluramine hydrochloride (Redux)	Cardiac valvulopathy
1997	Terfenadine (Seldane)	Drug interactions/ventricular arrhythmias
1998	Mibepradil (Posicor)	Drug interactions/cardiac events
1998	Bromfenac (Duract)	Hepatotoxicity
1999	Astemizole (Hismanal)	Drug interactions/ventricular arrhythmias
1999	Grepafloxacin hydrochloride (Raxar)	Ventricular arrhythmias
2000	Troglitazone (Rezulin)	Hepatotoxicity
2000	Cisapride (Propulsid)	Drug interactions/ventricular arrhythmias
2000	Alosetron hydrochloride (Lotronex) <sup>c</sup>	Ischemic colitis and complications of constipation
2000	Phenylpropanolamine ingredient products (e.g., Dexatrim)	Hemorrhagic stroke
2001	Rapacuronium bromide (Raplon)	Bronchospasm
2001	Cerivastatin sodium (Baycol)	Rhabdomyolysis
2004	Rofecoxib (Vioxx)	Risk of myocardial infarction
2005	Hydromorphone extended-release (Palladone)	High risk of accidental overdose when administered with alcohol
2005	Thioridazine (Melleril)	Cardiotoxicity (UK)
2005	Pemoline (Cylert)	Hepatotoxicity (USA)
2005–2006	Natalizumab (Tysabri)	Voluntarily withdrawn from US market because of risk of progressive multifocal leukoencephalopathy; returned to market July, 2006
2006	Ximelagatran (Exanta)	Hepatotoxicity
2007	Pergolide (Permax)	Risk of heart valve damage (voluntary, USA)
2007	Tegaserod (Zelnorm)	Cardiovascular
2007	Aprotinin (Trasylol)	Increased risk of complications or death (used to control bleeding in surgery)
2007	Inhaled insulin (Exubera)	Withdrawn in the UK due to poor sales caused by national restrictions on prescribing, doubts over long-term safety and too high a cost
2007–2008	Lumiracoxib (Prexige)	Serious AEs, particularly hepatotoxicity
2008	Rimonabant (Acomplia)	Risk of severe depression and suicide
2009	Efalizumab (Raptiva)	Progressive multifocal leukoencephalopathy
2010	Sibutramine (Reductil/Meridia)	Cardiovascular risk
2010	Gemtuzumab ozogamicin (Mylotarg)	Veno-occlusive disease and lack of efficacy
2010	Propoxyphene (Darvocet/Darvon)	Increased risk of heart attacks and stroke when abused
2010	Rosiglitazone (Avandia)	Increased risk of heart attacks and death (EU)
2011	Drotrecogin alfa (Xigris)	Withdrawn by Eli Lilly worldwide following results of the PROWESS-SHOCK study that showed lack of efficacy (not because of toxicity like other drugs that have been withdrawn)

Source: Adapted from Fung *et al.* (2001). Reproduced with permission of SAGE Publications.

IND: investigational new drug.

<sup>a</sup>Determined from CT, not spontaneous reports.

<sup>b</sup>Based on animal studies.

<sup>c</sup>Based on CT data and spontaneous reports; reintroduced to the market in 2002.

Administration Task Force that addressed concerns raised in a Citizens' Petition in 1979–1980, and determined that the drug's benefits outweighed its risks. However, following another Citizens' Petition, propoxyphene was removed from the market in November 2010.

Rofecoxib (Vioxx), a popular NSAID used to treat chronic or acute pain, was withdrawn by its sponsor, Merck, due to the potential risk of heart attack and stroke.

### BENDECTIN

Bendectin (USA) or Debendox (non-USA) was a drug indicated for nausea in pregnancy marketed from 1956 until 1983. It combined three ingredients: 10 mg doxylamine succinate (an antihistamine with anti-nausea effects), 10 mg dicyclomine (an antispasmodic), and 10 mg pyridoxine (vitamin B6). The dicyclomine portion of the combination was later deemed unnecessary to efficacy and removed. Up to one-third of the pregnant women in the USA used Bendectin for treatment of nausea and vomiting of pregnancy. In the USA, Bendectin's manufacturer, Merrell Dow, in 1983 was subjected to many lawsuits that alleged that its use caused birth defects. The lawsuits were based on case reports, particularly of limb defects.

These claims were investigated. In 1979, the FDA's spontaneous reporting system had 67 reports of limb defects and only a few reports of other defects. This ratio of effects was judged to be unusual and supported a hypothesis that this product might be having similar effects to thalidomide. Contact with the WHO at the time spurred a search for similar data, increasing worldwide concern. The FDA found it important to explore this possible relationship and requested data on epidemiological studies of birth defects that might relate to this drug. Such interest spawned a number of studies, some of which were positive – but not for limb defects. The FDA also held a 3-day hearing to examine the topic, including a presentation by Dr McBride, one of the initiators of the hypothesis that Bendectin/Debendox was a teratogen (based upon studies in chicks). Ultimately, it was determined that there was no definitive conclusion that the drug was teratogenic.

Nevertheless, the company removed the compound from the market. A few years later, Robert L. Brent published a summary of the many epidemiological studies done and concluded that they did not support an association with birth defects. The allegations were studied extensively using pharmacoepidemiological cohort studies and case control studies; the claims were false (Brent, 1995).

The pooled estimate of the relative risk of any malformation at birth in association with Bendectin in the first trimester was 0.95 (95% CI 0.88–1.04). Separate analyses were undertaken for cardiac defects, limb reduction defects, oral clefts, and genital tract malformations. In these categories, the pooled estimates of relative risks ranged from 0.81 for oral clefts to 1.11 for limb reductions, with all 95 confidence intervals enclosing unity. These studies, as a group, showed no difference in the risk of birth defects between those infants whose mothers had taken Bendectin during the first trimester of pregnancy and those whose mothers had not. (McKeigue *et al*, 1994).

This nonvalidated signal spurred broad development of methods and resources for the epidemiological and other studies of birth defects. Although many systems and databases can now evaluate the risk of birth defects, spontaneous reports are still one of the most effective tools to identify serious teratogens early, since AE systems survey the entire population (databases and registries do not, and they accumulate information slowly). However, this system is dependent upon physicians' willingness to report, which is a major limitation for pharmacovigilance. One of the unfortunate results of the Bendectin story, following so closely on that of thalidomide, is that pharmaceutical companies have since been reluctant to develop drugs for use during pregnancy.

### THALIDOMIDE: TODAY'S APPROVED USES

Surprisingly, in spite of its history, thalidomide is currently approved for use in many markets worldwide. Sold under the trade name Thalomid®, it is specifically indicated for treatment of complications of leprosy (skin manifestations and neuritis) and, in combination with dexamethasone, for

treatment of newly diagnosed multiple myeloma patients (Calabrese and Fleischer, 2000; Matthews and McCoy, 2003; Chen *et al.*, 2010). It is available only with special restrictions, including limited dispensing via specific pharmacies, a patient registry, mandatory patient education, prohibition of unprotected sex by male and female patients, mandatory pregnancy tests and a strict ban on use in pregnant women.

## PHARMACOVIGILANCE IS NOT JUST FOR REGULATORS

Global pharmacovigilance today incorporates experience from a majority of countries worldwide. Its limitations include underreporting; incomplete data; absence of precise information on exposure to suspect and concomitant drugs, supplements, occupational exposures; and a host of other, often absent, factors. But pharmacovigilance exists to find “signals.” It is the most powerful method to survey a drug or biopharmaceutical after it enters the market.

Signal information is *qualitative*, not quantitative, since any collection of reports is an unknown proportion of the total events associated with a drug, and the actual population of exposure is usually poorly defined. It can never be used to establish incidence of an AE, but can signal a potential association between a drug and an event. These signals must then be examined rigorously through appropriately conducted pharmacoepidemiology studies.

Nevertheless, pharmacovigilance is central to the efforts of regulators of biopharmaceutical products and drug sponsors to assure products are safe and effective. More recently, pharmacovigilance has become important to managers of large distribution programs in the less-developed world of HIV, malaria, and other related drugs (e.g., the Gates Foundation, Pepfar, and similar programs) to identify potential problems early to effect optimal safe use through label or package modifications or to effect withdrawal.

In closing, it is very important to emphasize that a signal can only be examined and any causal association with a drug or other medical product noted

if it is reported. Therefore, the first step in pharmacovigilance is *vigilance* by the medical community and a commitment to report AEs. Thus, there is a very great need to incorporate an interest in pharmacovigilance and, in particular, reporting of suspected AEs to both sponsors and regulatory authorities in medical, pharmacy, and nursing schools globally. At present, the reporting rate remains low, and thus the discovery of new adverse effects in larger, diverse populations is unnecessarily delayed. This, in turn, compromises the effectiveness of pharmacovigilance, a critically important tool to assure that marketed biopharmaceuticals are optimally safe.

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## **Part I**

# **THE REGULATORY BASIS OF PHARMACOVIGILANCE**



# 3

## Legal Basis: European Union

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### INTRODUCTION

As of July 2012, the European Union (EU) pharmaceutical legislation for pharmacovigilance (PV) was introduced. This was the most substantial change since the current regulatory system and European Medicines Agency (formally EMEA, now EMA and referred to in the legislation as “the Agency”) was established on January 1, 1995.

Within the EU, there are five types of implementing legal acts:

- a regulation;
- a directive;
- a decision;
- a recommendation;
- an opinion.

According to Article 288 of the Treaty on the Functioning of the European Union, regulations, directives, and decisions are binding acts. Regula-

tions are applied in their entirety in all member states (MSs) in the same way as national legislation, without any further action on the part of the national authorities, with only one version. Directives are decentralized legislation which are binding on the MSs but leaves them the choice of the way they adopt the objectives of the directive within their national legal system. Inevitably, transposition into national law leads to differences between MSs. Recommendations and opinions are not legally binding upon those to whom they are addressed. Finalized legislation is published in the *Official Journal of the European Union* (OJ), which gives timelines for the implementation with transposition into law as 18 months from the date of OJ publication. This allows MSs to develop guidelines, new processes and technology, and changes to national regulation.

By creating delegated acts as a new category of legal act, the Treaty of Lisbon enables the European Parliament (the Parliament) to delegate to

the European Commission (the Commission) the power to adopt acts amending non-essential elements of a legislative act. For example, delegated acts may specify certain technical details or they may consist of a subsequent amendment to certain elements of a legislative act. This avoids overly technical debates. However, this delegation of power has strict limits. In effect, only the Commission can be authorized to adopt delegated acts. Furthermore, the legislator sets the conditions under which this delegation may be implemented. Article 290 of the Treaty on the Functioning of the European Union specifies that the Council of the European Union (the Council) and the Parliament may revoke a delegation or limit its duration.

One of the driving principles behind EU legislation is subsidiarity, which was introduced by the Treaty of Maastricht and regulates the exercise of powers in the EU. The subsidiarity principle is based on the idea that decisions must be taken as closely as possible to the citizen: the EU should not undertake action (except on matters for which it alone is responsible) unless EU action is more effective than action taken at national, regional, or local level. It is important to understand these arrangements as they illustrate the legal complexity of the EU and inevitable differences in the way legislation is implemented across the MSs.

All medicinal products placed commercially on the market within the EU must have a marketing authorization (MA) which signifies that a medicinal product complies with criteria for quality, safety, and efficacy laid out in Directive 2001/83/EC of November 6, 2001, on the Community Code relating to medicinal products for human use, as amended by Directive 2002/98/EC of January 27, 2003, Directive 2003/63/EC of June 25, 2003, Directive 2004/24/EC of March 31, 2004, Directive 2004/27/EC of March 31, 2004, and Regulation (EEC) No. 726/2004 laying down European Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing the EMA. Both are still in force but have been amended by the new legislation. Accordingly, marketing authorizations for products to be placed on the EU market can follow three routes:

- nationally the competent authority (CA) of an MS (where the product will be marketed in one MS only); or
- through the mutual recognition and decentralized procedures, where a marketing authorization granted by the CA of an original ('Reference') MS is accepted by the CA of other MSs; and
- through the centralized procedure by the Commission applying throughout the European Economic Area (EEA – the EEA consists of the EU plus three other MSs: Norway, Liechtenstein, and Iceland).

For investigational medicinal products used in clinical trials, PV requirements are set out in the Clinical Trials Directive 2001/20/EC. Volume 10 of "The Rules governing medicinal products in the European Union" (The Rules) contains the guidelines referred to in Articles 8, 9, 11, 13 and 18 of Directive 2001/20/EC, and Articles 1, 16, 22, and 29 of Directive 2005/28/EC. Article 1(2) of 2005/28/EC states:

When applying the principles, detailed guidelines and requirements referred to in paragraph 1, Member States shall take into account the technical implementing modalities provided for in the detailed guidance published by the Commission in The Rules.

This subsequently appeared in April 2006 as ENTR/CT 3 (revision 2) entitled "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" and was revised and published in the OJ on June 11, 2011, as a communication from the Commission.

However, this chapter will discuss PV for authorized products and should be read as an update on the previously published chapter of this textbook.

Up until July 2012, Directive 2001/83/EC, as amended, laid down the rules for manufacture, distribution, authorization, and post-authorization supervision of nationally authorized products with a corresponding Regulation (EC) No 726/2004 of the Parliament and the Council for centrally authorized products as well as Regulation (EC) No 540/95

and guidance (first there was Volume 9 in 2004, followed by Volume 9A in January 2007). Although the legislation was reviewed in 2004 (the so-called “2001 Review”) the changes to the PV provisions were relatively minor. The Commission recognized that the PV provisions had become gradually more complex over time so that they did not keep up with public health needs and that different implementation by MSs had led to complex and diverse reporting requirements. In addition, there were continuing concerns about harm from adverse drug reactions (ADRs), all of which heightened public and political pressure for change. After a complicated review process, the newly amended PV legislation was adopted by the Council and Parliament on December 15, 2010.

For medicinal products authorized under the centralized procedure, the relevant legislation is Regulation (EC) No. 726/2004 and (EC) 1394/2007 (for advanced therapies). Both regulations were amended by Regulation (EU) 1235/2010 (and this will be referred to in this chapter as “The Regulation”). This new regulation came into force on July 2, 2012. For medicinal products authorized under national or mutual recognition/decentralized procedures, the relevant PV legislation is primarily Title IX of Directive 2001/83/EC, as this and its amendments are replaced by Directive 2010/84/EU (and this will be referred to in this chapter as “The Directive”). Both the Directive and Regulation were published in the OJ on December 31, 2010. This means that they entered into force on the 20th day following publication (i.e., January 20, 2011). MSs had until July 21, 2012 to adopt the provisions of the Directive. There was also a Corrigendum to Directive 2010/84/EU correcting implementation dates. The regulation largely implements PV obligations by cross-reference to the relevant articles in the directive. EU legislation can be found on the Commission website [http://ec.europa.eu/health/documents/eudralex/index\\_en.htm](http://ec.europa.eu/health/documents/eudralex/index_en.htm).

This legislation has been underpinned by Commission Implementing Measures Regulation (EU) No. 520/2012, Delegated Acts (see Article 87b-d of the Regulation and Article 121a of the Directive) and a series of modules on Good Pharmacovigilance Practice (GVP). The final versions of seven

of these (GVP) modules were published June 25, 2012, and were entitled:

Module I:	Pharmacovigilance systems and their quality systems
Module II:	Pharmacovigilance system master file
Module V:	Risk management systems
Module VI:	Management and reporting of adverse reactions to medicinal products
Module VII:	Periodic safety update reports
Module VIII:	Post-authorisation safety studies
Module IX:	Signal management

Subsequently, further GVP modules were released later in 2012 and 2013:

Module III:	Pharmacovigilance inspections
Module IV:	Pharmacovigilance audits
Module X:	Additional monitoring
Module XIII:	Incident management (no longer in development)
Module XV:	Safety communication
Module XVI:	Risk-minimisation measures: selection of tools and effectiveness indicators (released for consultation but not finalised)

A further three GVP modules are due for release for public consultation second quarter 2014:

Module XI:	Public participation in pharmacovigilance
Module XII:	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication
Module XIV:	International cooperation

The GVP modules refer to the implementing regulation, a legally binding act published by the Commission in June 2012. This regulation provides details on the operational aspects for the new legislation.

Volume 9A will be phased out as of July 2012. The EMA estimates that some features of the new PV legislation (such as EudraVigilance) will only be fully functional at the earliest by 2016; transitional provisions are in place (see Article 3 of the Regulation and Article 2 of the Directive and Questions and Answers (Q&As) published by the Commission and the joint publication by the EMA and Heads of Medicines Agencies). The rest of this chapter will describe the main changes in the new PV legislation.

## **REORGANIZATION OF THE EUROPEAN UNION REGULATORY SYSTEM**

On matters concerning PV, the EMA has been advised by a scientific committee, the Committee for Medicinal Products for Human Use (CHMP), which in turn, up until July 2012, was advised by a subcommittee: the Pharmacovigilance Working Party. As of July 2012, this subcommittee has now been replaced by the Pharmacovigilance Risk Assessment Committee (PRAC). The mandate of the PRAC is described in Article 61a of the Regulation, as:

all aspects of the risk management of the use of medicines including detection, assessment, minimisation and communication related to the risk having due regard to the therapeutic effect use of the medicine, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

This means that PRAC will be responsible for PV and risk management issues for all medicinal products at the Community level. In Article 28a of the Regulation, PRAC

shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement of any subsequent action as regards the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

As described in Articles 5(2) and 56(1) (aa) of the Regulation, the CHMP will "rely on the scientific assessments and recommendations of PRAC." Article 28b states that where opinion of CHMP and PRAC differs, CHMP "shall attach its opinion a detailed explanation of the scientific grounds for the differences." Article 27 of the directive refers to a coordination group (already in existence and known as the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)) who shall rely on the scientific assessment and the recommendations of the PRAC for the fulfillment of its PV tasks. Article 61a of the Regulation describes the composition of PRAC.

## **OBLIGATIONS OF BEING A MARKETING AUTHORIZATION HOLDER AND BEING GRANTED A MARKETING AUTHORIZATION**

Article 104 of Directive 2001/83/EC sets out the obligations of marketing authorization holders (MAHs). This is further amended as follows:

As part of the pharmacovigilance system, the marketing authorisation holder shall be required to:

- (a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;
- (b) maintain and make available on request a pharmacovigilance system master file;
- (c) operate a risk management system for each medicinal product;
- (d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions or requirements in the marketing authorisation pursuant to Articles 21a, 22 or 22a;
- (e) update the risk management system and monitor pharmacovigilance data to determine whether there are new or changed risks or whether there are changes to the benefit-risk balance of medicinal products.

The qualified person referred to in point (a) of the first subparagraph shall reside and operate in the Community and shall be responsible for the establishment and maintenance of the pharmacovigilance system.

Articles 21a and 22 refers to the additional measures that may be granted, such as certain measures to ensure safe use, post-authorization safety studies, stricter obligations to record or report suspected adverse reactions, conditions or restrictions with regard to safe and effective use, existence of an adequate PV system, and post-authorization efficacy studies. The obligation to conduct such studies shall be based on the delegated acts as defined in Articles 22b and 108a of the Directive. The number of conditions attached to the marketing authorization is likely to increase. A simplified route for the registration of traditional-use herbal medicinal products also exists; the requirement to operate a PV system also applies to these products.

For marketing authorization applications, Article 8(3) of Directive 2001/83/EC required a Detailed Description of Pharmacovigilance system. This has now been replaced by a summary of the applicant's PV system, which is described in Article 8(3) as follows

- proof the applicant has at his disposal a qualified person responsible for pharmacovigilance, commonly known as the QPPV,
- the Member States in which the qualified person resides and carries out his/her tasks,
- contact details of the qualified person,
- statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in Title IX,
- reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

Article 16(4) of the Regulation and Article 23(4) of the Directive require the MAH to provide a copy of the PV system master file (PSMF) to the Agency or national CA within 7 days. Article 18 of the Regulation explains that “the supervisory authority for pharmacovigilance shall be the competent authority of the Member States in which the pharmacovigilance system master file is located,” but this appears to only apply to MAs authorized through the centralized route. As mentioned in Article 111 of the Directive, the PSMF will be inspected.

Article 3 of the Regulation and Article 2 of the Directive entitled Transitional Provisions explains that the PSMF will be required after July 21, 2012, if an MA is renewed or by July 21, 2015. The content of the PSMF is similar to that of the Detailed Description of the Pharmacovigilance System (DDPS) but with greater emphasis on the quality system with the added provision described in Article 104 (2) of the Directive which states that

The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and followed. Once the corrective actions have been fully implemented, the note may be removed.

Further details about the PSMF can be found in GVP Module II. The PSMF should be based at the site where the main PV activities are performed or at the site where the QPPV operates. There must also be a physical address for the MAH, or contracted third party, within the EU. Therefore, the most relevant EU site should be selected, the default being the QPPV site in the absence of an appropriate site for selection. The MAH must inform the QPPV (GVP Module II) and third parties/partners of significant changes which are described in this module.

## SIGNAL DETECTION AND RISK MANAGEMENT

Article 28a of the Regulation and Article 107h of the Directive describe the responsibilities of the CAs, the Agency and PRAC as regards monitoring risk minimization measures, updates to risk management systems and data in the EudraVigilance database. In particular, PRAC will perform initial analysis and prioritization of new signals, and determine timelines and actions commensurate with seriousness and extent. Article 28a of the Regulation and Article 107h(3) of the Directive state that

the Agency and national competent authorities and the MAH shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

All risks are required to be notified, including those detected in use outside of the terms of the MA (Article 23(2) of the Directive and Article 16(2) of the Regulation). Article 16(4) of the Regulation and Article 23(4) of the Directive describe that the Agency/CA may at any time ask the MAH to forward data demonstrating that the risk-benefit balance remains favorable and that the MAH shall answer fully and promptly any of these requests.

Further detail for MAHs are provided in GVP Module IX: Signal management. MAHs are expected to monitor all available data for signals, including emerging data, and perform worldwide signal detection activities, check data in EudraVigilance at a frequency proportionate to identified and potential risks or need for additional information. Thus, MAHs will need to define processes about how they confirm and validate signals, as once a signal is validated the CAs need to be informed. MAHs will be expected to collaborate with the PRAC for the assessment of the signals by providing additional information upon request. MAHs and CAs should establish tracking systems to capture the outcome of the validation of signals, including the reasons why signals did not suggest a new potentially causal association or a new aspect of a known association, as well as information that would facilitate further retrieval of the cases and assessment of the signal.

In Article 1 of the Directive, point 28b defines a risk management system as “a set of PV activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.” Whereas point 28c defines a risk management plan (RMP) as “a detailed description of the risk management system.” As described in Article 104a of the Directive, for MAs granted before July 21, 2012, a risk management system is not required, unless there is a RMP in existence for an authorized product. However, in Article 21(2) of the regulation and Article 104a(2) of the Directive, the Agency or

national CAs may impose a risk management system “if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product” as well as a plan with timelines. Article 21(3) of the regulation and Article 104a(3) of the Directive describe the opportunity to appeal against this obligation.

As described in the GVP Module V: Risk management systems, the RMP will take on a modular format in seven parts. The contents are similar to the current template described in Volume 9A with three significant changes. A section in module SVI deals with aspects of pediatric use not covered in module SIV (see V.B.8.6.5. of the GVP). This means RMPs will need to include issues identified in pediatric investigation plans and any recommendations for long-term follow up of safety or efficacy issues in relation to the pediatric population.

Part IV of the RMP template concerns plans for post-authorization efficacy studies. The MA applicant will need to summarize the efficacy of the product, the level of certainty that the efficacy shown in clinical trial populations will be seen in everyday medical practice, and from that extrapolate the need for post-authorization studies on efficacy.

As described in Article 106(c) of the Directive, a summary of the RMP will be made publicly available on national CA web portals. The format for this summary is provided in Part VI of the new template.

Article 1(15) of the Directive provides an amended definition of a post-authorization safety study (PASS) as

Any study with an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

Article 22a of the Directive has clarified the legal basis for PASS, in that a CA that granted an MA may require a PASS “if there are concerns about the risks of an authorised medicinal product,” and if a PASS is required, this shall be a condition for the MA. In addition, more detailed rules on PASS,

including the supervisory role of PRAC, have been provided in Articles 107m–107q of the Directive. The obligation of the MAH to notify the CAs of any new information from PASS that might influence the evaluation of the risk–benefit balance has been emphasized in Article 107m(7) of the Directive. If a safety concern applies to more than one medicinal product, the national CA shall, following consultation with PRAC, encourage the MAHs concerned to conduct a joint post-authorization safety study. The MAH will have to submit a draft protocol to PRAC with any subsequent major amendments. The study protocol and the abstract of the final study report shall be entered in a publicly accessible electronic study register. The MAH shall send the final report to the CAs within 12 months of the end of data collection.

Article 23 of the Regulation, describes how the Agency and MSs will set up, maintain, and make public a list of medicines that are subject to additional monitoring. The Agency shall remove a medicinal product from the list 5 years after the Community reference date. However, the Commission or the CAs may, following a recommendation of PRAC, extend that period until such time as the regulatory conditions have been fulfilled. For medicinal products included in that list, the summary of product characteristics and the patient information leaflet shall include the statement “This medicinal product is subject to additional monitoring.” That statement shall be preceded by a black triangle, which shall be selected by the Commission following a recommendation by the PRAC.

## REPORTING REQUIREMENTS

Article 107 of the Directive describes simplification of individual case reporting, in that MAHs will only have to submit EU domestic ADRs and all serious third-country ADR reports to EudraVigilance (the database maintained by EMA). This means there will be 15-day reporting for serious EU and third-country case reports and 90-day reporting for non-serious EU case reports. Patient reports qualify for expedited reporting. Further to Article 107 in the Directive, GVP Module VI.B.7 describes the clock for expedited reporting of individual case

as starting when a valid individual case safety report (ICSR) is first received by a company belonging to the same MAH in the EU, or having concluded contractual arrangements with the MAH in the EU. GVP Module VI.A.2.1 clarifies the definition of an adverse reaction as a response to a medicinal product which is noxious and unintended including adverse reactions which arise from:

- use of a medicinal product within the terms of the MA;
- use outside the terms of the MA, including overdose, misuse, abuse, and medication errors;
- occupational exposure.

There are relevant chapters in GVP Module VI describing the management of spontaneous reporting programmes (VI.B), including requirements for reporting in special situations (VI.B.6) and for expedited reporting of ICSRs (VI.B.7). Appendices 5, 6 and 7 of Module VI discuss nullification of cases, data quality, and electronic exchange and duplication. Article 107a of the Directive advises that MSs shall not impose any additional national reporting requirements on MAHs “unless there are justifiable grounds resulting from pharmacovigilance activities.”

Article 24 of the Regulation describes the obligations that the EMA has to maintain EudraVigilance and enable access to the CAs and MAHs. Under the supervision of PRAC, the EMA will have to conduct an independent audit to ensure full functionality has been achieved. Prior to this, interim arrangements for expedited reporting will exist, as detailed in the GVP. Article 57(2) of the Regulation defines the need to electronically submit information on medicinal products by July 2, 2012. Article 11 of the Directive requires standard text asking healthcare practitioners to report suspected ADRs through their national spontaneous reporting system specifying the different ways of reporting available.

Article 27 of the Regulation describes how the EMA will search selected literature for individual cases and publish a detailed guide about this monitoring. Section VI.C.2.2.3, Reports published in the scientific and medical literature, discusses how MAHs must monitor all their active substances by

accessing widely used systematic literature review and reference databases. This includes exceptions for not reporting ICSRs, such as when an MAH can exclude ownership of a medicinal product in cases from literature articles, in cases arising from analyses of EU authority databases or summary data analysis from publicly available databases or in tables or line listings. Information that is not a valid ICSR but which may affect the risk–benefit balance of a medicinal product should be notified immediately as emerging safety issues to concerned CAs and the Agency.

Periodic safety update reports (PSURs) will in future be focused on evaluating risk–benefit and will follow a revised format, eventually no longer containing adverse reaction line listings, nor be required for low-risk medicinal products. Articles 107b–g of the Directive details the process for PSUR submission and assessment. Submission of PSURs by different MAHs holding authorizations for the same active substance will be harmonized. The CHMP or the coordination group shall, following the consultation with PRAC, either approve or deny requests to change the dates or the frequency of submission of PSURs, and this shall be made public by the Agency. The timelines for submission will change to within 70 and 90 calendar days of the data lock point for PSURs covering intervals up to 12 months and in excess of 12 months respectively.

Future PSURs shall contain cumulative data whilst retaining focus on new information.

The main changes are described in GVP Module VII and include cumulative subject exposure in clinical trials, cumulative and interval patient exposure from marketing experience, cumulative summary tabulations of serious adverse events from clinical trials, and cumulative and interval summary tabulations from post-marketing data.

During the transitional phase (i.e., until 12 months after the establishment of the functionalities of the PSUR repository has been announced by the Agency), MAHs shall submit the periodic safety reports to the Agency and all MSs in which the medicinal product has been authorized or according to the submission requirements of MSs which shall be published on the Agency website. Further changes to technical requirements for sub-

mission of electronic PSURs shall be published by the Agency. Article 28 of the Regulation refers to the PRAC assessment of PSURs. Article 107f of the Directive explains that each PSUR assessment will be accompanied by a recommendation for regulatory action which shall include maintaining, varying, or revoking the MA. This directly links the PSUR to enforcement.

PRAC will have a fundamental role in supervising the PSUR process for all types of marketing authorizations by

- allocating a Rapporteur and Co-Rapporteur for PSUR assessment where appropriate and defining a process for assessing PSURs with published timelines (see Article 62 of the Regulation and 107b, e, g of the Directive);
- approving specifications for and confirming full functionality of a repository for PSURs (see Article 25a of the Regulation).

Article 14 of the Regulation and Article 24 of the directive concern renewal submissions, which will be made 9 months before MA expiry (instead of the current 6 months).

## TRANSPARENCY AND COMMUNICATION

Article 106 of Directive describes how the EMA will establish a “medicines safety web portal” to make available safety data, including:

- PRAC members, meeting agenda, and minutes;
- summary of RMPs;
- list of products subject to “additional monitoring”;
- location of PSMFs and contact information for enquiries;
- information and forms for patients and professionals to report ADRs;
- reference dates for PSURs;
- protocols and abstracts of results of PASS;
- information on the initiation of a Community assessment of safety issues, including data related to public hearings;
- assessment conclusions, recommendations, opinions, and decisions.

A similar requirement exists for MSs to set up publicly accessible national medicines safety web portals to include non-promotional information on medicines (Article 106 of the Directive).

Article 25a of the Regulation refers to the EMA setting up and maintaining a repository for PSURs and the corresponding assessment reports so that they are fully and permanently accessible to EU regulatory agencies. The new legislation has major implications for the performance of PV tasks by the EMA and CAs to be more open as described in Articles 28f and 29 of the Regulation and Article 101(2) of the Directive.

According to Article 107j of the Directive, the CHMP may hold public hearings when it considers it justified, particularly with regard to the extent and seriousness of the issue. The hearings shall be held according to requirements specified by the Agency and announced through the EMA web portal. In the public hearing, due regard shall be given to the therapeutic effect of the medicine.

## PHARMACOVIGILANCE ENFORCEMENT

Commission Regulation (EC) No 658/2007 concerns financial penalties in connection with centrally authorized medicinal products for non-compliant MAHs. This may include fines of 5% total EU revenue for a specific legislative breach. This regulation was amended December 12, 2012, to adapt to infringements of obligations introduced by the new PV legislation. Article 1 of the Penalties Regulation lists 23 obligations contained in Regulation (EC) 726/2004 the infringement of which may trigger financial penalties (the “Enforced Obligations”). As described in Article 102f of the Directive and Article 24(5) of the Regulation, CAs are responsible for enforcement by means of “... where appropriate, effective, proportionate and dissuasive penalties.” These can include fines and/or criminal penalties, depending on the MS. The UK has recently implemented an Infringement Notice procedure as detailed in the Human Medicines Regulations 2012. CAs are empowered to perform inspections through Article 111 of the Directive and Article 19 of the Regulation. All inspections

must be reported to the EMA and the Commission and shared with other MSs.

The regulatory powers are strengthened by Article 116 of the Directive, in that action can be taken via the licensing system if the risk–benefit balance is not favorable, conditions or requirements attached to the MA are not observed (including a failure to operate a risk management system or conduct a PASS), quality is not as declared, and therapeutic efficacy is lacking.

Urgent EU-wide assessment of benefit and risk is referred to in Article 107i–k of the Directive. PRAC will provide its recommendation for taking action and the coordination group and the CHMP would normally be expected to rely on this recommendation before giving their opinion.

## FURTHER INFORMATION ABOUT PROPOSED NEW LEGISLATION AND GUIDELINES

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Access to EU law, <http://eur-lex.europa.eu/en/index.htm>.

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# 4

## Ethical Oversight, Consent, and Confidentiality

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All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.

Galen (*c.* 130–210 AD)

### INTRODUCTION

Seldom does contemporary society contemplate the most extreme consequences of less than stringent ethical standards in the treatment of human participants in drug trials. However, not long ago, during World War II, syphilis and gonorrhea were spreading quickly among the US troops, and the well-intentioned urgency to find a cure had infamous results. In 1943, the Acting Chief of the US Public Health Service Venereal Disease program, John C. Cutler, had prisoners in the US Penitentiary at Terre Haute purposely infected with gonorrhea. In 1953, he had others at Sing Sing purposefully

infected with syphilis (Magnuson *et al.*, 1956). These actions were taken to test penicillin for its effectiveness in treating these diseases in a tightly controlled environment. Earlier, in 1932, the US Public Health Service had begun the Tuskegee Study of Untreated Syphilis in the Negro male to study the natural history of syphilis. The men recruited for this study received no informed consent. Instead, they were told that they were being treated for “bad blood” (CDC, 2011). Even after penicillin was identified as an effective treatment for syphilis, these men received no treatment. In 1972, after 40 years, the press finally reported on the study to the US public. The commitment that this unethical research should never happen again drove Congress to pass the National Research Act in 1974, establishing the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The commission was charged with identifying basic ethical principles and guidelines under which

research with human subjects should be conducted. The commission released its Belmont Report in 1979. The report delineates three ethical principles: autonomy (respect for persons), beneficence (protecting from harm and maximizing benefits), and justice (fair distribution of the burdens and benefits of research). The Belmont Report was adopted by the US Department of Health and Human Services as the basis for US regulations governing most federally funded human subjects research. These regulations were codified in 45 C.F.R. §46. Subpart A of these US Department of Health and Human Services regulations is known as the *Common Rule* and has been adopted by many other federal agencies.

Contemporary research ethics exist to protect patients and study participants from unknown and, to some extent, even unknowable risks (Resnik, 2011). They also ensure that study results, whether from clinical trials or observational studies, are accurate. Consequently, researchers' adherence to ethical norms is crucial not only for upholding society's moral values and fostering its understanding of and support for all research activities, but also for producing treatments of the greatest possible value and safety. This chapter illustrates the need for research ethics, traces the practical implications of ethical oversight, and explains the regulations that the USA has established to maintain the highest possible standards of research ethics and quality.

Ethical guidelines and regulations governing the protection of human subjects have been developed in the USA and worldwide. Both the Common Rule (which forms the basis for laws protecting human subjects in the USA) and the Declaration of Helsinki (WMA, 2012) reflect a philosophical framework that prioritizes individual autonomy, well-being, and just distribution of burdens and benefits in the conduct of research.

## PRACTICAL IMPLICATIONS OF ETHICAL OVERSIGHT

The way health research is conducted has changed from almost total reliance on *de novo* data collection – either interventional research, such as rand-

omized controlled trials (RCTs), or survey format – to a mix of *de novo* data collection and use of extant electronic health data. This change has increased ethical oversight, specifically new regulations governing the confidentiality and security of the electronic health data arising from health care.

The availability of electronic health data for drug safety research is increasing, which makes protecting patients' privacy and confidentiality even more important than it formerly was. Although the data used in research are typically de-identified, concern persists that these data, when linked with other data, may be used to re-identify individuals (Center for Democracy & Technology, 2009). In addition to collecting and using such health data ethically, researchers must appropriately design studies and plan analyses to produce scientifically sound results and conclusions.<sup>1</sup>

## THE PRIVACY AND SECURITY OF HEALTH DATA

When developing the original Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, legislators considered the value of electronic health data for public health activities and surveillance. The rule allowed disclosures, without patients' individual authorizations, of protected health information (PHI) for the following purposes:

preventing or controlling disease, injury, or disability, including, but not limited to, the reporting of disease, injury, vital events such as birth or death, and the conduct of public health surveillance, public health investigations, and public health interventions. (45 C.F.R. § 164.512)

In addition, the rule allows a regulated entity to track US Food and Drug Administration (FDA)-regulated products, to conduct postmarketing surveillance, to collect information about or report spontaneous adverse events, to recall drugs from the market, and to locate and notify individuals who have received recalled products. Thus, HIPAA

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<sup>1</sup>For Guidelines for Good Pharmacoepidemiology Practices (GPP), see International Society for Pharmacoepidemiology (2007). Available at: [http://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](http://www.pharmacoepi.org/resources/guidelines_08027.cfm)

allows disclosures of PHI without patients' individual authorization for pharmacovigilance activities.

Since April 14, 2003, the date by which all "covered entities" were required to comply with the HIPAA Privacy Rule, the media have reported several significant breaches.<sup>2</sup> In 2006, a laptop with PHI from 26.5 million US veterans was stolen from a Veteran's Administration (VA) employee's home (American Health Information Management Association, 2009). A class action lawsuit resulted in a \$20.5 million fine, primarily because the VA took 3 years to inform the affected veterans. In 2007, a VA information technology specialist lost a hard drive containing PHI for 1.3 million physicians and about 250 000 veterans (HIPAA Weekly Advisor, 2007). Since these breaches, the VA has enhanced security procedures to require encryption of PHI.

### THE LINKAGE OF ELECTRONIC HEALTH DATA

HIPAA emerged in response to the public's concern about the confidentiality of PHI. Its provisions reach beyond safeguarding PHI, however, to impeding linkage of electronic health data sets to create a more complete analytic file. In the USA, as early as 1972, researchers realized the value of data linkage when development of the National Death Index (NDI) was considered despite critics' decrying its cost, difficulty in matching records, potential loss of privacy and confidentiality, and limited usefulness (Chase, 1972). The NDI was linked to census records (Rogot *et al.*, 1983), a large cardiovascular RCT (Wentworth *et al.*, 1983), and, a year later, the Nurses Health Study (Stampfer *et al.*, 1984). Using the NDI linking algorithm another 9 years later, Potosky *et al.* (1993) linked the Surveillance, Epidemiology, and End Results cancer registry files to the Medicare files. Notably, these linkages that have proven valuable for research were made before the HIPAA legislation; they may have been impossible in today's regulatory climate.

Both the precedent for and the value of data linkage had been shown well before passage of the HIPAA Privacy Rule in 1996, but the legislation

has resulted in real and perceived barriers to linking identifiable electronic health data, such as health insurer claims with electronic health records (EHRs).

### THE CONDUCT OF SCIENTIFICALLY SOUND STUDIES

As all who are involved in pharmacovigilance know, when regulatory agencies approve a medication, little is known about the drug's safety in those who have multiple comorbidities and take many different medications. Over time, additional studies clarify the safety and risks of medication use in diverse populations. Some of the studies may be large pragmatic trials, whereas others may be observational studies; for either study design, data may be from health insurer claims, or EHRs or may be collected *de novo*. Pharmacovigilance researchers have an ethical duty to design the studies well, analyze them properly, and report the results accurately, regardless of the study's findings. Studies that are scientifically unsound unnecessarily burden study participants or produce results that are misleading and, therefore, unethical for both individuals and society.

Whether conflict of interest plays a role in the publishing of research must be considered. Is it in the funder's or perhaps the researcher's best interests to publish studies that are inconclusive or do not show drug effectiveness? Typically, journal reviewers focus conflict-of-interest concerns on the pharmaceutical industry because it has so much at stake for any studies it supports. Might federally funded researchers have some conflicts of interest with regard to publishing findings that fail to support their hypotheses? How do they win their next grant to fund expansion of their body of research?

Potential for publication bias appears to be greater for industry-funded studies than for federally funded studies. Specifically, industry-funded research tends to favor the medication marketed by the sponsoring company (Lexchin *et al.*, 2003; Bero *et al.*, 2007; Bourgeois *et al.*, 2010). Because conducting large-scale RCTs is costly, however, pharmaceutical companies will not pursue Phase 3 studies of experimental compounds that fail to

<sup>2</sup>"Covered entities" include health care providers, health plans, and health care clearinghouses.

show promise in earlier phases. Also mitigating the potential for industry-funded bias, ClinicalTrials.gov, initiated in 2000 (US National Library of Medicine and National Institutes of Health, 2011), requires the registration of all trials within a month of the first patient's enrollment. This registry should yield information about trial start and end dates, as well as favorable and unfavorable study outcomes, even if the studies are not published.

## **ETHICAL OVERSIGHT AND PRIVACY LAW AND RESULTING DILEMMAS**

Three separate categories of laws govern treatment of human subjects and confidentiality issues in epidemiologic and outcomes research in the USA: the Common Rule (and the related FDA human subjects regulations), state laws, and HIPAA.

### **THE COMMON RULE**

The Common Rule was designed to protect human subjects in federally funded or regulated research. It expresses a federal policy not to spend federal money on research inconsistent with societal and ethical values. The Common Rule covers research, which is defined as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Only activities that qualify as research need institutional review board (IRB) review. Pharmacoepidemiology or outcomes research studies would be considered research and, as such, will require IRB review. However, pharmacovigilance activities that fall under public health "practice" includes developing disease registries and conducting other forms of surveillance, emergency and outbreak response, and governmental program evaluation and oversight do not require IRB review and approval. Complicating the distinction of public health research from practice, however, is the fact that execution of public health practice activities often requires research components. Any research component must still attain IRB approval, regardless of the overarching public service intent.

The Common Rule, as well as the regulatory authority of the agency administering it, applies only to research conducted by federal agencies that have adopted the rule and to institutions and researchers awarded grants or contracts by those agencies. Additional human subjects regulations under the US FDA (21 C.F.R. § 50 and 21 C.F.R. § 56) cover any research that involves the use of an FDA-regulated drug, biologic device, or medical device.

Research conducted by private clinics or commercial research institutions without federal research funding remains outside the scope of the Common Rule. However, because in their epidemiologic and outcomes studies commercial research organizations often use data collected by institutions subject to the Common Rule, they must have research protocols reviewed by their own human subjects oversight boards (IRBs).

Under the Common Rule, IRBs must review research protocols to identify and weigh the risks to research participants and to ensure that participants can provide voluntary informed consent to participate (for required elements of informed consent, see 45 C.F.R. § 46.116). The IRB must give special consideration to vulnerable populations, such as children, prisoners, pregnant women, and the decisionally impaired.

Informed consent is critical in interventional research, which involves physical manipulation of or intervention in a patient's care. The physical risks and rigors of the research will directly affect the participants and their health and well-being. Informed consent minimizes the potential for coercion and ensures that the participant understands the risks and benefits of the research and maintains control over treatment received under the research protocol. In effect, it embodies society's valuation of the individual's integrity and autonomy.

Unlike interventional research, an epidemiologic or outcomes research study using electronic health data presents no physical or psychological risk to the already-treated patient. Risks related to research using electronic health data do stem, however, from the privacy interests of data subjects; these subjects may be harmed if their data are used for nonresearch purposes. Consequently, risks to such subjects derive from any weakness in data security

procedures and from any data disclosures made by dishonest or careless researchers. For this kind of research, informed consent differs conceptually from consent to participate in an intervention or treatment study. If data security arrangements and protection of direct identifiers are adequate, the research itself poses minimal risk to the data subject. When IRBs review protocols for such studies, they can waive the requirement for obtaining the consent of the subjects whose data are being used if some conditions are met (45 C.F.R. § 46.116).

As clinical interventions become more complex and privacy regulations become more involved, IRBs bear responsibility for analyzing a broadening range of risks: identifying known and unknown risks of research protocols, evaluating the appropriateness of the proposed data security procedures, and predicting damages that could result from any nonresearch misuses of personal information.

## STATE LAWS

The informed consent provisions of the Common Rule state:

The informed consent requirements in this policy are not intended to pre-empt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. (C.F.R. § 46.116)

Virtually all states have some form of medical privacy law or law defining the informed consent with which IRBs and researchers must comply. In practice, however, compliance with these laws has not impeded epidemiologic research. Because states usually have no provisions for waiver of consent, the affirmative federal policy has been assumed to govern. Many states have proposed legislation more restrictive than the Common Rule with respect to waiver of consent.<sup>3</sup> As such laws go into effect, IRBs may find that fewer epidemiologic protocols meet these new criteria for waiver of consent.

<sup>3</sup>See, for example, 2001 Tex. Sess. Law Serv. Ch 1511 (S.B. 11 (Vernon)).

Even more troubling, the increasingly prevalent state laws regulating informed consent and information disclosure make genetic testing or genetic information problematic. As health care interventions increasingly use genetic analyses to diagnose conditions and to select appropriate pharmaceutical interventions, more medical records will include genetic information. Consequently, as IRBs review research protocols using data from medical records, they must increasingly consider the social sensitivity of genetic information, because a confidentiality breach surrounding genetic information can have disastrous consequences for the data subject.

## THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT

HIPAA was passed by the US Congress in 1996. The primary goals of this legislation were to allow individuals to continue their health insurance after loss of employment, to reduce fraud, and to simplify health coverage administration. The HIPAA Privacy Rule, developed under the administrative simplification provisions and issued by the US Department of Health and Human Services in 2001, with amendments in 2002 and 2009, required the adoption of standards to protect individually identifiable health information. Health information is considered to be PHI if it is held or transmitted by a covered entity and contains any of 18 specific identifiers.<sup>4</sup> Covered entities must tell a patient, by means of a Notice of Privacy Practices, that they will use the patient's PHI to treat the patient, render payment to the provider, or conduct their regular operations, without obtaining authorization from the patient for these uses. The notice must explain

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<sup>4</sup>The HIPAA identifiers that define PHI are names, telephone numbers, any elements of dates (other than year), geographic subdivisions smaller than a state (street address, city, county, precinct, zip code, and geocodes, except for the initial three digits of a zip code), fax numbers, electronic mail addresses, Social Security numbers, medical record numbers, health plan beneficiary numbers, account numbers, certificate/license numbers, vehicle identifiers and serial numbers, device identifiers and serial numbers, Web universal resource locators (URLs), Internet protocol (IP) address numbers, biometric identifiers (finger and voice prints), full-face photographic images and any comparable images, and any other unique identifying number.

how this health information will be protected. Research use of PHI is unrelated to treatment, payment, or operations.

Epidemiologic or outcomes research not requiring access to individually identifiable information is not subject to HIPAA; however, when formulating the Privacy Rule, the US Department of Health and Human Services set an extremely high standard for health information to be considered “de-identified.” The regulation provides two methods of “de-identification” of health information: “safe harbor” and statistical verification. The safe harbor method requires that all 18 specific identifiers be removed and that the covered entity have no actual knowledge that the information could be used alone or in combination with other information to identify participants. Stripping the data of all 18 identifiers would, it was reasoned, substantially reduce the possibility of triangulating the data with other data sets and re-identifying the individuals; however, removal of dates and geographic information renders a data set of little value for epidemiologic and outcomes research.

The only alternative to safe harbor de-identification is for an expert statistician to find that the “risk is very small that the information could be used by an anticipated recipient to identify an individual who is the subject of the information” (45 C.F.R. § 164.514). Under this statistical verification method, the expert determines that little risk exists that the information could be used alone or in combination with other reasonably available information to identify an individual, and he or she documents the methods and analyses used to make this determination (45 C.F.R. § 164.514).

Because research use of PHI is unrelated to health care treatment, payment or operations, it is not authorized under the covered entity’s Notice of Privacy Practices. To obtain the PHI, the researcher may become a “business associate” of the covered entity and enter into a business associate agreement (BAA) with the covered entity (see 45 C.F.R. § 160.103). Alternatively, the researcher who is not a business associate of the covered entity must either obtain individual authorization from each patient (45 C.F.R. § 164.508), or follow one of the research provisions not requiring authorization (45 C.F.R. §

164.512). The research provisions not requiring authorization require the following:

- obtaining a waiver of authorization from an IRB or privacy board;
- receiving a “limited data set” from which direct patient identifiers have been removed (Note: dates and geographic information may remain in a limited data set);
- using the PHI only for activities “preparatory to research” (e.g., to determine whether the number of patients with a condition are sufficient for study validity); or
- using PHI for only deceased individuals.

The Privacy Rule defines each of these options and under what circumstances each may be used.

#### DILEMMAS ARISING FROM THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT

When seeking authorization from the individual patients, the researcher must tell each patient what PHI will be used, who will have access to it, how it will be used, and how they can revoke authorization. Researchers may not ask patients for broad authorization to allow their PHI to be used for multiple, unspecified future studies. Patients generally grant authorization at initial data collection for the study, often when they are receiving clinical care, which can be problematic in two ways. First, these patients are likely too overwhelmed with their current health issues to make a truly informed decision to grant use of their PHI research; therefore, seeking such authorization, or any consent to participate in the study, at the point of care may be unethical. Second, the exact uses of the PHI for the research study may be unknown at the point of care; if so, the authorization is invalid.

Requiring authorization for research uses of PHI also affects the quality of the resulting research (Casarett *et al.*, 2005). Requiring authorization for studies using existing data may reduce the available sample size in settings where sample sizes already barely suffice to detect with precision a relationship between the medication and rare disease. Requiring authorization for such studies also induces selection bias in the population under study (Jacobsen

*et al.*, 1999; Armstrong *et al.*, 2005; Nass *et al.*, 2009; Beebe *et al.*, 2011). Specific subpopulations, such as older persons or persons with severe illness, may be more likely or less likely to refuse authorization for their PHI to be used for research.

Obtaining authorization from each patient whose PHI is to be used for an epidemiologic or outcomes study is impracticable because, typically, hundreds of thousands of patient records are used. In these cases, a researcher may follow one of the other HIPAA research provisions. The research provisions applicable to epidemiologic and outcomes research are *waiver of authorization* and *limited data set*.

Obtaining a waiver of authorization from an IRB or privacy board requires that the following three conditions be met:

- use or disclosure of the information must pose no more than “minimal risk” to the patients’ privacy;
- the research cannot be practicably conducted without the waiver; and
- the research cannot be practicably done without use of the PHI.

IRBs are accustomed to evaluating risks for research protocols that involve interaction or intervention with human subjects; however, use of PHI for research poses data security and confidentiality risks not under the typical purview of IRBs. To meet the *minimum risk* criterion under the HIPAA waiver, the research must have an adequate plan to protect identifiers from improper use or disclosure and adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by 45 C.F.R. § 164.512.

Of the alternatives available to researchers requiring PHI in order to conduct studies, only the waiver of authorization is viable for researchers conducting database linkage research. Obtaining authorization from each patient whose data are to be linked is impracticable, however, because of the numbers of records involved. Moreover, the *minimal risk* requirement is difficult to meet if the link between the databases is a direct identifier or combination

of identifiers, especially if one of the identifiers is the Social Security number. If the researcher cannot convince the IRB or privacy board that this requirement is met, waiver is unlikely. The *limited data set* option is unfeasible, because linkage requires the use of direct identifiers. The other two options – use that is preparatory to research and use from deceased patients – do not apply to linkage research.

Another option approvable by an IRB or privacy board is to use a trusted third party to link two or more data sets. The trusted third party must enter into a BAA with the covered entities that hold the PHI. As noted above, BAAs are intended for use with activities related to treatment, payment, or operations and are not intended to support research activities under HIPAA. BAAs have been used when PHI is obtained from covered entities for research, however, and this option should be considered when a trusted third party will link data sets across covered entities by using several of the HIPAA direct identifiers.

The BAA allows the trusted third party to receive the data sets from two or more covered entities, conduct the linkage by using the personally identifiable information, remove the personally identifiable information, assign an anonymized identifier that links the two data sets, and then release the linked data set to the researcher. When this procedure is used, the trusted third party cannot be involved with the analysis of the linked data set. Part of the 2009 American Reinvestment and Recovery Act, the Health Information Technology for Economic and Clinical Health (HITECH) Act expands the data security breach penalties to business associates. The effect of this expansion on negotiation of BAAs and whether the expansion will affect linkage research that uses PHI are unknown; therefore, whether BAAs will remain an option for linking data after passage of the HITECH Act is also unknown.

The Institute of Medicine convened a committee whose primary purpose was to evaluate the effects of the HIPAA Privacy Rule on research (Nass *et al.*, 2009). The committee found that “the Privacy Rule does not protect privacy as well as it should,” and “as currently implemented, the HIPAA Privacy Rule impedes important health research” (Nass *et al.*, 2009: 2). Furthermore, the committee felt

that requiring that individuals consent to having their data used for research in no way enhances the privacy of their data. The Institute of Medicine report elaborated as follows:

Obligations to safeguard privacy, such as security, transparency, and accountability, are independent of patient consent. In fact, preventing [emphasis added] the secondary use of personal [health] data is the only privacy obligation that consent can potentially address. (Nass *et al.*, 2009: 251)

#### DIRECTIONS FOR FUTURE ETHICAL OVERSIGHT AND PRIVACY PROVISIONS

Current US ethical oversight and privacy provisions are problematic for research using electronic health data. Researchers must work with ethicists, policy makers, and the public to identify possible solutions that will permit the conduct of large epidemiologic studies relying on these data for drug safety research.

Because electronic health data are invaluable for drug safety surveillance and evaluation of safety signals, researchers must engage in significant education of the public about the value of epidemiologic and outcomes research and about the privacy protections routinely used. In particular, they need to share how these data have informed important health solutions and encourage public discussion about the careful use of electronic health data. Researchers should engage policy makers in discussions about the need for broad consent to have electronic health data used for research. Having societal buy-in is preferable to using opt-out provisions that will likely lead to selection bias and potentially invalid study results.

Researchers have been able to use the business associate provision under HIPAA to allow a trusted third party to link data from two or more covered entities by using personally identifiable information and assigning anonymized identifiers. With passing of the HITECH Act, which expands the data security breach penalties to business associates, negotiating BAAs to allow use of identifiers for linkage may be more difficult and therefore negatively affect use of electronic health data for research. Now is the time for the US Department of Health

and Human Services to consider exempting data-driven epidemiologic and outcomes research from HIPAA and permitting the Common Rule to guide research protections for human subjects.

HIPAA was established to safeguard the confidentiality of electronic health data that originates as a byproduct of health care. Having the Common Rule rather than the HIPAA standards guide the ethical use of these identifiable data would allow IRBs more flexibility in weighing confidentiality risks to the data subjects in relation to the data security procedures proposed by the researchers and the societal benefits of the research.

The public interests in privacy and in the health care quality that research makes possible require a more equitable approach to ensuring that the burdens of research are shared by those who benefit. Governmental oversight, private oversight, or both could minimize risks to all by establishing data security standards and holding individuals accountable for violations. Equally critical are allowances for researchers to keep select identifiers with electronic health data for linkage, carefully structured release policies and data tagging to ensure adequate safeguards on sharing sensitive data, and requirements for very secure technologies to protect these identifiable data. As a society, we need to make use of the ever-increasing amount of electronic health data to support public health, an important element of which is drug safety surveillance.

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# 5

## Pharmacovigilance-Related Topics at the Level of the International Conference on Harmonisation<sup>1</sup>

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### INTRODUCTION

Authorizations for the marketing of medicinal products need to be based on the universal criteria of quality, safety, and efficacy whilst taking into account local public health needs. This, together with the product information instructing the users of medicines on how to use the product effectively and safely, shall ensure a positive benefit–risk balance of the product and its use in individual patients. The development of medicines based on these criteria requires time as well as resources and aims at submitting an application for marketing authorization. Such an application includes all data and is assessed through the process of marketing authorization evaluation. Part of this process is a continuous dialogue between the applicant and the

authorities, as further data emerge from ongoing or follow-up studies initiated by the applicant or requested by the authorities. More and more companies choose to apply for marketing authorization in different countries of the world at the same time; in any case, products may eventually become available worldwide. Given this background, but moreover from a scientific point of view, it is obvious that standards for how to investigate quality, safety, and efficacy should be universal too.

A major step to achieve this was taken in April 1990 when the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 1997a) was established in Brussels, after preparation at the margins of the 5th International Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989, a conference organized regularly by the World Health Organization (WHO) for their member countries as a forum to strengthen international collaboration between their authorities (Sauer, 1996).

<sup>1</sup>Disclaimer: The views expressed in this chapter are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

The ICH was established with the objective of harmonized interpretation and application of technical guidelines and requirements for marketing authorization, to

- reduce duplication of testing;
- increase economical use of resources; and
- eliminate unnecessary delay in availability of new medicines,

whilst safeguarding quality, safety and efficacy. The five categories agreed for harmonization are

- 1 new types of medicinal products;
  - 2 lack of harmonization of current technical requirements;
  - 3 transitions to technically improved testing procedures;
- (categories 1 to 3 require development of new ICH guidelines or recommendations);
- 4 review of existing ICH guidelines resulting in major changes; and
  - 5 maintenance of existing ICH guidelines requiring minor changes.

The ICH covers the three regions European Union (EU), Japan, and the USA, where most pharmaceutical innovations have been developed, and consists of the so-called "Six Parties"; that is, the authorities and associations of innovative industry in these three ICH regions:

- 1 the European Commission, representing the 28 member states of the EU;<sup>2</sup>
- 2 the European Federation of Pharmaceutical Industries and Associations (IFPMA);
- 3 the Ministry of Health, Labour and Welfare of Japan;
- 4 the Japanese Pharmaceutical Manufacturers Association (JPMA);

- 5 the US Food and Drug Administration (FDA); and
- 6 the Pharmaceutical Research and Manufacturers of America (PhRMA).

In addition, there are three ICH observers:

- 1 the WHO;
- 2 the European Free Trade Area ([www.efta.int/about-efta](http://www.efta.int/about-efta)), represented by the Swiss authority (Swissmedic)<sup>3</sup>; and
- 3 Canada, represented by the Canadian authority Health Canada.

The Six Parties develop scientific consensus through discussions between experts from the authorities and industry. The draft consensus ICH guidelines and recommendations undergo public consultation. Once adopted, the regulatory parties commit themselves to implement the ICH guidelines or recommendations within their local regulatory framework.

The ICH process is administered by the ICH Steering Committee (ICH SC) and supported by the ICH Secretariat that is run by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) in Geneva. The ICH SC consists of two voting members from each ICH party, one non-voting member from IFPMA, and one non-voting observer from each ICH observer party.

In 1999, the ICH SC set up a subcommittee, the ICH Global Cooperation Group (GCG), which a few years later was expanded for active engagement with other harmonization activities. It used to comprise one representative from each ICH party, the ICH Secretariat, WHO, EFTA,<sup>3</sup> Health Canada, and from six regional harmonization initiatives; namely, the Asian-Pacific Economic Cooperation (APEC), the Association of Southeast Asian Nations (ASEAN), the East African Community (EAC), the Gulf Cooperation Countries (GCC), the Pan-American Network on Drug Regulatory Harmonization (PANDRH), and the Southern

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<sup>2</sup>In addition, the European Commission represents Iceland, Liechtenstein and Norway; that is, the three countries that are members of EFTA and follow the EU in the field of pharmaceuticals on the basis of the Agreement on the European Economic Area (EEA) between these countries and the EU.

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<sup>3</sup>EFTA consists of the four members Iceland, Liechtenstein, Norway and Switzerland, out of which Switzerland is the only country that is not a member of the EEA.

African Development Community (SADC). In May 2005, a revised mission statement was adopted for the GCG, strengthening their role in promoting mutual understanding of regional harmonization initiatives to facilitate the regional and global harmonization related to ICH guidelines and recommendations. Their observership at ICH SC level has been increased accordingly. A further expansion of the GCG was agreed in 2007, and regulators were invited from countries with ICH guidelines implementation or major production and clinical research; namely, Australia, Brazil, China, Chinese Taipei, India, the Republic of Korea, Russia, and Singapore.

So far, ICH has published more than 60 guidelines in the three areas of quality, safety, and efficacy,<sup>4</sup> and in addition provides recommendations in the following multidisciplinary areas:

- M1: MedDRA – Medical Dictionary for Drug Regulatory Activities;
- M2: ESTRI – Electronic Standards for the Transfer of Regulatory Information;
- M3: Non-clinical Safety Studies;
- M4: CTD – Common Technical Document for marketing authorization applications;
- M5: Data Elements and Standards for Drug Dictionaries;
- M6: Virus and Gene Therapy Vector Shedding and Transmission;
- M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risks;
- M8: eCTD – Electronic Common Technical Document.

## THE INTERNATIONAL CONFERENCE ON HARMONISATION STEP PROCESS

A new topic for harmonization may be proposed for the ICH process by an ICH party or an ICH

observer who has to describe the proposal in a concept paper for submission to the ICH SC. The ICH SC decides upon the acceptance of the proposal as ICH topic and the composition of the ICH Expert Working Group (ICH EWG). An ICH EWG consists of experts from all Six Parties (usually two per party) and, if an extension is considered appropriate, of additional experts from interested parties beyond the Six Parties and the ICH observers. One expert from each of the ICH observers may be nominated for any ICH EWG. Each of the Six Parties nominates one of their experts as ICH Topic Leader, who then acts as a contact point for the party they belong to during the ICH process. The ICH SC will ask one of the Six Parties to nominate the ICH Rapporteur, who is responsible for the drafting process. The development of an ICH guideline or of ICH recommendations is a process of five steps.

### ICH STEP 1: DEVELOPMENT OF DRAFT CONSENSUS ICH GUIDELINE OR RECOMMENDATIONS

The ICH EWG develops the draft consensus ICH guideline or recommendations, usually over a time not longer than two years. During this consensus building from a scientific point of view, the ICH Topic Leaders consult the proposals within the so-called “Contact Network” of experts each party has established within their regions and organizations, to ensure that they reflect the policies and views of their party. Once consensus is reached between the Six Parties, the ICH EWG performs a sign off of the draft ICH guideline or recommendations provided by the Rapporteur with the status of ICH Step 1 for transmission to the ICH SC.

### ICH STEP 2: CONFIRMATION OF SIX PARTY CONSENSUS

The ICH SC discusses if there is sufficient scientific consensus to agree with the draft ICH guideline or recommendations for transmission to the authorities in each of the three ICH regions. If they agree, then each ICH party performs a sign off at the level

<sup>4</sup>The area of an ICH guideline is identifiable by its code, where Q stands for quality, S for safety, as established *in vitro* and *in vivo* preclinical studies, and E for efficacy, as established in clinical studies, with E2 identifying a guideline on safety data from humans. M identifies multidiscipline areas.

of the ICH SC, assigning the status of ICH Step 2 to the draft ICH guideline or recommendations.

### ICH STEP 3: REGULATORY CONSULTATION

The draft ICH guideline or recommendations are then presented to the authorities in each of the three ICH regions for release for public consultation according to the rules established in each region for public consultation of guidance documents. Within each ICH region, comments are collected from all interested parties and discussed by the Contact Network. The draft ICH guideline or recommendations are also published by the ICH Secretariat for comments from authorities, industry associations, and interested parties outside the ICH regions to be submitted to the WHO or IFPMA. Out of the three ICH Topic Leaders from the authorities, an ICH Regulatory Rapporteur is designated to draw up the final draft ICH guideline or recommendations, taking into account all comments received during the public consultation, as considered relevant by the respective Contact Network. The final draft ICH guideline or recommendations are signed off by the three ICH Topic Leaders from the authorities and transmitted to the ICH SC.

### ICH STEP 4: ADOPTION OF TRIPARTITE ICH GUIDELINE OR RECOMMENDATIONS

The final draft ICH guideline or recommendations and a report on the comments received during public the consultation are presented by the ICH Regulatory Rapporteur to the ICH SC for consideration as to whether the consensus achieved at ICH Step 2 has been substantially altered in the final draft. If not, the ICH SC adopts the ICH guideline or recommendations with a status of ICH Step 4 for recommendation for adoption by the authorities in the three ICH regions. If yes, the ICH SC considers the alterations in the final draft and, if all parties are satisfied, adopts it with the status of ICH Step 4. If one or more parties from industry are of the opinion that the draft has been substantially altered or introduces new issues, the parties from the authorities may agree to further consultation.

### ICH STEP 5: IMPLEMENTATION OF ICH GUIDELINE OR RECOMMENDATIONS

Immediately after ICH Step 4, the ICH guideline or recommendations are processed for adoption by the authorities and implementation in the three ICH regions according to the rules established in each region for any guidance documents.

The ICH step process is also followed for the maintenance of existing ICH guidelines resulting in major changes, whereas an abbreviated process has been put in place for the maintenance requiring only minor changes.

### PHARMACOVIGILANCE-RELATED INTERNATIONAL CONFERENCE ON HARMONISATION TOPICS

During the first decade of the ICH, pharmacovigilance-related topics entered the ICH process in two waves. The first wave resulted in adoption of ICH-E2A in 1994 and E2B and E2C finalized between 1996 and 1997. The second wave started in 2002 with three further ICH topics, E2D, E2C Addendum, and E2E, finalized between 2003 and 2004. Thereafter, further developments took place as the need arose, resulting in the agreement to redevelop E2B in 2006, adoption of E2F in 2010, and in initiating the revision of E2C in November 2010 (Table 5.1).<sup>5</sup>

### TOPIC ICH-E2A: CLINICAL SAFETY DATA MANAGEMENT – DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

This guideline (ICH, 1994), adopted at ICH Step 4 in 1994, represents the first one with relevance to pharmacovigilance. It forms part of Good Clinical Practice (GCP), and although it deals with expedited reporting of cases of serious, unexpected adverse drug reactions (ADRs) occurring in clinical trials during the pre-authorization phase, it has also

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<sup>5</sup>Whilst Table 5.1 provides an overview, by guideline number, in the main text the guidelines are ordered by their contents.

Table 5.1 Overview of currently applicable pharmacovigilance-related ICH guidelines.

Code	Topic	Adoption by ICH SC at Step 4
ICH-E2A	Clinical Safety Data Management – Definitions and Standards for Expedited Reporting	October 1994
ICH-E2B(R2) and (R3)	Clinical Safety Data Management – Data Elements for Transmission of Individual Case Safety Reports	R2: November 2000 R3: November 2012, implementation planning ongoing
ICH-E2C (R2)	Clinical Safety Data Management – Periodic Benefit-Risk Evaluation Report	November 2012
ICH-E2D	Post-Approval Safety Management – Definitions and Standards for Expedited Reporting	February 2003
ICH-E2E	Pharmacovigilance Planning	November 2004
ICH-E2F	Development Safety Update Report	August 2010

Table 5.2 Key points addressed in the ICH-E2A guideline.

Definitions for AE and ADR in the pre-authorization phase
Criteria for serious AE/ADR
Expectedness of an AE/ADR based on clinical observation and its documentation in the applicable product information
Causality assessment as good case practice for AE/ADR cases from clinical trials
Implied possible causality for spontaneously reported ADR cases
Standards for expedited reporting from clinical trials
Definition of minimum case report information for report submission to authorities
Follow-up reporting
Unblinding procedures for serious ADRs
Reporting of emerging information on post-study ADRs
Reporting requirement for active comparator

been used in the post-authorization environment (Table 5.2). Reasons for this may have been the absence of an ICH guideline for the post-authorization phase, but more importantly the fact that the ICH-E2A guideline was based on the Council for International Organisations of Medical Sciences (CIOMS) I and CIOMS II Reports for marketed medicinal products (CIOMS, 1990, 1992).<sup>6</sup> The guideline also incorporated definitions

agreed within the framework of the International Drug Monitoring Programme established by the WHO for pharmacovigilance of marketed medicinal products.

#### ICH-E2D TOPIC: POST-APPROVAL SAFETY MANAGEMENT – DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

During the second wave of pharmacovigilance-related ICH topics, it was considered important to issue an ICH guideline on ADR case reports specifically for the post-authorization phase (Table 5.3). Therefore, the ICH-E2D guideline (ICH, 2003a) was finalized in 2003 at ICH Step 4, formalizing the application of relevant elements of ICH-E2A in the post-authorization phase and responding to further harmonization needs with regard to the definitions and management of case reports for expedited reporting in this phase. Such further harmonization needs had previously been

<sup>6</sup>CIOMS is an international, non-governmental, non-profit organization set up in 1949 under the auspices of the WHO and the United Nations Educational, Scientific and Cultural Organisation; since 1986, CIOMS sets up working groups to facilitate discussion on policy matters between pharmaceutical industry and drug-regulatory authorities in the field of drug safety (CIOMS, 1990).

Table 5.3 Key points addressed in the ICH-E2D guideline.

Definitions for AE and ADR in the post-authorization phase
Criteria for serious AE/ADR in accordance with ICH-E2A
Expectedness of an AE/ADR based on clinical observation and its documentation in the authorized product information; explanations regarding class effects
Differentiation between sources of unsolicited and solicited reports
Explanation on stimulated (but unsolicited) reporting
Standards for expedited reporting in post-authorization phase
Definition of minimum case report information for report submission to authorities with explanations
Follow-up reporting
Lack of efficacy reporting needs
Guidance on ADR narratives
Guidance on ADR case assessment
Management of cases of exposure during pregnancy
Explanation on reporting responsibility of marketing authorization holder despite any contractual relationship in place

discussed in the CIOMS V Report (CIOMS, 2001), which formed an important basis for ICH-E2D.

#### ICH-E2B TOPIC: CLINICAL SAFETY DATA MANAGEMENT – DATA ELEMENTS FOR TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS

More specifically to reporting cases of ADRs/adverse events (AEs), the ICH-E2B guideline (ICH, 1997b), which evolved from the European Commission project EUROScape (Moore *et al.*, 1994), was developed to define the data fields for electronic reporting between all stakeholders and adopted at Step 4 in 1997. Also, this ICH guideline took into account the CIOMS I Report (CIOMS, 1990). In parallel, the M2 EWG developed the related ICH-M2 recommendations ICH-ICSR DTD (synonym: ICH-M2 E2B(M)), first also adopted at Step 4 in 1997, describing the document type definition (DTD) of the electronic transmission of individual case safety reports (ICSRs, synonym: ADR case reports). With the mandate to further improve the definitions and specifications

Table 5.4 Key points addressed in the ICH-E2B(R2) guideline.

Description of all data elements of ADR case reports with title and content of each data field
Technical specifications, such as field length and field value for each of the data fields and the related additional technical data fields
List of abbreviations for units
List of units for time intervals
List of routes of administration

provided in both these documents, a Maintenance EWG was established in 1999 and revised documents were adopted at Step 4 in 2000 (ICH, 2000, 2001), recoded later as ICH-E2B(R2) (Table 5.4). These were supplemented by a questions and answers document, last revised and adopted at Step 4 in March 2005 (ICH, 2005b). To incorporate adjustments on the basis gained through the implementation in the ICH regions, a second revision process of ICH-E2B was initiated aiming at additional data fields, greater granularity, and better use of terminologies (Marr, 2010). ICH-E2B(R3) was signed off at Step 2 in May 2005 (ICH, 2005a) for public consultation. In 2006, the ICH SC decided to continue further development of the technical specifications of ICH-E2B(R3) in collaboration with standards development organizations (SDOs) and submitted the topic to the International Organization for Standardization (ISO),<sup>7</sup> in order to enable specifications that are more global and applicable not only in the regulatory environment, but more broadly in healthcare. This will allow for more comprehensive data records and increase efficiency through interoperability of the different data recording systems (ICH, 2011a). ISO, Health Level 7 International (HL7),<sup>8</sup> the European Committee

<sup>7</sup>The ISO is a non-governmental organization with its secretariat in Geneva that maintains the network of the national standards institutes of 162 countries and develops International Standards, often of technical nature or for management (<http://www.iso.org/iso/home/about.htm>).

<sup>8</sup>HL7 is a USA-based not-profit organization developing standards for the exchange and retrieval of electronic health information as support to health services. HL7 has more than 2000 individual or institutional members worldwide, including about 500 companies which represent more than 90% of the healthcare information systems vendors (<http://www.hl7.org>).

for Standardization (CEN),<sup>9</sup> the Clinical Data Interchange Consortium (CDISC),<sup>10</sup> the International Health Technology Standards Development Organisation (IHTSDO),<sup>11</sup> and GS1<sup>12</sup> collaborate as members of a joint initiative to develop the standard, based on the HL7 model, within the ISO process, which also involves ICH representatives (ICH, 2011b). The resulting standards, ISO/DIS 27953 Health informatics – Pharmacovigilance – Individual case safety report Parts 1 and 2, are used to meet reporting requirements of ADR/AE cases for human medicines (ICH, 2011c). In order to support the standard through the ICH framework, an implementation guide which covers the use of the fields defined by ICH-E2B(R3) was adopted at ICH Step 3 in June 2011 for public consultation (ICH, 2011d) and was finalized at Step 4 in November 2012. This guide is called ICH-E2B(R3) Implementation Guide for electronic transmission of individual case safety reports (ICSRs) – E2B(R3) data elements and message specification (ICH, 2013a). It defines how the International Standards (IS) and which IS data fields should be used and how to construct valid electronic messages for ADR/AE case report transmission (see Table 5.5). It hence also provides the pathway for the development of electronic reporting forms and user interfaces. It may be complemented by regional implementation guides, which may recommend the use of additional IS data fields (ICH, 2011c). At ICH level, an ICH-E2B(R3) Implementation Working Group has been established in accordance

Table 5.5 Key points addressed in the ICH-E2B(R3) guideline.

Definition of all data elements of ADR/AE case reports with title, content, and technical specifications for each data field and defined interrelationships between elements
Description of message standard for ADR/AE case reports
Definition of minimum information for valid ADR/AE report
Use of extensible markup language (XML)
Use of English for free text fields for international transmission
Definition of codes sets, terminologies, and vocabularies to be used, in particular ISO
Identification of Medicinal Products (ICH-M5) and MedDRA (ICH-M1)

with a concept paper endorsed by the ICH SC in July 2013 (ICH, 2013b). While implementation is ongoing, ICH-E2B(R2) remains applicable.

#### ICH-E2C TOPIC: CLINICAL SAFETY DATA MANAGEMENT – PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

Besides the reporting of ADR case reports in the so-called “expedited manner,” periodic reporting of ADRs and other safety information was also covered in the first wave of pharmacovigilance-related activities at ICH level by adopting the ICH-E2C guideline at Step 4 in 1996 (ICH, 1996). This guideline described the specifications for format and content of periodic safety update reports (PSURs) reflecting the safety profile based on worldwide data and concluding upon need for action (Table 5.6). Also, ICH-E2C was based on the work achieved by CIOMS; that is, the CIOMS II and CIOMS III Reports (CIOMS, 1992, 1995).

After 1996, good experience had been gained with the concept of the PSURs, in particular in the EU, and so it was agreed to promote the concept by providing clarification and flexibility for the application of ICH-E2C in different product types and different circumstances by means of the ICH-E2C Addendum (Table 5.7) (ICH, 2003b). The need for such clarification and flexibility had been discussed before in the CIOMS V Report (CIOMS, 2001), which was therefore used when

<sup>9</sup>CEN is a non-profit organization set up under Belgian law as the only body recognized under EU legislation for the development and adoption of European Standards in all areas of economic activity with the exception of electrotechnology and telecommunication. CEN has 31 national members (<http://www.cen.eu/cen/pages/default.aspx>).

<sup>10</sup>CDISC is a US-based not-profit organization developing global standards for the exchange and archiving of clinical research data and metadata (<http://www.cdisc.org>).

<sup>11</sup>IHTSDO is a not-profit organization based in Denmark acquiring, owning, and administering the rights to the health terminology SNOMED CT and other health terminologies ([www.ihtsdo.org](http://www.ihtsdo.org)).

<sup>12</sup>GS1 is an international not-for-profit association based in Belgium with member organizations in over 100 countries and dedicated to the design and implementation of global standards and solutions to improve the efficiency and visibility of supply and demand chains through bar codes and other product identification and traceability tools ([www.gs1.org](http://www.gs1.org)).

Table 5.6 Key points addressed in the ICH-E2C guideline.

Inclusion of all product presentations in one PSUR
Concept of international birth date of a product to determine the data lock points of PSURs
Provision to submit a set of PSURs, each covering subsequent 6 months, to facilitate PSUR submission according to local frequency
Description of all data sources to be covered in a PSUR
Inclusion of worldwide information on marketing authorization status and regulatory safety-related action, ADR, and exposure data
Use of company core safety information (CCSI) as reference and concept of unlistedness of an ADR (i.e. unlisted in comparison with the CCSI versus unexpected in comparison with locally authorized product information)
Presentation of individual case histories
Formats of ADR line listings and summary tabulations
Presentation of exposure data
Overall safety evaluation and conclusion: analysis and discussion of data by marketing authorization holder with a view to possible safety-related action
Explanation on responsibilities of marketing authorization holders in contractual relationship
Annex of medically unconfirmed ADR case reports to be submitted as requested locally

drafting the ICH-E2C Addendum. The ICH-E2C Addendum was adopted at Step 4 in 2003 and later merged with the original ICH-E2C and published as ICH-E2C(R1).

In November 2010, the ICH SC discussed safety update reporting in the light of further experiences with PSURs and latest benefit-risk approaches in pharmacovigilance and approved the development of ICH-E2C(R2) as a guideline on periodic benefit-risk evaluation reporting. The revision aimed at improving safety documentation and evaluation as well as risk minimization and overall benefit-risk evaluation including their planning. The interface with ICH-E2E and ICH-E2F should also be addressed (ICH, 2010b-d). ICH-E2C(R2) on periodic benefit-risk evaluation report (PBRER) was developed accordingly and adopted, after public consultation, at Step 4 in November 2012 (ICH, 2013c) (Table 5.8). An ICH Implementation Working Group has been established for putting ICH-E2C(R2) into practice.

Table 5.7 Key points addressed in the ICH-E2C Addendum guideline.

Clarification regarding the inclusion of all product presentations in one PSUR
Executive summary as new part of the PSUR
New statement on proprietary information to be included in PSUR
Use of reference safety information in relation to time covered by PSURs
Further guidance on the presentation of exposure data
Organization of some PSUR parts by system organ class
Risk management programs to be discussed in PSUR
Separate benefit-risk analysis, if conducted recently for the product, to be discussed in PSUR
Recommendations for PSUR submission during transition period of harmonization towards international birth date; clarifications for such harmonization
Clarification on restart of PSUR submission frequency
New concept of PSUR summary bridging report supporting submission of a set of single PSURs
New concept of PSUR addendum report to cover the period between the last PSUR and local regulatory data submission dates; e.g., marketing authorisation renewal date

## ICH-E2E TOPIC: PHARMACOVIGILANCE PLANNING

This guideline (ICH, 2004) was the last one being developed during the second wave and was adopted at Step 4 in 2004. This ICH topic was inspired by the excellence model for pharmacovigilance developed in the UK with international colleagues' input (Waller and Evans, 2003). Also, the Japanese concept of early post-marketing phase vigilance (EPPV), published by the Japanese Health Ministry in 2000 as a program of communication between marketing authorization holders and healthcare professionals on newly marketed medicinal products to ensure safe roll-out to the market and to strengthen the spontaneous reporting system in the early phase of marketing (MHW, 2000), was considered in this context. However, pharmacovigilance planning is a different concept; it is intended to aid marketing authorization holders and authorities in planning data collection, especially, but not exclusively, during the early phase of marketing. Such planning is based on the so-called "safety specification," summarizing

Table 5.8 Key points addressed in the ICH-E2C(R2) guideline.

Focus on safety and efficacy/effectiveness of the authorised product in healthcare with specific focus on new data, including from use in other than authorised indications and clinical trials
Inclusion of all product presentations in one PBRER
Explanation on responsibilities of companies in contractual relationships
Concept of international birthdate of a product to determine the data lock points of PBRERs
Advice on submission frequency and managing differences in frequencies
Use of company core data sheet or other specified document as reference for new information and integrated evaluation
Description of all data sources to be covered in a PBRER
Inclusion of worldwide information on marketing authorisation status and regulatory safety-related action, including action for investigational products
Inclusion of data on exposure, use patterns and medication errors
Cumulative and interval summary tabulations for adverse events/reactions
Summary of safety findings from clinical trials and non-interventional studies
Overview on signals and their evaluation
Summary of important identified risks, potential risks and missing information
Summary on effectiveness of risk minimisation
Guidance for separate risk and benefit evaluations as well as evaluation of the benefit-risk balance for approved indications based on cumulative data and considering the medical need
Presentation of proposals for action to improve the benefit-risk balance as needed, including changes to reference information (changes to regional product information in annex)
Modular approach for sharing harmonised content of corresponding sections of PBRER, DSUR and pharmacovigilance plan

identified, potential, and unknown risks for the medicinal product. Various methods for data collection may be used, and ICH-E2E therefore provides, in addition to a format for pharmacovigilance plans, harmonized terminology for methods of active and passive surveillance as well as principles for the conduct of pharmacoepidemiological studies of non-experimental design (i.e. observational studies, non-interventional studies) (Table 5.9).

Table 5.9 Key points addressed in the ICH-E2E guideline.

Elements for the safety specification as summary of identified risks, risks potentially arising from populations and situations that have not yet been adequately studied, and potential other risks
Format of a pharmacovigilance plan based on the safety specification
Within the pharmacovigilance plan, the description of routine pharmacovigilance as minimum and inclusion of a safety action plan for specific issues/missing information as needed
Format of safety action plan, with the description of rationale for action and timetable for evaluation and reporting ("milestones")
Possible synchronization of timetable with regulatory timetable for post-authorization assessment, such as PSUR assessment or marketing authorization renewal assessment
Principles for design and conduct pharmacoepidemiological studies of non-experimental design with references to international guidelines
Overview of methods for data collection to investigate the known or unknown risks and references

ICH-E2E is a framework for the formal preparation of pharmacovigilance in the pre-authorization assessment phase as well as for a continued proactive approach throughout the post-authorization phase. Although ICH-E2E is not a summary of risk minimization tools to be implemented for a particular product, the contents of a pharmacovigilance plan may refer to such tools, as the safety specification may depend on the risk minimization systems in place, in particular where prescribing, dispensing, and other health services come into play. Likewise, the planned data collection methods will depend on the health service systems and linked risk minimization tools.

#### ICH-E2F TOPIC: DEVELOPMENT SAFETY UPDATE REPORT

This guideline was developed between 2006 and 2010 and adopted at Step 4 in August 2010. It was based on the CIOMS VII Report (CIOMS, 2006) and describes the specifications for format and content of development safety update reports

Table 5.10 Key points addressed in the ICH-E2F guideline.

Format for presenting safety data from all ongoing clinical trials for an active substance in a single DSUR by sponsor
Single DSURs for a clinical trial or clinical development program with more than one sponsor
Concept of development international birth date to determine the data lock points of DSURs
Status of the clinical development program
Update on study results
Inclusion of relevant safety data from observational post-authorization and non-clinical studies
Inclusion of data published in the literature
Inclusion of data on manufacturing changes
Inclusion of lack of efficacy data with impact on subject safety
Formats of AE line listings and summary tabulations
Presentation of exposure data
Investigator's brochure as reference safety information
Evaluation if data are consistent with previous knowledge or represent new safety concerns
Overall safety evaluation and conclusion: analysis and discussion of data by with a view to management of identified and potential risks, protection of clinical trial subjects, benefit-risk considerations and need for safety action in relation to the clinical development program

(DSURs) summarizing and analyzing data from clinical trials for active substances without as well as with a marketing authorization (Table 5.10). The intention was to make available a common standard for the annual safety reporting required by the authorities in the EU and USA for medicines under development. Annual safety reporting forms part of the overall continuous risk assessment during clinical trials and is an important communication and assessment tool for involved stakeholders (ICH, 2010a).

## HISTORY OF REGIONAL IMPLEMENTATION AND DISCUSSION

The ICH initiatives in the area of pharmacovigilance have to be seen not only given the general need for universal standards for the investigation

on medicinal products, but moreover in the context of efforts in strengthening pharmacovigilance in the three ICH regions.

## FIRST WAVE GUIDELINES AND THEIR FURTHER DEVELOPMENT

At the time of the first wave of pharmacovigilance-related ICH guidelines, the main focus was on gathering worldwide data in an efficient manner for comprehensive assessment. Therefore, standards for electronic reporting of ADR case reports were introduced as well as the concept of the PSUR. Latest technical developments offered new possibilities with regard to electronic reporting, which would reduce paperwork and facilitate database entries and data sharing. For the purpose of signal identification and risk-factor identification, algorithms and statistical methods had already been applied to data available in other electronic formats using efficient, automated analysis by computer (data mining) (Moore *et al.*, 1997; van Puijenbroek, 2001; Clark, 2002; Clark *et al.*, 2002; Edwards *et al.*, 2002; Evans, 2002), and methods have been refined since then.

In accordance with EU legislation (EC, 1993: Article 51(c); EC, 2000: Article 1(7)), the data processing network and management system EudraVigilance was made available by the European Medicines Agency for expedited reporting and data storage in accordance with ICH-E2B(R2) as well as MedDRA. Electronic expedited reporting using EudraVigilance became mandatory in the EU by legislation in November 2005. EudraVigilance allows networking and work sharing in relation to data and signal management between the authorities in the EU, a necessity for the EU regulatory system. Aspects of ICH-E2A relevant to the post-authorization phase were implemented in the EU in Volume 9 of the Rules Governing Medicinal Products in the EU since its first version of 1997 (EC, 1997–2004), and ICH-E2D was reflected in the revision of Volume 9A in 2006. In 2012, Volume 9A was replaced, under new legislation, by the EU Good Pharmacovigilance Practices (GVP) (EMA, 2013).

In the USA, the FDA developed their adverse event reporting system (AERS), now called FAERS for FDA Adverse Event Reporting System, likewise

based on ICH-E2B(R2) and MedDRA and enabling electronic reporting (FDA, 2013). For post authorization safety reporting, the principles of ICH-E2A and ICH-E2D were incorporated by the FDA in their Proposed Rule on Safety Reporting Requirements (Raczkowski, 2003).

In Japan, electronic submission of ADR case reports, in accordance with ICH-E2B(R2) and MedDRA/J (Japanese translation of MedDRA), was implemented in October 2003, using a specific secure electronic reporting system (U. Kimura and M. Yamate, personal communication, November 2, 2011).

The fact that marketing authorization holders can submit ADR case reports to the authorities in the three ICH regions according to the same technical standards represents major work facilitation, and the enabled data sharing is considered a key contribution to patient safety. This is expected to be enhanced further by the IS for ADR case reports and facilitate the development of software, which will be inter-operational across healthcare record management worldwide.

The implementation of ICH-E2B(R3) is now subject the progress of the ICH-E2B(R3) Implementation Working Group. While implementation is ongoing, ICH-E2B(R2) remains applicable. For Japan, the implementation is planned for April 2016 (H Kosuke and T Misu, personal communication, 25 October 2013).

The PSUR format had been implemented, immediately after the adoption of ICH-E2C, in the EU and in Japan, and this experience was judged very positively, so that the ICH parties agreed to develop ICH-E2C Addendum during the second wave of pharmacovigilance-related ICH guidelines. ICH-E2C Addendum opened further opportunities for the useful application of the PSUR.

In the USA, both these ICH guidelines were published in the Federal Register Notice. The ICH format for PSURs was included by the FDA in their Proposed Rule on Safety Reporting Requirements (Chen, 2003; Khan, 2004), and since 2001 there is the option for marketing authorization holders to submit a waiver request if they want to use the ICH format for the mandated safety reporting.

Again, the availability of an agreed standard was meant to allow marketing authorization holders to

submit the same PSUR in the three ICH regions and also promote co-operation between authorities. However, some legal issues in relation to harmonization of data lock points and submission dates remained, and guidance in this respect was recently added by means of ICH-E2C(R2) (ICH, 2012). More importantly, this revision finalized in 2012 resulted in a new format for periodic reporting, the PBRER with a focus on the evaluation of the benefit-risk balance of medicinal products. This focus makes periodic reporting much more fit for purpose a regards product-related regulatory decision-making. In addition the new format also reflects technical progress and regulatory requirements for electronic reporting and data bases for individual case safety reports, so that line listings of case reports are not necessary anymore as part of the PBRER.

Japan accepts the ICH-E2C(R1) as well as, since May 2013, the (R2) format, and in the EU, GVP has been subject to revision in 2013 to incorporate the (R2) format.

In the decade before, the EU had started to successfully pilot and then implement work sharing, and peer review between its member states' authorities in relation to PSUR assessment for nationally authorized products. This work sharing required harmonization of data lock points going beyond the product; that is, agreeing substance birth dates, as well as of submission schedules. This example shows how an ICH concept can be used for an even higher degree of harmonization within a region. In 2010, work sharing between member states and EU-wide single PSUR assessments obtained a legal basis (EC, 2010a), and the PBRER is now the format for the legally mandated PSUR in the EU, as incorporated in GVP. Overall from an EU perspective, the pharmacovigilance-related ICH guidelines have formed the basis for the processes in operation in the pharmacovigilance system of the EU today.

## SECOND WAVE GUIDELINES

After the first wave of pharmacovigilance-related ICH guidelines was completed in 1997, the representatives from the authorities of the three ICH regions monitored the implementation of the

guidelines and the need for further harmonization at their regular meetings from 1999 onwards and expressed interest in increased cooperation between the authorities on methods and product-related issues in pharmacovigilance. The ICH initiative has certainly been providing a framework for confidence building and formal cooperation beyond personal contact.

The second wave of pharmacovigilance-related ICH guidelines was then prepared by the Japanese Ministry in 2000, at the same time that they strengthened the Japanese pharmacovigilance system. The measures taken in Japan included the concept of EPPV described above.

In the USA, the FDA published their risk management strategy in 1999 and their Strategic Action Plan for Protecting and Advancing America's Health in 2003, which included goals of risk management and patient safety (FDA, 2003). In accordance with the Prescription Drug User Fee Act (PDUFA) III authorized in 2002, the FDA, following public consultation, finalized three guidance papers in 2005 on risk assessment during the pre-authorization phase, on risk minimization action plans, and on good pharmacovigilance practices and pharmacoepidemiologic assessment (FDA, 2005a–c). The risk minimization action plans, called RiskMAPs, were replaced in 2007 by the improved risk evaluation and mitigation strategies (REMS), which the FDA has the legal authority to require from the company for product-related risk management (FDA, 2009).

In the EU, the European Commission initiated in early 2001 a stakeholders' High Level Group on Innovation and the Provision of Medicines (2002: G10 Medicines), and one of their recommendations was to optimize data collection processes in pharmacovigilance. Furthermore, welcoming proposals from the European Medicines Agency, the Heads of Medicines Agencies Ad Hoc Working Group in the EU (2003, 2005a,b) started developing a risk management strategy in 2002. More specifically with regard to products centrally authorized by the European Commission, the Agency (EMEA, 2004b) established a procedure for assuring high-quality pharmacovigilance in both the pre-authorization and the post-authorization phase. Further initiatives were announced in its Road Map

to 2010 (EMEA, 2004a), taking into account the revised legislation (EC, 2004a,b) and the needs expressed by patients (EMEA/CHMP Working Group with Patient Organisations, 2005). The revised legislation introduced the concept of risk management systems to be put in place by marketing authorization holders, and guidance was provided in the revised Volume 9A (EC, 2006) which incorporated ICH-E2E. Needs expressed by patients included a proactive approach in pharmacovigilance. In 2010, the EU legislation was further revised with the aim of strengthening the system, and in particular risk management (EC, 2010a,b). (see Chapter 13a), and the new GVP developed under this legislation incorporates, like the previously applicable Volume 9A, all pharmacovigilance-related ICH guidelines and recommendations (EMA, 2013).

In Japan, new guidance on risk management plans incorporating ICH-E2E was developed, integrating risk management with EPPV and pre-/post-marketing surveillance (U. Kimura and M. Yamate, personal communication, November 2, 2011), and has been in place since April 2013.

The ICH-E2F format for DSURs is so far the last guideline of the ICH E2 series with impact on pharmacovigilance; its implementation, however, falls to those responsible for clinical trial regulation and oversight. In the EU, the ICH-E2F has been included in Volume 10 of the Rules Governing Medicinal Products in the EU on guidelines for clinical trials, as the format for the annual safety report (EC, 2011) as of September 2011. The implementation in Japan followed in December 2012.

Part of the developments during the second wave was the fundamental revision of ICH-E2C resulting in the new PBRER format which integrates periodic benefit-risk evaluation reporting with the ICH-E2F format for the DSUR and the ICH-E2E format for safety specifications.

## CONCLUSIONS AND OUTLOOK

All the past and ongoing activities in the three ICH regions reflect the high demand for strengthening pharmacovigilance from the public health, political, and public points of view. Consequently, the

limited available resources have to be used efficiently, and the ICH guidelines are important for global industry as well as the authorities in the three ICH regions. How to use resources efficiently and monitor that resources are used to the best serve patient safety, should be subject to future regulatory science research.

Looking, furthermore, at the importance of pharmacovigilance and patient safety beyond the three ICH regions, one needs to reflect upon the discussions of the ICH GCG and welcome the still rather new participation of technical experts from China, Korea, and Singapore in ICH expert working groups, including the one on ICH-E2C(R2). The GCP looks much at training on ICH guidelines and recommendations and respective capacity building in relation to quality of manufacturing and clinical trials. The application of agreed standards worldwide is essential for international trade and supply of medicines, as well as for their development. The necessary trust between regulators worldwide for the purpose of inspections and multiregional clinical trials can only be based on common agreement upon the standards and their implementation.

However, successful implementation needs a sufficiently strong structure in terms of capacity and systems for approval of medicines, inspections, clinical trial oversight, and pharmacovigilance. In many countries of the world these structures are still weak, and hence the work of the WHO and other development initiatives to support building up these systems is vital. More specifically for pharmacovigilance, the work of the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring, needs to be noted: the UMC supports countries in establishing pharmacovigilance systems, provides training, and offers an international networking structure as well as many services for their 117 member countries. Amongst those, VigiBase is the database where the ADR case reports submitted by each member country are stored for retrieval by any member country and automated signal identification from worldwide data at the level of the UMC. VigiBase is compliant with the ICH-E2B(R2) guideline and accepts cases coded in the ADR terminology WHO-ART as well as in MedDRA (VigiBase, 2008). Looking at safety of medicines from a global

perspective, and in particular not neglecting the needs of developing and emerging countries, the following needs to be considered. Efficacious and safe use of a medicinal product depends on the product, the patient with their genetic, acquired, and culture-related factors, the health services, and the regulatory control. Countries where new medicinal products are marketed first need strong pharmacovigilance systems. Countries with weak regulatory control, weak pharmacovigilance, and weak health services need reliable information on effective and safe use of a medicinal product from elsewhere while making all efforts to improve their systems, taking into account local health needs. In such circumstances, priority in data collection and pharmacovigilance planning should be given to local specificities and investigations if data from other populations and/or from other health service/regulatory/cultural environments can be extrapolated. Extrapolation of safety data from clinical trials to an ethnic population other than the trial population is addressed in the ICH-E5 guideline with regard to intrinsic and extrinsic factors (ICH, 1998), and data justifying extrapolation of the clinical trial data may be used also for the interpretation of data emerging in the post-authorization phase.

However, there is more work to do, such as research into relevant aspects relating to epidemiology, health priorities, health services, pharmacogenetics, drug utilization, medical anthropology, communication, and media use. This will be the major future challenge for risk minimization and its evaluation, both being crucial to the risk minimization and optimization of effective use of innovative medicines, as well as those widely in use already for a longer time. When working toward worldwide access to safe medicines and providing medicines to multiethnic populations, cooperation within regional and international structures is of key importance for all countries.

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# 6

## The Council for International Organizations of Medical Sciences Working Groups and Their Contributions to Pharmacovigilance

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### INTRODUCTION

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization. CIOMS celebrated its 60th anniversary in 2009.

In 1986, CIOMS set up its first pharmacovigilance working group (WG) to discuss international reporting of adverse drug reactions (ADRs). Over more than two decades, several different CIOMS WGs have published reports covering specific areas of drug development and drug safety with the goal of achieving harmonization and standardization

across regulatory jurisdictions. WG reports also serve as educational material at various training institutes and seminars, and in particular for new staff within the pharmaceutical industry and regulatory authorities. Experts worldwide within the area of drug safety still use the standardized principles for reporting of ADRs as compiled in the data elements and fields of the CIOMS forms developed more than 20 years ago.

Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. Two major themes for CIOMS within the field of biomedicine have been bioethics and the development and use of drugs.

The independent status of CIOMS has permitted it to coordinate the contributions and expertise of

senior scientists from research-based biopharmaceutical companies, national drug regulatory authorities, academia, and representative bodies of medical specialties to harmonizing and strengthening drug-safety surveillance measures. The scientists are invited based on their recognized specific expertise and, if required, in consultation with their background institution.

As the CIOMS WGs have no legal jurisdiction or mandate to make binding decisions, reliance is placed on other bodies to incorporate the CIOMS recommendations, guidelines, or good practices into a regulatory or legislative framework. In many instances the reports of the CIOMS WGs have served as the basis for International Conference for Harmonisation (ICH) topics (see Chapter 5), and have either been included as such or with changes, or are referenced in ICH topics that have been included into legal frameworks governing the development and use of medicinal products, in the EU, USA, Japan, and elsewhere.

Reports of the CIOMS WGs IV, V and Reporting Adverse Drug reactions: Term and Criteria for Their Use, are printable from the website of CIOMS (<http://www.cioms.ch/index.php/publications/printable-publications>) as well as the CIOMS Form I (<http://www.cioms.ch/index.php/cioms-form-i>).

As previously mentioned by Roden and Gibbs (2007), there has, over the years, been a collaboration with the ICH and below is a reproduction of two tables from their chapter (Tables 6.1 and 6.2), with contributions from CIOMS WGs up to the end of 2005. ICH has, for example, processed the CIOMS initiatives (CIOMS, 1990, 1995) on expedited and electronic reporting (ICH, 1994, 1997) as well as having used the CIOMS II recommendations as the basis for the requirements for periodic safety update reports. As a more recent example, in 2011, the support of a concept paper and business plan for the CIOMS Standardised MedDRA® Queries Implementation Working Group (IWG) proposed to enhance the broader understanding and implementation of standardized MedDRA queries (SMQs) by the Medical Dictionary for Regulatory Activities (MedDRA) subscribers may be mentioned.

Since the end of 2005, four additional CIOMS WGs have been created; see Table 6.3.

Table 6.1 The CIOMS initiatives.

Working group	Initiative
CIOMS I	Expedited reporting of individual ADRs (1990)
CIOMS IA	Harmonization of data elements and fields for electronic reporting of individual ADRs (1995)
CIOMS II	Periodic safety updates (CIOMS, 1992)
CIOMS III	Core clinical-safety information (1995, 1999)
CIOMS IV	Benefit-risk evaluation (1998)
CIOMS V	Good case management and reporting practices (CIOMS, 2001)
CIOMS VI	Management of safety information from clinical trials (2005)

Table 6.2 Uptake of CIOMS initiatives by ICH.

Working group	Initiative	Uptake
CIOMS I	Expedited reporting	ICH E2A October 1994 (ICH, 1994)
CIOMS IA	Data elements for electronic reporting	ICH E2B July 1997 (ICH, 1997)
CIOMS II	Periodic safety update reports	ICH M2 November 2000 (ICH, 2000) ICH E2C November 1996 (ICH, 1996b)
CIOMS IV	Benefit-risk evaluation	ICH E2E November 2004
CIOMS V	Post-approval safety data management	ICH E2D November 2003 (ICH, 2003b)
PSURs		ICH E2C (Add) February 2003 (ICH, 2003a)

## CIOMS/WHO WORKING GROUP ON VACCINE PHARMACOVIGILANCE

### BACKGROUND

Both CIOMS and the WHO recognized that vaccines represent a special group of medicinal products, and that there was a need to focus on

Table 6.3 Ongoing CIOMS WGs 2006 to 2012. Reproduced with permission of CIOMS (Council for International Organizations of Medical Sciences).

Working group	Initiative
CIOMS/WHO WG	Vaccine pharmacovigilance (2012)
CIOMS WG on standardized MedDRA® queries (SMQs)	SMQ development
CIOMS WG VII	The development safety update report (DSUR): harmonizing the format and content of periodic safety reporting during clinical trials (published 2006)
CIOMS WG VIII	Practical aspects of signal detection in pharmacovigilance (published 2010)
CIOMS WG IX	Practical considerations for development and application of a toolkit for medicinal product risk management
CIOMS WG X	Considerations for applying good meta-analysis practices to clinical safety data within the biopharmaceutical regulatory process

addressing issues specific to the monitoring and assessment of vaccine safety. Several factors in the development of vaccines and the settings of post-approval vaccine use are issues for special consideration, and it was felt that there was a need for continued work to harmonize terms and concepts for use in the conduct of vaccine pharmacovigilance by all relevant parties. As the Brighton Collaboration has been the unique initiative in the area of developing standardized case definitions for adverse events following immunization (AEFIs; Bonhoeffer *et al.*, 2002), the coordination with this process was one of the goals and expected to be elaborated by the WG.

## SCOPE

This WG was created in November 2005. The scope was to develop general definitions strictly focused

on vaccine pharmacovigilance and to contribute to the development, review, evaluation, and endorsement of definitions of adverse events following immunization as developed by the Brighton Collaboration process, and to their dissemination. This, according to the report of the WG (CIOMS, 2012), was performed by (a) endorsing already existing definitions, (b) participating in the review of definitions under development, (c) proposing priorities for the development of new definitions, and (d) facilitating the translation and dissemination of the definitions. In addition, the WG collaborated with other CIOMS WGs, especially that on SMQs and CIOMS WG VIII on signal detection. In relation to the third objective, the WG contributed with an evaluation of the comparability between SMQs and Brighton Collaboration case definitions and provided vaccine expertise to support the work and published the report of CIOMS WG VIII on Practical Aspects of Signal Detection in Pharmacovigilance.

## PROCESS

The establishment of this WG was supported by both the WHO and CIOMS. It was organized and coordinated by CIOMS and included experts from the WHO as well as representatives from the Brighton Collaboration, vaccine manufacturers, academia, regulatory agencies, and governmental institutions. As vaccines are manufactured and widely used in resource-limited settings, it was crucial to invite expert members representing these regions to participate in the WG. The work is based on several consecutive meetings convened by CIOMS over 5 years (2005–2010).

During this process, helpful discussions were held with concerned parties such as the Brighton Collaboration, the US Centers for Disease Control and Prevention, the Public Health Agency of Canada, and the Maintenance and Support Services Organization (MSSO) of the MedDRA. A number of parties, including relevant regulators in the European Union via the Committee for Human Medicinal Products (CHMP) Pharmacovigilance Working Party at the European Medicines Agency, the Global Advisory Committee on Vaccine Safety of the WHO, and selected individual vaccine safety

experts, were consulted on the general definitions for AEFIs.

## RECOMMENDATIONS

Three definitions relevant to the monitoring of the safety of vaccines during clinical trials and for the purposes of vaccine pharmacovigilance in the post-approval period were developed by the WG: vaccination failure, vaccine pharmacovigilance, and a general definition of AEFI. In addition to the latter, further specified definitions of cause-specific adverse reactions and a coincidental event have been formulated.

The new definitions, as stated 2008 in a position paper on the CIOMS website and slightly revised in the final report (CIOMS, 2012), are:

- 1 *Vaccine pharmacovigilance*, which, is defined as the science and activities relating to the detection, assessment, understanding, and communication of AEFIs, and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.
- 2 *Confirmed clinical vaccine failure*, which is defined as the occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.
- 3 *Suspected vaccine failure*, which is defined as the occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease; for example, invasive pneumococcal disease of unknown serotype in a fully vaccinated person. Applying this definition also requires that the incubation period and the normal delay for the protection to be acquired as a result of immunization have been taken into account.
- 4 *Immunological failure*, which is defined as failure of the vaccinee to develop the accepted marker of protective immune response after being fully and appropriately vaccinated. This definition requires that there is an accepted correlate or

marker for protection, and that the vaccinee has been tested or examined at an appropriate time interval after completion of immunization. The definition of a suspected immunological vaccine failure is similar except that testing of biomarkers of immune response has been inappropriate.

5 *AEFI*, which is defined in general terms: any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.

The proposed terminology will facilitate communications and exchange of information on vaccine safety between regulatory authorities worldwide and with industry and other stakeholders. Vaccine-specific definitions of failure may serve as examples for appropriate classification of individual cases and in the review of vaccination failure in periodic safety update reports (PSURs) and other aggregate data reports in the future. In addition, the concepts in the vaccination failure position paper can support vaccine effectiveness studies and other investigations.

Finally, the WG envisions that the endorsement of Brighton Collaboration case definitions should improve their acceptance and use in a variety of settings by multiple stakeholders. WG members from regulatory agencies encourage their use through regulatory guidance documents and discussions with the vaccine industry.

The WG also highlighted the differences between vaccines and drugs in signal detection.

Based on a recommendation from this CIOMS/WHO WG, Brighton Collaboration WGs should now routinely consider MedDRA mapping during case definition development. New vaccine-specific terms proposed by the CIOMS/WHO WG, and added to MedDRA by the MSSO, should improve the coding of vaccine reports and their retrieval from vaccine databases. In addition, the development of new SMQs and modification of existing SMQs based on Brighton Collaboration case definitions should improve the ability to retrieve AEFI cases from regulatory agency, industry, and other databases. The experience with influenza A/H1N1

vaccine pharmacovigilance during 2009–2010 illustrated the need for harmonized case retrieval tools and case definitions. It was recommended for the future to have a continued endorsement of harmonized case definitions, such as those of the Brighton Collaboration, by a scientific WG including representatives of various stakeholders active in vaccine pharmacovigilance.

## CIOMS WORKING GROUP ON STANDARDIZED MEDDRA® QUERIES

### BACKGROUND

MedDRA is a standardized medical terminology that was developed by ICH to classify native language descriptions of medical concepts. Classification is important for data exchange and subsequent cumulative analysis because uncontrolled verbatim terms can describe an adverse event, for example, in many different ways, and this could possibly obscure important safety information. Data classification impacts scientific evaluation of data from the first clinical trial in humans and throughout the lifecycle of the product. Thus, drug regulatory authorities, the biopharmaceutical industry, and other organizations have implemented MedDRA to classify and display certain regulatory and safety data for biopharmaceutical and other medical products. However, the size, complexity, and granularity of MedDRA (over 70 000 terms organized in a five-tier hierarchy) create unusual challenges when trying to retrieve individual case safety reports (ICSRs), primarily because different users may select different search terms for a target medical condition. In addition, availability of standardized queries, which are maintained and published in step with the MedDRA terminology (twice per year), can reduce duplication of effort required to recreate and maintain queries that may be needed or desired by various business partners.

Following an organizational meeting in May 2002, a CIOMS WG on the Rational Use of MedDRA Terminology for Drug Safety Database Searches was established in September 2002. The original 24 members were senior scientists representing seven drug regulatory authorities, seven

pharmaceutical companies, and other organizations (e.g., WHO). Subsequently, the MedDRA MSSO and the Japanese Maintenance Organization joined the group and a decision was taken to consolidate efforts, such that SMQs would subsume the then ongoing development of other cooperative data query efforts; that is, work on MedDRA special search categories and MedDRA analytical groupings would be sunset. The joint collaborative effort was designed to take full advantage of technical expertise, administrative functions, access to MedDRA-coded regulator and company databases, distribution services, and maintenance capabilities. In May 2003, the reconstituted WG was renamed the CIOMS Working Group on Standardised MedRA Queries.

Work has been conducted under a memorandum of understanding between CIOMS and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), which owns MedDRA as trustee for the ICH Steering Committee.

### SCOPE

SMQs are groupings of terms from one or more MedDRA system organ classes that relate to a specific, defined medical condition or area of interest. Terms included in a given SMQ may describe diagnoses, signs, symptoms, syndromes, physical findings, or laboratory data. SMQs were designed to facilitate retrieval of ICSRs from large MedDRA-coded databases. As such, SMQ development has focused on specific scientific/pharmacovigilance questions that can be defined and are not addressed by the current MedDRA hierarchy or an existing SMQ. Topics selected for SMQ development either have a known high-attributable medical product risk or have been associated with important scientific or regulatory concerns in evaluating the safety of medical products. Generally, SMQs are developed for regular use rather than for single-use situations.

### PROCESS

The CIOMS WG designed and adopted a process to facilitate a consistent and uniform approach to

SMQ development, documentation, and subsequent fit-for-purpose testing in regulatory and industry databases. This process is described in Chapter II of the report of the CIOMS WG (CIOMS, 2004). The ICH MedDRA Management Board endorsed this multistep, iterative development and testing process.

In summary, a subteam carefully defines the medical condition of interest, performs top-down and bottom-up searches in the MedDRA hierarchy for relevant terms, performs searches of regulatory and industry databases, collects documentation, and analyzes results of testing with the entire WG. Depending on the medical condition of interest and the number and complexity of associated MedDRA terms, a given SMQ is organized to produce the most relevant output; that is, the SMQ is organized as a narrow, broad, or algorithmic search (see the following Recommendations section). Once an SMQ “package” is accepted by the WG, an ICH MedDRA Advisory Panel, which represents the ICH parties and whose members are also part of the WG, evaluates and, if acceptable, forwards a signed recommendation to IFPMA for ICH adoption and publication by the MSSO in the regular MedDRA versioning cycle (each March and September) for production use by MedDRA subscribers.

Requests for new SMQs, or modification of existing SMQs, may be submitted to the MSSO for evaluation by the ICH MedDRA Advisory Panel. The advisory panel is responsible for deciding which requests should be developed into SMQs, using the following criteria:

- 1 What is the scientific/pharmacovigilance question that led to the request for this SMQ?
- 2 Is the current MedDRA hierarchy (e.g., high-level terms, preferred terms) or any existing SMQ suitable to address the question? If not, what are the deficiencies in the hierarchy or existing SMQs that should be addressed?
- 3 Would your organization be able to address this question without this new SMQ? And if so, how? (That is, what would be the strategy and terms used?)
- 4 Which SMQ structure (i.e., broad/narrow, hierarchical, algorithm) do you think would best address the question?

- 5 How often would your organization need this SMQ (e.g., only once to address a very specific emerging issue or regularly/routinely)?

## RECOMMENDATIONS

SMQs impact the scientific evaluation of data from the first clinical trial in humans and throughout the lifecycle of the product. Indeed, SMQs are often applied as a first search strategy in ICH regions. However, care must be taken to read and apply all documentation provided with each SMQ and only use an SMQ that is matched to the MedDRA version used to code the database. Furthermore, results of SMQ application ordinarily represent merely a starting point for understanding a possible safety concern and, alone, would usually not provide justification for regulatory action. To help ensure a common understanding of this starting point, the CIOMS WG recommends that SMQs be used as published, without modification. If there is a compelling reason to modify a query, it becomes non-standardized and must be documented as such.

Three basic search designs have been utilized for SMQs:

- 1 Narrow searches are specific. While they are highly likely to identify ICSRs that represent the condition of interest, it is possible that some cases will be missed.
- 2 Broad searches are sensitive, as they include all terms from the narrow search plus other terms that could produce “noise”; that is, all possible cases should be retrieved, but results will likely include ICSRs that do not represent the condition of interest). Note that a given MedDRA term may be included in the narrow search of one SMQ, while being included in the broad search of another SMQ.
- 3 Algorithmic searches are designed to improve case retrieval by grouping a defined combination of selected terms.

Some SMQs are hierarchical; that is, a set of related sub-queries is organized under one named SMQ. The SMQ hierarchies vary with the SMQ and are not related to the standard five-tier

MedDRA terminology hierarchy. Depending on the safety concern, one or more subordinate SMQs may be combined to create a more inclusive query.

SMQs may be utilized in clinical trials and in the post-marketing setting. In clinical trials, where the safety profile of the product is evolving, SMQs may be useful as periodic screening tools. Specific SMQs can be used to monitor identified risks or potential risks; for example, risks suggested from non-clinical sources or that are related to a certain class of product. In post-marketing pharmacovigilance programs, SMQs can be used as part of a risk management plan or to identify ICSRs that could be relevant to an emerging safety issue. SMQs can also be used for safety signal detection and in routine aggregate reporting; for example, in development safety update reports (DSURs), PSURs, and in periodic benefit–risk evaluation reports.

In 2012 it was decided to continue the CIOMS SMQ work as an IWG. The IWG carried on with work on “home grown” MedDRA queries, MSSO consultations with 18–24-month reviews and remaining queries, having a balanced participation by stakeholders from ICH regions. Regarding the development of further guidance, the CIOMS IWG decided to initiate an update of the CIOMS “Red Book” publication “Development and Rational Use of Standardised MedDRA Queries (SMQs)”. Editorial work is ongoing.

## **CIOMS WORKING GROUP VII: THE DEVELOPMENT SAFETY UPDATE REPORT: HARMONIZING THE FORMAT AND CONTENT OF PERIODIC SAFETY REPORTING DURING CLINICAL TRIALS**

### **BACKGROUND**

Protecting patient safety and managing safety risks to subjects during the clinical development of biopharmaceutical products, particularly when efficacy information is unknown or evolving, requires constant focus of investigators, subjects, sponsors, and regulators. The overall management of safety information from clinical trials was addressed by CIOMS WG VI (CIOMS, 2005), which established the background for periodic reviews and communica-

tion of aggregate data from clinical trials. The report of WG VI noted that different regulatory requirements have developed in various jurisdictions regarding the format, content, and periodicity for sponsors to communicate drug development data and assessments prior to applying for marketing authorization. The CIOMS WG VII on the DSUR was established to develop a consensus approach to these latter activities. A consensus approach is important to protect the rights and welfare of clinical trial subjects, regardless of whether a clinical development program is global, with dozens of clinical trial protocols, or whether the program includes only a single trial conducted by a commercial or non-commercial sponsor. Goals of having a standardized report include (a) minimizing discrepancies in information provided by sponsor to different regulators, (b) enhancing efficiency of report products, and (c) providing transparency to assure stakeholders that safety data have been collected and assessed using a timely and thoughtful process.

### **SCOPE**

The scope of the project focused on an annual summary of safety information for investigational biopharmaceutical products under study in experimental conditions, whether the product could be classified as a drug, biologic, or vaccine. A key objective of WG VII was to provide pragmatic advice on the analysis and presentation of important safety data from development programs that include interventional clinical trials. Another objective was to provide useful recommendations that could be applied to large, global development programs, as well as single-protocol, single-site studies conducted either for commercial or non-commercial purposes. In addition, scope was limited to sponsor responsibilities and does not address how regulators might approach review and interact with sponsors in the context or timing of such a review.

### **PROCESS**

WG VII was formed in early 2005 and was composed of 24 senior scientists from the public and private sectors in Australia, Europe, Japan, and

North America. Once a draft outline of the contemplated WG VII report was agreed, subgroups were formed to propose draft text for individual topic chapters and other sections; subgroup proposals were reviewed, discussed, and debated several times by the entire WG VII. WG VII met five times at various venues during 2005–2006. An editorial group produced the final text of the WG VII report for publication by CIOMS.

## RECOMMENDATIONS

The WG VII report (CIOMS, 2006) recommends a standard approach to periodic evaluation and presentation of safety information collected during the clinical development of biopharmaceutical products. As envisioned by WG VII, this standard approach would result in an internationally harmonized document, the DSUR, which is modeled after the PSUR for marketed products. The recommended approach includes a standard format, content, and timing and applies to all development program designs, regardless of number of protocols or subjects and whether or not the program has a commercial objective.

As stated in the WG VII report, the DSUR is intended to:

- Present all pertinent, new safety-related information, both clinical and non-clinical, since the most recent report.
- Provide a cumulative summary of key safety findings.
- Relate the clinical data to patient exposure.
- Provide information on any marketing authorizations in different countries and any significant variations related to safety.
- Provide a summary of emerging and/or urgent safety issues (e.g., a major signal identified during period).
- Include a cumulative summary of important risks that are tracked from report to report.
- Indicate whether the information reported for the period is in accord with previous knowledge of the product's safety profile.
- Provide a summary of significant changes made during the review period to the development core safety information (DCSI), safety sections

of the investigator brochure, or other reference safety information that might be used (e.g., by independent sponsor-investigators). The version in effect at the beginning of the review period is used as the reference safety information.

- On the basis of the data, indicate whether changes should be, or have been, made to clinical trial protocols, informed consent, or the investigator's brochure/DCSI to improve management of risk; the implications of such changes should be discussed.

A model DSUR is provided in the WG VII report.

The WG VII report strongly recommends that a formal process be established by each sponsor that would enable detection of emergent safety signals and to place risks in the context of anticipated (or demonstrated) efficacy. The DSUR is another tool to ensure that important risks to trial subjects are recognized, assessed, and communicated. While much of the information is time-bound (i.e., related to the 1 year interval the report covers), it is also recommended that certain information be presented in a cumulative fashion. For example, the WG VII report recommends that serious adverse events be presented in cumulative summary tabulations.

In general, the WG VII recommendations address obligations of clinical trial sponsors. However, both sponsors and regulators may use the DSUR to enhance process and workflow efficiencies. A sponsor, for example, may integrate annual updates to the DCSI or investigator brochure to preparation of the DSUR. Both sponsors and regulators may link late-state DSURs to development of a risk management plan (or risk minimization plan) that accompanies a marketing application.

While the overall goals of a clinical development program are to develop safety and efficacy profiles and to characterize benefit–risk in a specific patient population, the WG VII report designates the following as out of the intended scope of a DSUR:

- formal assessment of benefit-risk;
- comprehensive integrated safety summary;
- compendium of all case reports for the program;
- signal detection tool; or
- “expert report.”

Finally, WG VII recommends an ambitious future project in the context of a product's entire lifecycle. Separate periodic reports, with different formats and contents, are required for pre- and post-authorization phases. During discussions of how to address safety assessment needs across the lifecycle continuum of a product, WG VII realized that requirements for two separate reports resulted in inefficient processes for sponsors and regulatory reviewers and also did not facilitate communication of a consistent safety message to the various stakeholders. Thus, WG VII envisioned a future integrated periodic reporting model that would transcend the DSUR–PSUR interface. The WG VII report provides a detailed rationale for a single, integrated report for the pre- and post-approval situations and also addresses practical aspects of development, when a product is authorized in some markets and still under development in others.

WG VII expressed the hope that its vision for a DSUR, along with proposals for content, format, and timing, would be adopted and implemented by relevant stakeholders. To that end, the WG VII report formed the basis for ICH to adopt the DSUR as an official ICH Topic (E2F) in October 2006. The ICH DSUR guideline was adopted by ICH in August 2010 (ICH, 2010) and the DSUR became a regulatory requirement in the European Economic Area in September 2011 (EMA/CHMP, 2010). As of August 23, 2011, the DSUR can be submitted in the USA in lieu of an annual investigational new drug (IND) report, as long as the existing regulatory requirements are met (FDA, 2011; HHS, 2011).

## **CIOMS WORKING GROUP VIII: PRACTICAL ASPECTS OF SIGNAL DETECTION IN PHARMACOVIGILANCE**

### **BACKGROUND**

Before 1960 there was basically no systematic surveillance of drugs for unexpected adverse drug reactions performed post-authorization. Following key factors such as the thalidomide catastrophe in the 1960s, the development of a more sophisticated environment of pharmacovigilance began. The tra-

ditional pharmacovigilance approaches with review of individual cases or case series of reported adverse events and aggregated analyses of these were built up, and spontaneously reporting systems spread globally. In the late 1990s, new methodology for applying more complex statistical methods of signal detection in pharmacovigilance developed. However, this also created a general uncertainty about what was the optimal way of performing signal detection in pharmacovigilance.

### **SCOPE**

The WG was created in 2006 and its work published 4 years later (CIOMS, 2010). The emphasis was on providing practical, focused, and timely information about the application of proactive systems that couple statistical and analytical methods with sound clinical judgment mainly of spontaneous case reports of adverse drug or vaccine reactions/events. Ideally, a post-marketing safety surveillance system should be able to detect adverse drug/vaccine reactions that were not identified during the pre-authorization phase, including drug or disease interactions, medication errors, or characteristics of specific patient populations both on the group and individual levels (e.g., pharmacogenomics) that could increase the susceptibility for adverse reactions. The WG also decided to address new developments of active surveillance methods and future directions in pharmacovigilance in a special chapter. The objective of the CIOMS WG VIII report was to provide useful information to industry, regulatory agencies, health authorities, and additional international monitoring centers.

### **PROCESS**

The WG met at six formal meetings in Europe and North America during a period of 3 years, starting in 2006 and ending in 2008. Initially, at the first meeting, the group agreed on the outline of the project. It became obvious how important signal detection was as a tool for drug safety monitoring. The WG decided to focus on the lifecycle of safety signals, including aspects of signal detection, signal prioritization, and signal evaluation. A specific appendix addresses signal detection of vaccines.

However, safety signals related to types of medical products, such as medical devices, blood products, and dietary/herbal supplements, were not covered. Risk communication, risk minimization, and regulatory actions based on the outcome of signal detection were only discussed in relation to the timing of these activities and not in any further detail.

## CONCLUSIONS AND RECOMMENDATIONS

The WG concluded that traditional methods of reviewing case reports with simple quantitative filters will continue to be a pillar of signal detection based on spontaneous reports. The traditional pharmacovigilance approaches, based on spontaneous reporting systems, are particularly important in the assessment of rare events or designated medical events. Studies of patient and consumer reporting are so far encouraging, though further research is required. Universally understood and accepted definitions of adverse events and reactions, suspected reactions, and medication errors are critical to effective management of data, including communications. The definitions of *signal* and *risk* were reviewed – see Table 6.4. It was considered important to select a definition of *signal* that was relevant to all sources of information. Different types of signals can be either new and previously unknown or an increased severity or increased specificity. A signal does not imply a causal relationship.

Investigating strategies to conduct signal detection using numerator plus denominator of spontaneous data are supported. Data mining using statistical methods for disproportionality analysis developed for systematic signal detection in large databases from the spontaneous reporting systems

(SRS) maintained by health authorities and drug monitoring centers will supplement traditional signal detection. The common features of data mining algorithms (DMAs) supporting disproportionality analyses are condensing complex data sets onto  $2 \times 2$  contingency tables. See Table 6.5.

Assessing the sensitivity and specificity of DMAs is essential for further development and application of these tools. The WG recommended that transparent practices be reflected in standard operating procedures and that a cross-functional team of qualified personnel must ensure appropriate management and interpretation.

A key issue for SRS databases is data quality and the amount of duplicates. A special consideration

Table 6.4 Two definitions related to pharmacovigilance. Reproduced with permission of CIOMS (Council for International Organizations of Medical Sciences).

Signal	Information that arises from one or multiple sources (including observation and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or a set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify confirmatory action (adapted from Hauben and Aronson (2009)).
Risk	The probability of developing an outcome. <i>Note:</i> The term <i>risk</i> normally, but not always, refers to a negative outcome. When used for medicinal products, the concept of risk does not involve severity of an outcome (adapted from Lindquist (2007)).

Table 6.5 Contingency table used in disproportionality analysis. CIOMS (2010). Reproduced with permission of CIOMS (Council for International Organizations of Medical Sciences).

	Reports for event of interest	Reports for all other events	Total
Reports for drug of interest	A	B	A + B
Reports for all other drugs	C	D	C + D
Total	A + C	B + D	A + B + C + D

must be given to variability in structure and content between databases. In addition to SRS databases, other datasets of observational or active surveillance may be considered for data mining. However, there is a need for further research to determine whether data mining of healthcare administrative claims databases for signal detection yields a higher positive predictive value than data mining of SRS datasets.

## **CIOMS WORKING GROUP IX: PRACTICAL CONSIDERATIONS FOR DEVELOPMENT AND APPLICATION OF A TOOLKIT FOR MEDICINAL PRODUCT RISK MANAGEMENT**

### **BACKGROUND**

Post-authorization activities are limited in their ability to capture important, new biopharmaceutical product risks. Risk management systems with different concept and sets of pharmacovigilance activities and interventions were introduced at the beginning of the 21st century (EMA, 2005; FDA, 2008). However, these activities are not efficient in promoting early decision making in the face of residual uncertainty at the global level because associated risk management tools have evolved in an uncoordinated manner in different regulatory jurisdictions. Different tools and modifications have been proposed in different geographic and regulatory regions. For example, there are several tools that support the lifecycle process of biopharmaceutical product development in EU member states, Japan, and the USA, but, at present, these tools are not harmonized. Some of these tools are IND reports, annual safety reports, DSURs, PSURs, risk management plans, risk evaluation mitigation strategies, summaries of product characteristics, patient information leaflets, med guides, distribution and prescriber qualification, package inserts, and others.

A need has been defined for a harmonized risk management toolkit, providing outlines for content and usage of the toolkit, and describing the steps for its development and maintenance as the science of risk management evolves.

### **SCOPE**

The overall objective of the CIOMS WG IX project is to consolidate concepts of risk minimisation tools and propose their application in order to protect public health globally and to positively impact prescriber–patient interactions. CIOMS WG IX is to develop a pragmatic consensus publication that would contain a harmonized list of tools for managing risks of medicinal products intended for human use, as well as considerations governing potential application of these tools. In an augmentation of its standard procedures, CIOMS will endeavor to consult with stakeholders, including patient groups, during the development of the CIOMS IX recommendations.

### **PROCESS**

The first meeting was held at the European Medicines Agency, London, in 2010. This has been followed by a number of face-to-face meetings at different locations. It is anticipated that the WG will continue its work for 3 years, ending with a publication in 2014.

### **RECOMMENDATIONS**

The publication is expected to present recommendations related to its scope with focus on risk minimisation and specifically additional risk minimisation tools.

## **CIOMS WORKING GROUP X CONSIDERATIONS FOR APPLYING GOOD META-ANALYSIS PRACTICES TO CLINICAL DATA WITHIN THE BIOPHARMACEUTICAL REGULATORY PROCESS**

### **BACKGROUND**

Meta-analyses have been increasingly used in the scientific evaluation of efficacy and safety for benefit–risk assessments, as well as pricing and reimbursement of biopharmaceutical products. When applied to relevant datasets with a careful understanding of the strengths and limitations of the data source(s), meta-analyses can save time and

resources and positively contribute to public health. Pooling available data from different studies is intended to increase the number of observations and thereby improve the power to detect effects of interest. However, there are methodological aspects that always need consideration and guidelines, and a number of articles of how to conduct and report meta-analyses have been published (Bero and Rennie, 1995; Egger and Smith, 1997; Higgins and Green, 2011).

During the last several years, the outcome of meta-analyses has been both debated and used as evidence within the regulatory process of human medicinal products. Sometimes the interpretation of meta-analyses has been controversial and has contributed to different regulatory actions on the same product. This specific use has revealed several aspects that are in need of further consideration and, if feasible, harmonization.

## SCOPE

The discussion is still ongoing. It has been decided to focus mainly on meta-analyses of safety data. Apart from many methodological caveats, there are also other important issues to consider, such as availability of comprehensive study information and access to sources of all relevant data, resources to reanalyze available data, and the possibility to interact with the researchers involved in the original studies. The combining of available information from both randomized clinical trials and epidemiological studies to generate an integrated result is controversial. Criteria as to how this should be done, particularly for safety data, need to be elaborated and general principles should be established.

## PROCESS

This WG had its first meeting at the WHO in Geneva in 2011. It is envisioned that the WG will have a series of meetings over a period of 3 years, aiming for a publication shortly thereafter.

## RECOMMENDATIONS

Once the work of the group is finalized, it is expected to present recommendations related to the scope of its mandate. Recommendations are

also needed regarding access to relevant unpublished studies and data submitted only to regulatory agencies or remaining in the files of biopharmaceutical companies. With increasing amounts of data available in digitized form, meta-analyses of clinical data will likely also increase. Thus, there will be a commensurate demand for publication and communication of results. The perception of the public is of major importance. This will impose requirements on the publisher/journalist concerning the understanding of methodological caveats and how the publication will impact on regulatory processes, reimbursement possibilities, patient preferences, and physicians' treatment practices. It is expected that points to consider regarding good publisher practice will be further elaborated by the WG and points to consider incorporated in the recommendations.

## A NEW CIOMS WORKING GROUP ON VACCINE SAFETY

A new CIOMS WG was established in 2013. The first meeting was held at the EMA, London, May 29–30, 2013. The new WG links to the Vaccine Safety Blueprint of the WHO. This is a global strategic plan for all stakeholders in vaccine safety aiming to assist low- and middle-income countries and to contribute to a global vaccine safety support infrastructure. The Global Vaccine Safety Initiative (GVSI) of the WHO is the implementation mechanism for the Blueprint.

The new CIOMS WG on Vaccine Safety was established in order to provide a forum for information exchange and interaction between all stakeholders, as well as to establish a “think-tank” that will develop and propose new concepts to GVSI and other global harmonization efforts in the field.

The main objectives of the CIOMS WG on Vaccine Safety are: (a) to promote a more efficient and rapid collection and exchange of information between national regulatory agencies, multilateral agencies, and vaccine manufacturers; (b) to develop and endorse harmonized tools and methods for vaccine safety monitoring activities between national regulatory agencies, multilateral agencies, and vaccine

manufacturers; and (c) to propose mechanisms for vaccine safety monitoring in difficult settings (i.e., those with minimal infrastructure).

The ambition of the WG is to produce a consensus publication and/or guides, perhaps in a series, in approximately 2–3 years.

## CONCLUDING REMARKS

CIOMS WGs with their members have been and still are important developmental tools for pharmacovigilance. The description of the work done by CIOMS WGs I–VI in the second edition of this book and of CIOMS WGs VII–X, the CIOMS/WHO WG on vaccine pharmacovigilance, and the CIOMS MedDRA SMQ WG in this edition highlight their great impact on the safety surveillance systems of medicinal products, including vaccines, of both regulatory agencies and industry. The CIOMS WGs have focused on ways forward for global harmonization, identifying gaps of topics not previously addressed by guidelines or regulations, seeking clarifications and simplicity, streamlining terminology and presenting considerations based on scientific review.

The successful working model of CIOMS forming small WGs in an unofficial environment with constructive individuals of relevant expertise, dedicated to the topic and representing different aspects of a shared problem was introduced by the late Zbigniew Bankowski, the Secretary-General of CIOMS from 1974 until his retirement at the end of 1999. It should be emphasized that all members of the WGs have participated fully voluntarily in their own capacity as experts, demonstrating their personal interest to collaborate, for which CIOMS is very grateful. During the last decade, there has been an exponential development of safety systems and regulations worldwide. However, innovations and improvements will always be needed within the area of safety surveillance. In the future, an increased involvement of patients and patients' organizations is anticipated, and new challenges and requirements may be identified. Promoting public health globally is of the utmost importance, and hopefully future CIOMS WGs will be able to continue supporting developments within this area

and contribute to globally sustainable safety surveillance systems.

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# Terminologies in Pharmacovigilance<sup>1</sup>

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## INTRODUCTION

This chapter presents the most widely used terminologies or dictionaries that are used to encode medicines, adverse events and other medical information relating to patients who are enrolled in clinical trials or who experience adverse reactions to marketed medicines. The aim of coding is to impose order on the large number of ways in which medical conditions may be described and on the huge number of medicines to which patients may be exposed. The objective is to accurately represent the information in a consistent manner so that the data can be entered into a computer database. The intention is that the relevant information can then be retrieved from the database at the case level – concerning an individual patient or subject and their medical history or adverse event(s) experienced –

or as aggregate data relating to one or more specified medicines that can then be analyzed and tabulated.

## MedDRA®: MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES

### BACKGROUND

MedDRA® is a structured vocabulary of medical and other terms relevant to the development and use of medicines in humans. It was designed for use in the pharmaceutical industry/regulatory environment, to support all stages of the regulatory process concerning human medicinal products. It began life in the early 1990s as a refinement of the dictionary being developed for the UK regulatory agency's postmarketing safety database. Developed by an international committee of regulators and industry staff, the new terminology had its first incarnation as MEDDRA (Medical Dictionary for

<sup>1</sup> MedDRA® trademark is owned by IFPMA on behalf of ICH.

Drug Regulatory Affairs) in 1993, then being nurtured and transformed by the International Conference on Harmonisation (ICH) M1 Expert Working Group into the subtly renamed MedDRA (Medical Dictionary for Regulatory Activities) (Brown *et al.*, 1999).

Its release as an international ICH-approved standard took place in March 1999. By this time, its ownership had been taken over by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for ICH, with oversight by the MedDRA Management Board answerable to the ICH Steering Committee. However, the interface with users, who purchase access rights through a system of licensing, is via the MedDRA Maintenance and Support Services Organization (MSSO; <http://www.meddra.org>) and the corresponding, but distinct, Japanese Maintenance Organization (JMO). The work of these bodies is undertaken on a commercial basis – currently by Northrop Grumman (for MSSO) and the Pharmaceutical and Medical Device Regulatory Science Society of Japan (for JMO). The MSSO and JMO release to subscribers updated versions of MedDRA (currently) every 6 months by Internet download.

Guidance for the use of MedDRA has been developed by the MSSO: this comprises an Introductory Guide that is provided to subscribers, as well as guidance on some MedDRA-specific issues, such as version control. In addition, ICH-endorsed guidelines on term selection (MedDRA Term Selection: Points to Consider. ICH-Endorsed Guide for MedDRA Users; see <http://www.meddra.org>) and on database searches and data presentation (MedDRA Data Retrieval and Presentation: Points to Consider. ICH-Endorsed Guide for MedDRA Users on Data Output; <http://www.meddra.org>) are issued (and updated at intervals) by a joint industry-regulators ICH working group. Another working group, under the aegis of CIOMS, has developed standard pharmacovigilance searches, the Standardised MedDRA Queries (SMQs, 2005).

## SUBSCRIPTIONS

MedDRA is available by subscription to the MSSO or JMO. The commercial subscription provides for

use throughout a company and its wholly owned subsidiaries. The commercial subscription supplies the subscribing company with two updated versions of MedDRA each year, together with the facility to request changes to MedDRA and other privileges (e.g., access to user groups). Changes that are accepted by the MSSO are referred to as supplemental changes, posted on the MedDRA website ([www.meddra.org](http://www.meddra.org)), and made available for general use in the next version of the terminology.

The commercial subscriptions are based on the annual revenue of the company, as published in the annual report. Regulatory authorities and non-profit organizations are eligible for free subscriptions, whilst there is a charge for system developers. There are additional charges for Japanese and Chinese translations.

## CONTENTS

The MedDRA terminology contains more than 70 000 terms for medical conditions, syndromes, diagnoses, clinical signs, symptoms, laboratory and clinical investigations, social circumstances, device-related issues, medication errors, and product quality issues. It thus differs from other dictionaries, such as WHO-ART (World Health Organization Adverse Reaction Terminology), which is more than an order of magnitude smaller and principally composed of adverse reaction terms. Since the initial release of MedDRA (v2.1) in March 1999, the terminology has included numeric or symbol codes from earlier terminologies. The codes are links from other terminologies to similar or identical terms in MedDRA. This includes codes from COSTART, WHO-ART, ICD9, ICD9-CM, HARTS, and J-ART. The intention was that the terms from these other dictionaries and classifications are retained in MedDRA mainly at the data entry level (lowest level term, LLT) to facilitate transfer of previously coded data from an existing safety database to a database using MedDRA – so-called “legacy data migration.” However, because most organizations have long since migrated their data to MedDRA, and to avoid potential confusion as these codes have not been maintained or updated since the original release of MedDRA, the MSSO has removed these codes

from all of MedDRA's files starting with the release of MedDRA v15.0 (March 2012).

MedDRA does not include terms for drug or device names (unless, exceptionally, these represent a typical medical diagnosis, such as *Digoxin toxicity*). It does not provide definitions of terms (and so perhaps does not strictly comply with the dictionary definition of a "dictionary"), although some are provided in SMQs. It does not include demographic descriptors within the text of the terms, such as those describing gender, age or race – unless these are a component of a discrete medical condition, such as *Infantile spasms* or *Cancer of male breast*. MedDRA also does not include numerical expressions within the terms, although there are again some exceptions such as *Type II hyperlipidaemia*; nor does it provide measures of severity. Once more, there are some exceptions, as in *Severe mental retardation* or *Grade 1 hypertensive fundus*. The implication is that MedDRA is intended for use with a database that can capture information about drug name, patient demography, and disease severity independently of MedDRA itself. It should be noted that MedDRA is limited to human experience: animal pharmacology and toxicology and veterinary terms are outside its scope.

## TRANSLATIONS

MedDRA is available in English: British English spelling appears in all term levels of the MedDRA hierarchy, whilst American English spelling is present only as LLTs. Translations are available in Chinese, Czech, Dutch, French, German, Hungarian, Italian, Japanese, Portuguese, and Spanish. Preservation of the unique MedDRA numerical code associated with each term facilitates translation from one language to another.

## APPLICATION

From its inception, MedDRA was intended for use throughout the regulatory process of the development of medicines in humans and also during their subsequent marketed use. In clinical studies, it can be used for recording baseline medical and social history, the names of clinical investigations and for recording and reporting adverse events. It can also

be used to describe adverse events in the Investigator Brochure, in Development Safety Update Reports, and in the safety sections of interim and final study reports. In the European Union (EU), its use is required for electronic reporting of individual case safety reports (ICSRs) to the EMA's EudraVigilance regulatory safety database. The ICH M4E(R1) guideline (ICH Harmonised Tripartite Guideline, 2002) on the Common Technical Document recommends the use of MedDRA in summary tables of adverse events to be included in the registration dossier for a new product (although the tables published as examples in the final guideline itself do not seem to use MedDRA!).

For marketed medicines, MedDRA may be used to present adverse reactions in the Company Core Safety Information and in reference safety information such as the package insert and Summary of Product Characteristics (SmPC), this latter being the subject of regulatory guidelines in Europe (EC, 2009).

The use of MedDRA for the recording and expedited reporting of adverse reactions for marketed products is required by regulation in the EU and Japan. Whilst the FDA accepts expedited reports coded in MedDRA, this is not currently mandatory. The use of MedDRA is recommended for expedited reporting to Health Canada and it is required for use in the product monograph. A requirement for its use for expedited reporting is also described in Australian regulatory guidelines.

The scope of MedDRA for use in ICSRs is summarized in the ICH E2B(R2) guidelines (ICH, 2001), to include coding of the following data fields: medical history of disease and surgical procedures; past drug history – indications and reactions; adverse reaction or event; therapeutic indication for suspect drug; effects of rechallenge; reported and autopsy-determined cause of death; and sender's diagnosis. An additional use is in the recording of findings of investigations of the adverse event. MedDRA is also required for use in the periodic safety update report in summary event tabulations.

## STRUCTURE

MedDRA is supplied as flat ASCII files. These files are linked and arranged in a hierarchical matrix.

Table 7.1 MedDRA hierarchy (version 16.0) (note: includes non-current terms).

Number of terms	Level of term	Example
26	System Organ Class	Respiratory, thoracic, and mediastinal disorders
334	High Level Group Terms	Lower respiratory tract disorders (excl. obstruction and infection)
1717	High Level Terms	Lower respiratory tract inflammatory and immunologic conditions
20057	Preferred Terms	Alveolitis allergic
71326	Lowest Level Terms	Pneumonitis allergic

Each MedDRA term is presented as words and also comprises an eight-number code. The terms are organized within 5 hierarchical levels: LLTs; Preferred Terms (PTs); High Level Terms (HTLs); High Level Group Terms (HLGTs); and System Organ Classes (SOCs) (Table 7.1). Conceptually, it can also be considered that the terms are arranged into 26 vertical axes, each represented by an SOC.

LLTs – around 71 000 in number as of MedDRA v16.0 – are at the bottom of the hierarchy and consist of synonyms, lexical variants, and other similar representations of specified medical or associated conditions. These terms are intended for entry onto a database for purposes of “coding” the data. The large number of available LLTs provides a high degree of probability that the words used by the individual (the verbatim or “as reported” term) – for example, from a doctor reporting an adverse reaction – will be represented in MedDRA as an identical, or very similar, LLT. However, some LLTs are referred to as “non-current.” These are obsolete, ambiguous or misspelt terms, sometimes inherited from other terminologies, or ones that breach MedDRA’s rules in some way, or that are in some other way unacceptable for routine use. They are retained in MedDRA to facilitate conversion of historical coded data but should not be used for

Table 7.2 Lowest Level Terms under a PT (MedDRA v16.0).

Alveolitis allergic
(“Ventilation” pneumonitis)
Alveolitis allergic*
Alveolitis extrinsic allergic
Bagassosis
(Baggasosis)
Bird fancier’s lung
Bird-fanciers’ lung
Extrinsic allergic alveolitis
Farmer’s lung
Farmers’ lung
Humidifier lung
Malt worker’s lung
Malt workers’ lung
Maple bark-stripers’ lung
Maple-bark-stripers’ lung
Mushroom workers’ lung
Mushroom-workers’ lung
(Other allergic pneumonitis)
(Other specified allergic alveolitis and pneumonitis)
Paint-stripper’s asthma
Pneumonitis allergic
Pneumonitis hypersensitivity
Suberosis
Summer-type hypersensitivity pneumonitis
Unspecified allergic alveolitis
(Unspecified allergic alveolitis and pneumonitis)
Ventilation pneumonitis
Wood worker’s lung

\*Note: each PT is duplicated as an LLT. Non-current terms are shown in parentheses.

coding new data. MedDRA terms are never deleted from the terminology, although terms may be demoted to the lowest level and then made non-current.

Similar LLTs are linked to the same PT, of which (as of MedDRA v16.0) there are of the order of 20 000. An example is shown in Table 7.2. Each PT is also duplicated as an LLT. The PT level is that favored for use in case retrieval and data presentation, each PT ostensibly representing a unique medical concept or a medically robust combination concept (e.g., PT *Diabetic nephropathy*). PTs associated with similar medical conditions are in turn grouped under some 1700 HTLs. Examples of PTs grouped under an HLT are shown in Table 7.3. HTLs are grouped as clusters under 300 or so

Table 7.3 PTs under a High Level Term (version 16.0) (representative sample of terms).

Lower respiratory tract inflammatory and immunologic conditions
Allergic granulomatous angiitis*
Alveolitis
Alveolitis allergic
Alveolitis necrotising
Pulmonary sarcoidosis
Pulmonary vasculitis
Rheumatoid lung
Systemic sclerosis pulmonary

\*Primary location is SOC Immune system disorders.

Table 7.4 High Level Terms under a High Level Group Term (version 16.0).

Lower respiratory tract disorders (excl obstruction and infection)
Lower respiratory tract inflammatory and immunologic conditions
Lower respiratory tract radiation disorders
Occupational parenchymal lung disorders
Parenchymal lung disorders NEC
Pulmonary oedemas

NEC: not elsewhere classified.

Table 7.5 High Level Group Terms under a System Organ Class (version 16.0) (representative sample of terms).

Respiratory, thoracic and mediastinal disorders
Bronchial disorders (excl neoplasms)
Congenital respiratory tract disorders
Lower respiratory tract disorders (excl obstruction and infection)
Respiratory tract infections
Respiratory tract neoplasms
Thoracic disorders (excl lung and pleura)
Upper respiratory tract disorders (excl infections)

HLGTs, an example of which is shown in Table 7.4. HLTs in turn are distributed among 26 SOCs, as shown in Tables 7.5 and 7.6.

These hierarchical groupings help bring together similar medical conditions for purposes of case-finding and presentation. Thus the HLTs and

Table 7.6 System Organ Classes (internationally accepted order).

Infections and infestations
Neoplasms benign, malignant, and unspecified (including cysts and polyps)
Blood and lymphatic system disorders
Immune system disorders
Endocrine disorders
Metabolism and nutrition disorders
Psychiatric disorders
Nervous system disorders
Eye disorders
Ear and labyrinth disorders
Cardiac disorders
Vascular disorders
Respiratory, thoracic, and mediastinal disorders
Gastrointestinal disorders
Hepatobiliary disorders
Skin and subcutaneous tissue disorders
Musculoskeletal and connective tissue disorders
Renal and urinary disorders
Pregnancy, puerperium, and perinatal conditions
Reproductive system and breast disorders
Congenital, familial, and genetic disorders
General disorders and administration site conditions
Investigations
Injury, poisoning, and procedural complications
Surgical and medical procedures
Social circumstances

HLGTs – which we will refer to as “grouping terms” – may help to subdivide large tables of aggregate data, as shown in Table 7.7. As with some other terminologies and classifications (e.g., WHO-ART or the International Classifications of Diseases), MedDRA is referred to as being “multiaxial.” This means that a PT (with its subordinate LLTs) may be represented in more than one SOC. MedDRA designates one SOC as being “primary,” for purposes of data presentation. The other locations (up to seven) of the PT are referred to as “secondary” locations. An example of the multiaxial structure of MedDRA is shown in Table 7.8.

A problem arises for some users of MedDRA because their database systems do not adequately handle the MedDRA data model. Hence, they may be unable to utilize the secondary location of terms. This is unfortunate, as secondary locations facilitate finding all cases relevant to a particular medical condition. Thus, for example, if there is interest in

Table 7.7 Display of data using primary System Organ Classes.

	HLT	PT
<b>SOC: Blood and lymphatic system disorders</b>		
<i>HLGT: Anaemias nonhaemolytic and marrow depression</i>		
HLT: Anaemias NEC	5	
PT Anaemia	3	
PT Hypochromic anaemia	2	
HLT: Marrow depression and hypoplastic anaemias	2	
PT Aplastic anaemia	2	
<i>HLGT: Haemolyses and related conditions</i>		
HLT: Anaemias haemolytic immune	2	
PT Coombs positive haemolytic anaemia	2	
HLT: Anaemias haemolytic NEC	1	
PT Haemolytic anaemia	1	
<i>HLGT: Platelet disorders</i>		
HLT: Thrombocytopenias	2	
PT Thrombocytopenia	1	
PT Thrombocytopenic purpura	1	
<i>HLGT: White blood cell disorders</i>		
HLT: Neutropenias	5	
PT Agranulocytosis	2	
PT Neutropenia	3	
<b>SOC: Cardiac disorders</b>		
<i>HLGT: Cardiac arrhythmias</i>		
HLT: Cardiac conduction disorders	3	
PT Adams-Stokes syndrome	1	
PT Atrioventricular block	2	
HLT: Rate and rhythm disorders NEC	6	
PT Arrhythmia	2	
PT Extrasystoles	3	
PT Nodal arrhythmia	1	
HLT: Supraventricular arrhythmias	5	
PT Atrial fibrillation	3	
PT Atrial flutter	2	
HLT: Ventricular arrhythmias and cardiac arrest	5	
PT Cardiac arrest	2	
PT Torsade de pointes	3	

finding all reports of ventricular arrhythmias, it is helpful that cases of *Sudden death* (primary location of the PT is in SOC *General disorders and administration site conditions*) would be retrieved in a search of SOC *Cardiac disorders* under HLT *Ventricular arrhythmias and cardiac arrest*, as the term has a secondary location there – if the database system functions adequately. This will be consid-

ered further in the section “Database Searches and Data Retrieval.”

## RULES AND CONVENTIONS

There are several MedDRA rules and conventions, some of which are presented here.

First, there are some linguistic/lexical conventions. Abbreviations are permitted if these are in common usage and unambiguous. An example is *ALT increased* as an abbreviation for *Alanine aminotransferase increased*. These abbreviations are LLTs and are unpunctuated.

Another convention concerns word order. This is generally as in normal language at the PT level, unless the terms constitute a list or index, such as *Pneumonia salmonella*, *Pneumonia staphylococcal*, *Pneumonia streptococcal*, and so on. PTs in English use the British spelling (*Oedema*, *Anaemia*, *Oesophagitis*). American English is represented at the LLT level. It is important to remember this, otherwise when looking at tables of adverse event data that are arranged alphabetically as PTs under SOC, for example, it is possible to miss events due to these spelling conventions.

Another convention concerns the anatomical location of terms under primary and secondary SOCs. In most instances, PTs relating to diseases or signs and symptoms are assigned to the SOC relating to the site of the prime manifestation. So, for PT *Dyspnoea*, the primary SOC is SOC *Respiratory, thoracic and mediastinal disorders* and there is a secondary link to SOC *Cardiac disorders*. However, there are the following exceptions:

- Congenital conditions and hereditary anomalies have their primary location in SOC *Congenital, familial and genetic disorders*. So the PT *Heart disease congenital* has its primary location there, with a secondary location under SOC *Cardiac disorders*.
- Infections have their primary location in SOC *Infections and infestations*. So, *Pharyngitis streptococcal* has its primary location in that SOC, with a secondary location under SOC *Respiratory, thoracic and mediastinal disorders*.
- Terms for neoplasms are assigned to SOC *Neoplasms benign, malignant and unspecified (incl*

Table 7.8 Multiaxial linkages for the PT *Purpura* (version 16.0).

	Primary SOC	Secondary SOC	Secondary SOC
SOC	Skin and subcutaneous tissue disorders	Blood and lymphatic system disorders	Vascular disorders
H LGT	Skin vascular abnormalities	Coagulopathies and bleeding diatheses (excl. thrombocytopenic)	Vascular haemorrhagic disorders
HLT	Purpura and related conditions	Purpuras (excl. thrombocytopenic)	Bruising, ecchymosis, and purpura
PT	Purpura	Purpura	Purpura
LLT	Purpuric rash	Purpuric rash	Purpuric rash

*cysts and polyps*) as the primary SOC, with the body site as the secondary SOC; this does not apply to cyst and polyp terms.

These primary SOC assignment rules were instituted in order to aggregate these issues into specific places in MedDRA to facilitate signal detection.

An important convention is that a distinction is made in MedDRA between reports of an investigational finding and reports of an apparent medical condition. Thus, a report of hyponatremia would be coded with the LLT *Hyponatremia*, for which the corresponding PT is in SOC *Metabolism and nutrition disorders*. However, a report of low serum sodium would be coded with the LLT *Serum sodium decreased*, for which the PT is present in the SOC *Investigations*. This is particularly important, because terms in SOC *Investigations*, like those in SOC *Social circumstances* and SOC *Surgical and medical procedures*, have no secondary SOC locations in MedDRA. Hence, similar cases might be represented in two separate locations in a table – some under SOC *Investigations*, others under the SOC for the respective body system or disease process. Another example: *Atrioventricular block first degree* is in SOC *Cardiac disorders*, whereas *Electrocardiogram PR prolongation* – the manifestation of this condition as an investigation finding – is in SOC *Investigations*.

A rule regarding the structure of MedDRA is worthy of mention here. Whilst a term may be represented in more than one SOC – multi-axiality – it cannot be present under more than one grouping term within a SOC. Thus, a PT is only associated with one HLT and one H LGT within its primary

SOC. It may be associated with a different (single) HLT and (single) H LGT in each of its secondary SOCs. Hence, for example, the PT *Gastric ulcer haemorrhage* is associated with the HLT *Gastric ulcers and perforation* in SOC *Gastrointestinal disorders*. It cannot therefore also be associated with the HLT *Gastric and oesophageal haemorrhages* in the same SOC. This has important implications for database searches (Brown, 2003; Bousquet *et al.*, 2005) that will be referred to under that heading below.

## CODING WITH MedDRA

The process of coding adverse event or other medical information with MedDRA involves the use of computer software: either a “browser” or an “autoencoder.” These are available commercially, or a free desktop browser may be downloaded from the MedDRA website or users can access a free web-based browser. A browser permits the user to search MedDRA for an LLT to match the verbatim or “as reported” term. Most browsers provide some type of Boolean search facility, with “and/or” commands, or the possibility to search for LLTs beginning with, or containing, selected parts of words (“bottom-up” navigation). Many browsers also present a view of the MedDRA “tree” and enable this to be searched starting with the SOC likely to contain the concept being searched, and then drilling down through the H LGT, HLT and PT until appropriate LLTs can be viewed and selected (“top-down” navigation). An illustration of the appearance of MedDRA using a browser is shown in Figures 7.1 and 7.2.

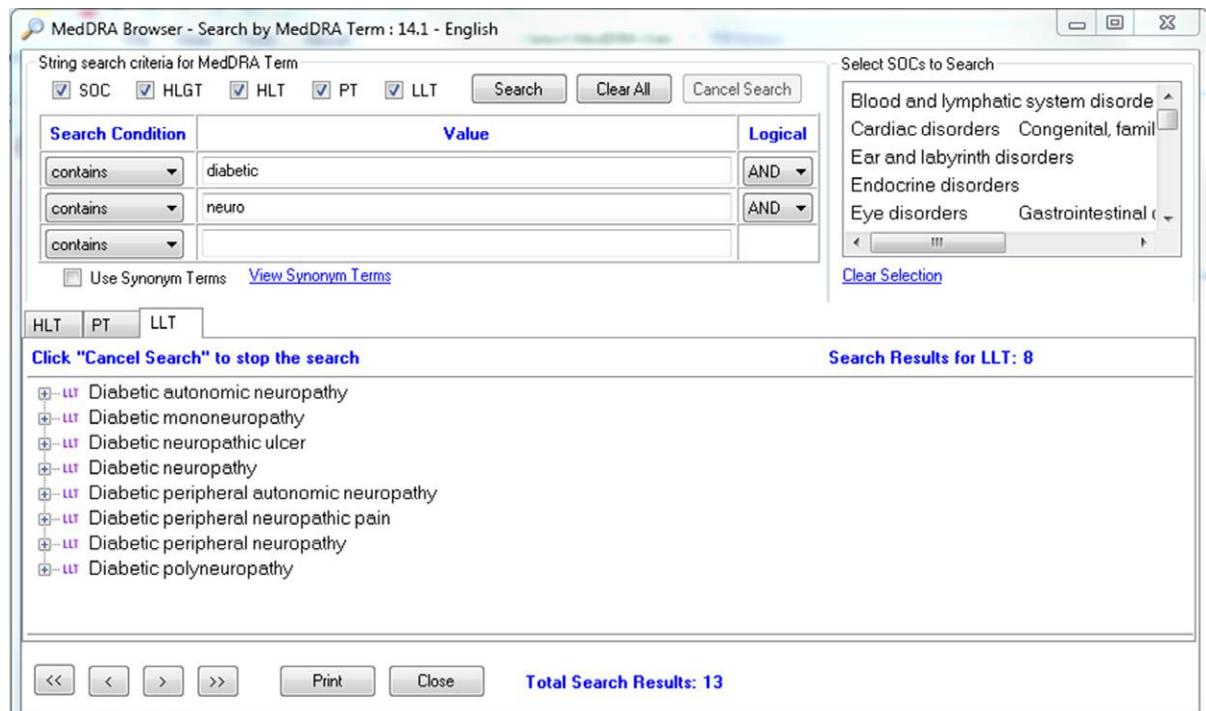


Figure 7.1 Bottom-up search using a browser. Reproduced with permission of MedDRA Maintenance and Support Organization (MSSO).

Autoencoders may have the additional capability of scanning narrative texts and presenting expressions likely to need coding. They may also store selections of LLTs that closely match verbatim terms coded historically, in order to improve consistency of term selection. They might also automatically code collections of verbatim terms, presenting the user with a list of identical or closely matching LLTs that can then be confirmed as being acceptable or rejected.

The ICH M1 Points to Consider Working Group maintains and develops a guide for MedDRA users on the selection of terms used to code clinical information (MedDRA Term Selection: Points to Consider). This document is updated with each release of MedDRA and is available on the MedDRA website. The reader of this chapter should refer to the guidelines for examples and details. Accurate and consistent coding of data are vital for the appropriate analysis and evaluation of safety data and the Term Selection guidelines emphasize the

need for training on MedDRA for personnel involved in its use.

## DATABASE SEARCHES AND DATA RETRIEVAL

This section considers principally the identification of cases of related medical conditions. In this respect, MedDRA provides some features that assist in the process, and also some challenges. Database searches and retrieval of data are performed for several purposes, including the review of possible safety signals, responding to medical information requests or regulatory authority enquiries about safety and so on. The search strategies and methods used to search for and retrieve the data might be different depending on the intended use of the output.

In general, it is the PT that is the focus of searches of safety databases. However, the categorization of these within MedDRA under primary SOC and then under HLGT and HLT assists in finding

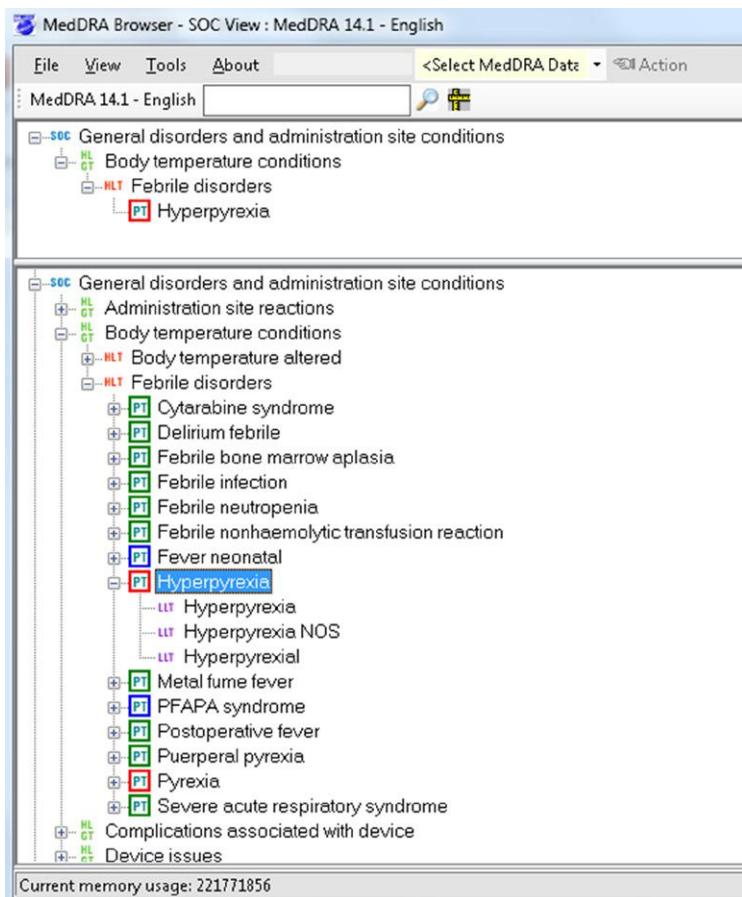


Figure 7.2 Top-down search using a browser. Reproduced with permission of MedDRA Maintenance and Support Organization (MSSO).

relevant cases according to medically relevant groupings. The fixed link between the PT downwards through the LLT, and hence to the case that was originally the subject of the report, provides the mechanism for identifying and retrieving the cases.

The multiaxial structure of MedDRA helps the user find terms related to the medical concept being searched for by presenting the terms in more than one SOC location, should this be appropriate medically. For example, a search of a database for terms relevant to cardiac failure might reasonably focus on SOC *Cardiac disorders*. If a multiaxial search is performed, this would additionally find relevant PTs for various dyspneas under the HLT *Dyspnoeas* and HLGT *Cardiac disorders signs and symptoms* even though their primary location is in SOC *Respiratory, thoracic and mediastinal disorders*.

Like-wise, the PTs for *Cardiac death*, *Sudden cardiac death* and *Sudden death* are found in their secondary location in SOC *Cardiac disorders* as well as in their primary location under SOC *General disorders and administration site conditions*.

However, it is essential to remember that terms in SOC *Investigations* (and also those in the SOC *Social circumstances* and SOC *Surgical and medical procedures*) do not have secondary locations in other SOCs. It is therefore necessary to look in those SOCs if relevant terms are not to be missed. It is also important to keep in mind that multiaxial locations in MedDRA are an aid to case finding and data retrieval but they should not be considered comprehensive (Brown, 2003).

It is the very attribute of MedDRA that is most useful for coding – its high specificity and large size – that presents challenges for database searches and case retrieval. For example, a table showing adverse events for a product might be presented as PTs under primary SOC location. For a large database, a printout of this table might run to many pages. Selecting the PTs relevant to a particular medical condition might be quite difficult, if these are only presented in alphabetical order (Brown and Douglas, 2000). In addition, it would be necessary to look at several SOCs – including SOC *Investigations*.

It may therefore be useful to show the PTs under the appropriate HLTs and HLGTs, in order to break down large tables into relevant groupings, as shown in Table 7.6. However, care still needs to be taken not to miss relevant terms. As an example, in searching for cases relevant to depression, looking in SOC *Psychiatric disorders*, it might be tempting to limit a search to PTs found under the HLGT *Depressed mood disorders and disturbances* and its subordinate HLTs *Depressive disorders* and *Mood alterations with depressive symptoms*. However, relevant terms (and hence cases) might also be found coded with terms under the HLGT *Adjustment disorders (incl subtypes)*, such as *Adjustment disorder with depressed mood*; or some terms under the HLGT *Suicidal and self-injurious behaviours NEC*. In addition, there could be PTs relevant to depression – such as *Intentional overdose* – under the HLGT *Medication errors* in SOC *Injury, poisoning and procedural complications*.

The type of search referred to above is illustrated in Figure 7.3. It is based on identifying relevant

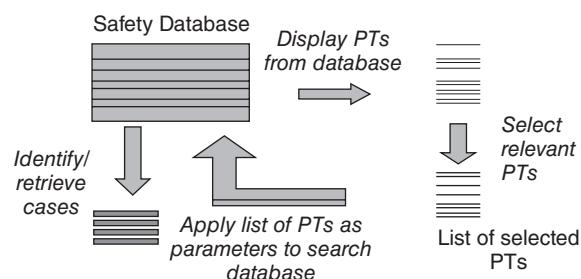


Figure 7.3 Searching a safety database for cases based on PTs in the database.

MedDRA PTs that have been included in a specific database – for one product, from one source, covering a specified time period (Brown, 2003). As such, the resulting list of PTs cannot be used for searching a database for another product or for the same product on a different database, or for the same database at a different time. In any of these situations, additional relevant PTs could be present in the database concerned that may not have been included in the initial search.

An alternative approach to searching the database is shown in Figure 7.4. Here, the search is based on a list of terms derived from the whole of MedDRA, rather than just derived from the database concerned (Brown, 2003). However, it is clearly a major task to construct such searches, and inevitably there will be disagreement over what the constituent terms should include. In order to address this, a CIOMS working group has prepared a series of pre-populated search term lists – called SMQs – which now span the most important topics for pharmacovigilance. At the time of writing, there are 90 SMQs in MedDRA, with over 100 subordinate searches. Examples include SMQs for *Rhabdomyolysis/myopathy*, *Torsade de pointes/QT prolongation*, *Hepatic disorders*, *Haemolytic disorders*, *Acute renal failure*, and *Severe cutaneous adverse reactions*.

SMQs comprise collections of PTs and are further subdivided for differing degrees of specificity and

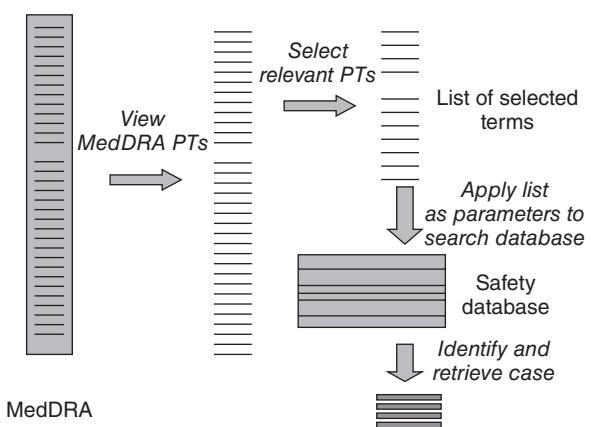


Figure 7.4 Searching a safety database for cases based on PTs in MedDRA.

sensitivity – thus, broad (more sensitive) searches and narrow (more specific) searches comprise subsets of these collections (SMQs, 2005). Some SMQs, such as that for *Anaphylactic reaction*, use an algorithm: in order to qualify for inclusion as a possible anaphylaxis report, a case must include PTs from more than one list of terms (for example, it must include events of both *Bronchospasm* and *Hypotension*, not just one of these terms). Some SMQs, such as *Hepatic disorders*, are hierarchical, with sub-searches of increasing specificity. An example of an SMQ is shown in Figure 7.5.

ICH-endorsed guidelines on data retrieval and presentation are maintained and developed by the same ICH M1 Points to Consider Working Group that creates the MedDRA Term Selection: Points

to Consider document. The MedDRA Data Retrieval and Presentation: Points to Consider document is updated twice a year with each MedDRA release and is available on the MedDRA website.

## DATA ANALYSIS AND PRESENTATION

Here, we are concerned with the quantifying and presentation of adverse event and other medical data that have been coded using MedDRA, as distinct from searching the database and finding the relevant cases. Important issues include the large number of terms in MedDRA, the most appropriate levels and groupings for the required purpose, multiaxiality, and version changes.



Figure 7.5 Standardised MedDRA Query: hepatic disorders.

Table 7.9 Clinical trial adverse events

Parallel group clinical trial: 100 patients in each treatment arm		
Adverse event	Treatment A	Treatment B
<i>Results using legacy dictionary PTs</i>		
Paraesthesia	10	2
<i>Results using MedDRA PTs</i>		
Burning sensation	2	0
Formication	1	0
Paraesthesia	3	2
Paraesthesia oral	1	0
Burning feet syndrome	1	0
Skin burning sensation	2	0

The large number of terms in MedDRA (in particular, PTs) may complicate analyses involving counts of events. For example, if adverse events from a parallel group clinical trial with 100 patients in each treatment arm had been coded using a legacy dictionary such as COSTART, we might see an event such as paresthesia (tingling or burning sensation) occurring in 10% of patients receiving Treatment A and in 2% of those receiving Treatment B. However, if there were actually more specific symptoms of paresthesia described by trial subjects and recorded by the investigators, the differences between treatment groups might be less apparent when using MedDRA PTs, as shown in Table 7.9.

By contrast, if analysis had been carried out using the respective HLT, *Paraesthesia and dysaesthesia*, the 10% versus 2% difference would have been maintained. The use of grouping terms in analyses might also prove problematic, however. Some HLTs – especially those in SOC *Investigations* – include PTs that represent opposing concepts. For example, the HLT *Platelet analyses* includes PTs *Platelet count decreased*, *Platelet count increased*, *Platelet count abnormal* and *Platelet count normal*. Such a grouping would not be helpful if comparing effects on platelets between two treatments. In other instances, MedDRA groupings may include terms representing concepts that, whilst not in

opposition, are significantly different medically. As an example, 10 reports of an adverse event represented by the HLT *Ventricular arrhythmias and cardiac arrest* might relate to 10 cases of *Torsade de pointes* (a particularly serious type of arrhythmia) or 10 cases of *Ventricular extrasystoles* (a generally benign and mild form of rhythm disorder).

A review of some of the adverse events commonly seen in clinical trials (Brown, 2004) showed that the use of MedDRA PTs might increase the number of available terms (and hence “dilute” differences between treatment arms) dramatically. However, in practice, the ratio of MedDRA to WHO-ART PTs in clinical trials has been reported as around 2:1 (Kubler *et al.*, 2005). The effects of MedDRA coding on clinical trial safety data analysis have been the subject of a systematic review by the Nordic Cochran Center (Schroll *et al.*, 2012).

## THE WHO DRUG DICTIONARY

### BACKGROUND

The WHO Drug Dictionary was developed by the WHO Collaborating Centre for International Drug Monitoring – the Uppsala Monitoring Centre – as a tool for signal detection in the program’s database of international ICSRs – VigiBase™. The dictionary is used by the program to code medical information in ICSRs (currently comprising over 7 million case reports from 106 countries). Because of the international nature of the data, there was a need for a dictionary with trade name and substance synonyms from all contributing countries (UMC, n.d.).

The dictionary was designed for signal detection based on the VigiBase data, but since the 1980s it has increasingly been used by pharmaceutical companies for clinical trial and postmarketing pharmacovigilance, and additional data and tools have been developed for these uses.

The dictionary contains a code system known as the Drug Code as well as the anatomical therapeutic chemical (ATC) classification. Additional classifications are being added to the dictionary – both for postmarketing signal detection and for use in clinical trials. The dictionary is available in two

formats: the B and the C format. The two formats contain similar information, but the C format includes more details, so that a trade name that appears in the B format can correspond to several entries in the C format, one for each country, dosage form, and so on (UMC, 2005). This chapter describes the general use of the dictionary but does not go into detail about the two formats.

Until 2004, the drugs entered into the dictionary were primarily those that had appeared in at least one case report; from 2004, additional sources – such as IMS Health and official information from the FDA and EMA – have become the primary sources of information in what is called WHO Drug Dictionary Enhanced.

#### THE WHO HERBAL DICTIONARY

The WHO Herbal Dictionary is an optional add-on to the WHO Drug Dictionary Enhanced which facilitates the correct coding, classification, and analysis of herbal products and their adverse drug reactions and interactions. The need for this has arisen out of the growing popularity of drugs of natural origin (herbal remedies) and the increased risk of serious interactions between conventional and herbal medicinal products.

#### WHO DRUG DICTIONARY IN POSTMARKETING PHARMACOVIGILANCE

The original use of the dictionary was to identify signals in the VigiBase data. All medications are coded with the dictionary, and the Drug Code and the ATC hierarchy are used to find relationships and patterns between substances and adverse reactions. The WHO Drug Dictionary is used by the pharmaceutical industry and associated organizations to code the company's products as well as any concomitant medication. These data on concomitant drugs may provide valuable information in the evaluation of the causality of individual adverse events, in identifying possible drug–drug interactions and may offer hints about underlying disease that are not recorded elsewhere (e.g., the use of asthma medication indicating that the patient has asthma).

#### WHO DRUG DICTIONARY IN CLINICAL TRIALS

The dictionary is used in clinical trials both for the monitoring of clinical safety – where the use is similar to that for postmarketing pharmacovigilance – and in the general coding of all drugs taken by the subject during a study. When a clinical trial protocol is designed it usually contains descriptions of drugs that should not be taken by subjects during the trial, or drugs that, if taken, require a wash-out period or special analysis. These “Medications of Interest” are often identified in lists based on the WHO Drug Dictionary, and the drugs recorded during the trial are analyzed to identify protocol violations or subjects that require special analysis. Many clinical trial sponsors produce *ad hoc* Medication of Interest lists and sometimes the lists are reused in later trials. The WHO Drug Dictionary user community has, together with the UMC, developed standardized general lists for the most common Medication of Interest classes. These lists are available as “standardized drug groupings” (SDGs) for all subscribers to the WHO Drug Dictionary Enhanced.

The SDGs can be based on any property of a drug. They are often divided into subclasses, and a broad/narrow classification is possible, with the broad scope sometimes being used to identify drugs that are related to the main category. For example, estrogens being the narrow scope and drugs with estrogen-like effects in the broad scope; see Figure 7.6.

The SDGs that are based on therapeutic or pharmacological classes are often used as Medication of Interest lists in clinical trials. Some SDGs are based on other properties, such as metabolic pathways and transport proteins. These groupings can be used in both Medication of Interest lists and in signal detection and other analyses. The metabolic and transport protein SDGs are divided into subclasses for inducers, inhibitors, and substrates. These SDGs can be used to help identify interactions both for clinical trial and postmarketing pharmacovigilance purposes.

In clinical trials, the metabolic SDGs can be used to identify potential interacting drugs for inclusion in the Medication of Interest list. The number of SDGs is growing, and new uses are being added.

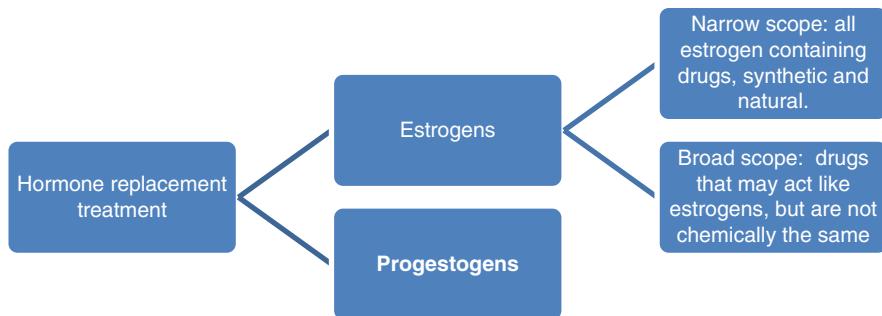


Figure 7.6 Standardized drug grouping for hormone replacement therapy.

For example, in 2012, a list of drugs known to cause QT-prolongation was produced and this can be used to identify concomitant medication that may contribute to the causation of QT prolongation in individual cases.

## THE DRUG CODE

The most important code in the dictionary is the Drug Code. Once a Drug Code is selected it is possible to learn more about the selected drug, such as its active ingredients and ATC classification. A Drug Code identifies a name – a trade name, generic name, or drug class. The Drug Code is a three-tier hierarchy that is an aggregation of Drug Record Number (Drecno), Sequence Number 1 and Sequence Number 2. The code is not only a unique identifier of a name; it also gives information about the active ingredient(s) and salt/ester form of the substance. With herbal products and insulins, the Drug Code can identify other subclassifications of the main ingredient. The *Preferred name* entries have the value “001” in the field Sequence Number 2. The preferred name entries can be subdivided into *Preferred base* entries (entries that have the value “01” in the field Sequence number 1) and *Preferred salt* entries (which have values higher than “001” in the Sequence Number 1). Examples of Preferred name and Preferred base are shown in Table 7.10. The two examples have different Drug Record Numbers, which means that they contain different active ingredients: ampicillin and paracetamol. All entries containing only ampicillin will

Table 7.10 Examples of Preferred name and Preferred base in the WHO Drug Dictionary.

Drecno	Seq 1	Seq 2	Name
000005	01	001	Ampicillin
000200	01	001	Paracetamol

Table 7.11 Representation of different salts in the WHO Drug Dictionary.

Drecno	Seq 1	Seq 2	Name
000005	01	001	Ampicillin
000005	02	001	Ampicillin sodium
000005	03	001	Ampicillin trihydrate

have the same Drug Record Number – regardless of the salts of the substance, different trade names and different countries.

In Table 7.11, the three entries all have the same active ingredient, ampicillin, but in different salt forms: sodium and trihydrate. They all have the same Drug Record Number, 000005, but different Sequence Number 1. All entries containing only ampicillin sodium will have the same Drug Record Number and Sequence Number 1, regardless of the different trade names and different countries: 00000502.

In Table 7.12, all the entries in the example contain ampicillin. The first three entries contain ampicillin in its base form but the following three contain ampicillin sodium. The associated trade names are also shown.

## THE MEDICINAL PRODUCT ID

The C format of the dictionary contains more information than the B format, and one entry in the B format often corresponds to several entries in the C format. In the example in Table 7.13 the entry for Albego in the B format is illustrated (the B format contains a number of additional data elements, but for the sake of this illustration only the Drug Code, drug name and active ingredient are included):

In the C format there are seven entries for Albego, as shown in Table 7.14.

Table 7.12 Representation of trade name, salt and Preferred name in the WHO Drug Dictionary.

Drecno	Seq 1	Seq 2	Name
000005	01	001	Ampicillin
000005	01	002	Ampicin
000005	01	003	Binotal
000005	02	001	Ampicillin sodium
000005	02	002	Binotal
000005	02	003	Polycillin-n

Table 7.13 B format representation of Albego.

Drug Code	Drug name	Active ingredient
00499101003	Albego	Camazepam

Table 7.14 C format representation of Albego.

MP ID	Drug Code	Drug name	Name specifier	Country	Company/MAH	Form	Strength
106812	00499101003	Albego					
1311186	00499101003	Albego		Switzerland	Inpharzam SA		
270746	00499101003	Albego		Switzerland	Inpharzam SA	Coated tablets, film	
270745	00499101003	Albego	Confetti	Switzerland	Inpharzam SA	Coated tablets, film	10 mg
270744	00499101003	Albego	10 confetti	Switzerland	Inpharzam SA		
1243932	00499101003	Albego		Germany			
29651	00499101003	Albego		Germany	Boehringer c.h. sohn ingelheim		

MAH: marketing authorization holder; MP: medicinal product.

These medicinal product IDs identify related entries with different amounts of data. This makes it possible to select an entry based on the information available in the verbatim – no additional information should be assumed.

## THE ANATOMICAL–THERAPEUTIC–CHEMICAL CLASSIFICATION

The ATC classification is an integral part of the WHO drug dictionaries. The ATC classification is maintained by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway. All drugs in the dictionary are assigned to at least one ATC class. In most cases the official ATC classification is used, but drugs of natural origin are often assigned to classes from the Herbal ATC classification that was developed for the WHO Herbal Dictionary. These classes are integrated with the official ATC hierarchy, and analysis can be made using the same methodology as with conventional drugs. In the ATC classification, drugs are divided into different groups according to the organ or system in which they act and their chemical, pharmacological, and therapeutic properties (WHO Collaborating Centre for Drug Statistics Methodology).

The ATC classification hierarchical levels are as follows:

- 1 Fourteen anatomical groups designated by the letters A–V (one letter).

Table 7.15 ATC anatomical groups.

A	Alimentary tract and metabolism
B	Blood and blood-forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides, and repellents
R	Respiratory system
S	Sensory organs
V	Various

Table 7.16 The ATC classification for metformin.

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Oral blood glucose lowering drugs (3rd level, pharmacological subgroup)
A10B A	Biguanides (4th level, chemical subgroup)
A10B A02	Metformin (5th level, chemical substance)

- 2 Therapeutic main groups (two figures).
- 3 Therapeutic/pharmacological subdivision (one letter).
- 4 Therapeutic/pharmacological/chemical subgroup. In this level the pharmacological properties and the chemical nature of the substance are taken into account (one letter).
- 5 Individual substance designated by numbers. This level is not used in the WHO drug dictionaries (two figures).

The hierarchical classification makes it possible to aggregate statistics and to produce queries and listings on different levels. Table 7.15 shows the ATC anatomical groups. Table 7.16 uses the example of metformin to illustrate the structure of the classification.

## USING THE WHO DRUG DICTIONARIES

All analyses commence with code selection. A verbatim description of the drugs taken by the patient or subject is turned into structured coded data. In most cases, the code selection is straightforward: the dictionary entry that corresponds to the verbatim is selected. The verbatim can contain information with different levels of precision, and it is possible to code to a trade name (or even a dosage form and the strength if the C format is used), the active ingredient, or to an “Umbrella entry” if only the drug class is known (pharmaceutical or therapeutic class). The generic names of drugs are in most cases based on the international nonproprietary names systems, but additional synonyms are available (e.g., acetaminophen as a synonym to paracetamol).

The drugs of natural origin in the WHO Herbal Dictionary are coded with the same principles as in the WHO Drug Dictionary Enhanced, so no additional coding conventions or analysis methodologies are necessary if the Herbal ATC classification is used together with the official ATC.

The coding of concomitant medication is in some ways similar to the coding of adverse events, but there are also differences. Thus, new substances and trade names are constantly being added to the market, drugs can change their composition without changing the product name, and sometimes products with the same name are available in different countries but with different compositions. Also, a good match one year may not be the best match a few years later. The WHO drug dictionaries are designed and versioned in order to facilitate management of these situations. These differences compared with the coding of adverse events should be kept in mind when standard operating procedures are written and coding software is designed.

Once the code has been selected, the dictionary can be used as an analysis tool – to identify patients/subjects that have taken a certain active ingredient (using the Drug Code), or class of ingredients (using the ATC or SDGs that can be retrieved from the Drug Code). The coded data can be used for signal detection, aggregation of statistics, and the production of line listings.

The WHO Drug Dictionary User Group portal contains a detailed guide that describes the dictionary in more detail. It also contains best practices/points to consider that describe how the dictionary can be used in certain situations, such as when a drug name appears with more than one composition.

## IN SUMMARY

This chapter has described the main features of MedDRA and WHO-DD, the principal terminologies used for coding medical conditions and medicines in the context of pharmacovigilance. The structures of these terminologies are quite complex, and their correct use is not always intuitive, but this reflects the extreme complexity of the diagnosis and treatment of disease in humans. Whilst there are traps for the unwary, familiarity with these terminologies, an understanding of their architecture and conventions, and thoughtful usage will result in accurate and consistent recording, retrieval, analysis, and presentation of data.

## ACKNOWLEDGMENTS

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# Nonclinical Toxicological Support for Phase I Trials<sup>1</sup>

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## INTRODUCTION

Recent advances in technologies, together with a much better understanding of pharmacodynamics (PD), pharmacology, and pharmacokinetics (PK), are leading to a better and more rational design of new therapeutic agents and also to their early Phase I clinical testing. However, pressure on resources and time demands approaches that are ever more efficient to facilitate the choice of suitable drug candidates for further clinical development. The pharmaceutical industry is, therefore, committed to increasing the numbers of drugs entering humans for the first time.

The development of new pharmaceutical agents consists of several development phases, starting

with drug discovery, nonclinical exploratory tests, Phase I (human pharmacology) including first human dose (FHD) studies, Phase II (therapeutic exploratory), Phase III (therapeutic confirmatory), and finally registration of the compounds at the country-specific authorities and postmarketing studies in Phase IV (therapeutic use). The first activities in clinical drug development are FHD studies. They are at a key point in development, where the first bridge from animal to human studies occurs, and where early safety and tolerability data together with PK data on the drug are collected.

Recent advances in biomedical research have led to an increase in the number of identified therapeutic targets, which in turn has resulted in the synthesis of a large number of molecules that need to be tested further. Current development of drugs can appear to be a rather inefficient process, in that for an average new molecule it takes around 10–15 years. It is also a very challenging process, associated with high costs and a very low success rate. It

<sup>1</sup> Any opinions expressed here are our own, are not necessarily shared by other assessors at the MHRA, and cannot be considered to be MHRA or EU policy.

is estimated that fewer than 10% of new molecular entities entering clinical Phase I testing progress beyond the investigational program. Crucial regulatory, scientific, and operational issues need to be confronted head on in order to avoid high costs and high-profile product failures. It is clear that new tools to help improve the efficiency of drug development are required.

Toxicological studies are done prior to anticipated future human dosing and aim, as their primary objective, to ensure safety of subjects to be dosed in clinical trials (Baldrick, 2008a,b; Brennan *et al.*, 2009; Senderowicz, 2010). To this end, the objectives of toxicity testing can be summarized as to:

- identify that a drug is not suitable for any human use;
- identify what may happen on dosing to humans (or in later studies in animals);
- determine at what dose and exposure effects occur;
- determine reversibility of any toxicity induced; and
- study a mechanism by which an effect arises.

Determining whether a particular set of toxicity studies is capable of supporting a particular clinical trial requires understanding of the objectives and design of that clinical study, as well as elements of the nonclinical dataset that do not fall under the heading of toxicology. These latter elements that complement toxicity studies include studies into the mechanism of action of the drug, its selectivity of action at the primary target, and its biological fate, as determined by kinetic and metabolic studies (see Table 8.1). Adequacy of toxicological studies for a particular clinical study cannot reasonably be judged in the absence of these considerations. Safety is the primary focus in initial Phase I testing; testing prior to human dosing should also permit an estimate of what range of dosing in humans may be needed to produce the intended therapeutic effect. Toxicity data are also key to determining what dose should first be given to humans and the extent of dose escalation proposed.

The first time that a novel, potentially therapeutic agent is given to humans represents a major step in drug development and follows years of effort by

Table 8.1 Nonclinical data complementing toxicity data.

Type of data	Description
Primary pharmacodynamics	Quantitative data that supports the intended therapeutic action
Secondary pharmacodynamics	Effects that are inherent properties of the drug, but not related to the intended therapeutic action
Safety pharmacology	Effects on vital systems, particularly cardiovascular, respiratory, and nervous systems
PK	Characterization of the biological fate of the test agent after its administration

a diverse group of highly skilled individuals. Phase I studies are conducted with the intent to explore properties other than efficacy of a potential therapeutic agent in humans and, most frequently, first-in-human studies are designed to start with a single dose given to healthy volunteers that will have no pharmacological effect, with increasing doses in sequential cohorts given with the intent to determine the maximum tolerated dose.

Subsequently, although now increasingly often within the same protocol, repeated doses will be studied in a similar manner; that is, starting with a low dose. Dose escalation then takes place in sequential cohorts, after a review of available data to make the best judgment that the next dose will be safe and with the eventual intent that the highest dose will produce mild, short-lasting, but notable adverse effects. This initial study will sometimes also include determination of the effect of food on kinetics of the test agent, or of effects in elderly subjects, and can also include a cohort of patients with a mild form of the disease being investigated. The objective of Phase I studies is to define a clinical safety profile, including identification of doses that could be used in future studies in which efficacy in patients will be tested and to describe PK of the agent (Buoen *et al.*, 2005; ABPI, 2011). Subsequently, as clinical testing progresses in patients

in Phase II and III studies, further Phase I studies may be conducted if needed. These may include drug–drug interaction studies or other types of study, including in patients with impaired renal or hepatic function or with radiolabeled versions of the test agent.

Initial human exposure can also be in an “exploratory clinical trial,” in which doses that are below those associated with any pharmacological or toxicological effects are administered (Jones, 2010). The purpose may be to study kinetics, or to examine interaction with a primary pharmacodynamic target, or to compare such properties of multiple test agents to assist in candidate selection for full development (ICH, 2009a).

In rarer circumstances, usually due to expected toxicity of the test agent, initial human testing is conducted in patients. This is especially true for products to treat cancer (Forster *et al.*, 2010; LoRusso *et al.*, 2010), where the intent is to kill the tumorous cell. Limitation on the degree of selective action against the cancer cell can result in a high degree of toxicity. If the first study in humans is to be in patients, the objectives of the Phase I trial are as above, but additionally include consideration of whether the individual patient could benefit. Withdrawing effective treatment in a patient who has no other options poses an ethical dilemma – in this situation, prolonged dosing can continue in patients in the absence of longer term general toxicity studies, where a judgment is made that the indi-

vidual patient benefits (ICH, 2009b). Patients are also enrolled in all Phase I clinical studies with cell-based and gene therapy products (see below).

Toxicological studies provide the rational basis on which to design a clinical study protocol that should ensure safety of each trial subject. This includes justification of doses, duration of dosing, and consideration of changes in exposure (in particular, drug accumulation on repeated dosing) and identification of particular parameters that merit close monitoring in the clinical trial and the suggested duration of monitoring necessary to ensure subject safety.

## TOXICITY DATA REQUIRED TO SUPPORT INITIAL TESTING IN HUMANS OF A NOVEL AGENT

Only drugs that have an apparently acceptable safety profile progress from nonclinical tests to Phase I studies. International expectations for toxicity data have been harmonized to a large degree between differing regions of the world. Regulatory guidance has been developed (ICH, 2009a) that reflects current expectations for those studies that should be conducted to support initial human testing and those that are additionally needed to support later clinical development.

Toxicity data can be grouped as follows (see Table 8.2):

Table 8.2 Toxicological studies for Phase I clinical trials.

Type of study	Description	Comment
<i>In vitro</i>	Typically, studies with human cells exposed to test agent to assess potential for specific risks; e.g., cytokine release, cell proliferation; cellular toxicity screens	Of greater emphasis where there are severe limitations on reliance on <i>in vivo</i> animal data
General toxicity	Assessment of systemic toxicity on repeated dosing in two species for at least relatively as long as the intended clinical exposure	Species relevance and assurance of exposure needed
Local tolerability	Assessment in a single species at the site of application of drug	Assessment of irritation can be included in general toxicity studies
Genotoxicity and carcinogenicity	<i>In vitro</i> and <i>in vivo</i> studies to assess interaction with the genome	<i>In vivo</i> data supersede <i>in vitro</i> data
Reproductive toxicity	Fertility Teratogenicity, usually in two species Peri- and postnatal developmental toxicity	Not usually needed for Phase I Not usually needed for Phase I Not usually needed for Phase I

- *in vitro* studies;
- general toxicity;
- local tolerability, including irritation and sensitization;
- genotoxicity;
- carcinogenicity;
- reproductive toxicity; and
- other types of study that are intended to address specific risks, such as phototoxicity and dependence potential; toxicity to the immune system can also be construed as a component of general toxicity that may require additional specific testing (ICH, 2005b).

### *IN VITRO STUDIES*

To date, there has been little progress in the use of *in vitro* studies as replacements for studies in animals. In some instances, *in vitro* screening with certain types of cell (e.g., skeletal muscle cells, hepatocytes) can assist in identifying potential for a particular type of toxicity. Nevertheless, *in vitro* studies are not yet seen as sufficient to replace testing in an intact living system, although reliance should increasingly be placed on their use as a component of integrated testing (Hartung and Gaston, 2010). Instead, the focus of these studies has been to provide information additional to that available from general toxicity studies in animals. An exception to this may be the use of *in vitro* methods to screen for potential for inhibition of cardiac conduction, leading to prolongation of the electrocardiographic QT interval and effects on ventricular repolarization. This risk is also assessed by *in vivo* safety pharmacology studies (ICH, 2000, 2005a).

It is relevant, however, to note that the MHRA have approved a clinical trial for a new biological compound with no supporting *in vivo* nonclinical toxicity data (Mexit, 2011).

In rare circumstances, no pharmacologically relevant animal species can be identified for use in toxicity studies, or there are quantitative differences between humans and animals such that *in vivo* animal testing provides only limited reassurance of expectation for human safety. In these cases, testing *in vitro* with human cells is often the most relevant data for ensuring safety of trial subjects. In 2006, substantial clinical toxicity arose in a clinical trial

in which a TGN1412, an agonistic antibody targeting CD289, was given to healthy volunteers (Sundaralingam *et al.*, 2006). This elicited calls for much greater reliance on use of human cells and tissues in culture (Bhogal and Combes, 2006; Horvath and Milton, 2009). Subsequent *in vitro* testing was able to indicate that this could have been predicted, but only when the antibody had been immobilized as it was presented to human white blood cells (Stebbins *et al.*, 2007). Even approved monoclonal antibody products have some risk of cytokine release; the capacity of *in vitro* testing to help determine the risk of cytokine release with a novel immunoactive test agent should be assessed in each case (Wing, 2008).

### GENERAL TOXICITY STUDIES

In considering general toxicity studies, the relevance of the species used in these studies and its capacity to potentially predict effects relevant to humans must be demonstrated. Where a particular species is lacking in its capacity to suggest effects of relevance to humans, then that species should not be used in toxicity testing as the data generated are of no relevance to predicting human safety (Bussiere *et al.*, 2009; Brennan *et al.*, 2010; ICH, 2011c). Relevance of species must take into consideration whether the primary pharmacodynamic action of the drug is present. This should include quantitative assessments of both binding and of biological activity. It is often the case that there are quantitative differences in binding activity at the primary pharmacological target between different animal species, and between animals and humans, and this can translate into differences in biological potency. If these are substantial and the animal seems less responsive than humans, this can impact on the judgment as to whether adequate exposure has been achieved in animals to support human dosing at defined doses.

There is divergence in different regions of the world on what to do if the chimpanzee is identified as the only species that responds pharmacologically. In Europe, testing in great apes is effectively banned (EC, 2010). In the unusual circumstance where there is no other appropriate animal species, limited clinical dosing can be supported by *in vitro*

with the test agent that may also be complemented by testing in other species with molecules with some degree of pharmacological similarity to the test agent. In the USA, *in vivo* studies in chimpanzees can be required, where they are the only relevant species, such as has been suggested for hepatitis C (Bukh, 2004). In 2010, however, the US National Institutes of Health (NIH) announce that they will sharply curtail medical research studies using chimpanzees after an expert panel said such studies are rarely warranted. The panel of experts said use of chimpanzees in government-funded medical research should be reserved only for studies where no suitable alternative is available or where testing in people would be unethical, and only for life-threatening or debilitating conditions.

A second aspect of species suitability applies to small chemical drugs, but not to biological products, and relates to characterization of metabolites. Where the animal species can be shown to generate the same metabolites as are identified in human tissue in *in vitro* studies, this supports the selection of that species as suitable for use in general toxicity studies (Baldrick, 2008a). Therefore, it is usually the case that the selection of species used in toxicity studies will be justified with reference to comparative metabolite profiling. Where novel human metabolites are identified by *in vitro* testing prior to any human dosing, then a judgment is needed as to whether it is reasonable to expose humans to the test agent without specific testing of that unique metabolite (ICH, 2009a). Usually, the human-unique metabolite is one of a number of different metabolites and confirmation and quantification of the putative uniquely human metabolite from *in vivo* human dosing will be permitted such that initial Phase I testing can proceed without dedicated testing of the unique human metabolite. Subsequent human testing may need further toxicity testing either of the novel metabolite that has been chemically synthesized for such testing, or testing in a different animals species in which it is generated.

For most novel agents, general toxicity studies should be conducted in two species and, unless there is good cause otherwise, in both genders (ICH, 2009a; EMA, 2010a). These studies should be conducted in compliance with good laboratory

practice (EC, 2004). Blood sampling should be planned, either in animals on study where this is feasible, or in groups of animals dosed in the same way but who are not included in the toxicity endpoints, to permit determination of kinetics. Such toxicokinetic data can be critical if they are used to support intended limits on human exposure in Phase I trials. For instance, a protocol may contain dose escalation criteria to the effect that mean  $C_{max}$  and AUC in trial subjects will not exceed those at the no observed effect level in the more sensitive animal species. In this way, a limit is not explicitly placed on dose administered. This approach requires plans to generate human kinetic data in a timely manner to support such dose escalation considerations.

Usually, general toxicity studies have three dose levels of test agent plus a control group who are treated in the same way except that they are not exposed to the test agent. However, recent developments favor a reduction in the number of test groups in later toxicity studies, if this can be done without compromising the applicability data to be generated (Chapman *et al.*, 2009, 2011; Sparrow *et al.*, 2011). There is very rarely the need to include positive control groups.

General toxicity can be further divided into acute (single-dose) toxicity and repeated-dose toxicity studies. Acute toxicity studies, where one dose of test agent is given, rarely provide information of critical value to ensuring the safety of trial subjects; determinations of lethal doses are also rarely of any interest. As relevant information can be generated from the first dose in repeated-dose toxicity studies, acute toxicity studies do not need to be conducted (ICH, 2009a). There is also little evidence that single-dose toxicity studies are of any value in management of cases of overdose in humans (Chapman *et al.*, 2010). However, where the intended human therapeutic use is as a single dose, acute toxicity studies can suffice, and in this case, and only in this case, acute toxicity studies should be done and comply with good laboratory practice.

Initial repeat-dose studies may represent the first formal assessment of toxicity in that species, and their design can reflect this (Smith *et al.*, 2005). It is not necessary for these first studies to comply with good laboratory practice, where subsequent

repeated-dose general toxicity studies provide data in compliance with good laboratory practices that will be used to support human dosing.

The duration of general toxicity studies in animals should support the intended duration of clinical dosing; that is, toxicity studies in animals should include dosing for at least the same period of dosing as is intended in humans (ICH, 1998, 2009a). In addition, as stated above, one objective of nonclinical development is to assess reversibility of induced toxic changes, and this requires a dose-free period after the last dose has been given. Concerning the assessment of recovery from toxicity, studies do not need to show full reversibility, and it is not necessary to show reversibility in every study (ICH, 2011a). If this has already been described in earlier studies, consideration of these aspects could result in a reduction of the numbers of animals used in general toxicity studies.

If the test agent is a biological product that is proved to be highly immunogenic, long-term repeated dosing studies may be compromised by a neutralizing response, and where this is demonstrated, the futility of conducting further studies has been demonstrated (ICH, 2011c).

Phase I studies that involve dosing to humans of greater than 21–28 days are extremely rare, and where they do occur they will typically be in association with a single dose of product that results in sustained exposure, such as with a monoclonal antibody, or a gene therapy product or use of a viral vector. To support relatively short exposure in clinical trials, the most common dataset to present to support Phase I clinical trials includes general toxicity studies in two species dosed by the intended clinical route for up to 1 month with a recovery period that takes into account the elimination half-life of the test agent. Shorter periods can be accepted, provided the duration in the toxicity studies is at least equal to that intended in the clinical trial. These studies will ideally be supported by toxicokinetic data, and in many instances these data can be used to support estimates of exposure in safety pharmacology studies too (ICH, 1994). The general toxicity studies should suffice to identify if the drug should not be given to humans at all (due, for instance, to significant toxicity at doses judged to be below those needed for therapeutic

activity), should indicate what type of toxicity may arise, and so influence what is monitored closely in trial subjects, should describe at what exposure such effects arise, and indicate whether the effect is expected to be reversible. For the most part, these studies will not indicate a mechanism by which an effect arises.

In early trials, the expected human exposure should not exceed that in animals at or around the no observed adverse effect level (NOAEL) from general toxicity studies, although exceptions can be made to this in particular circumstances where it is shown to be justified on risk–benefit considerations. For instance, where the test agent has anti-cancer potential, this restriction does not apply because off-target effects are expected at doses necessary to kill the cancerous cell.

## LOCAL TOLERABILITY

For Phase I studies, the pharmaceutical form to be marketed is not likely to be known. In most instances, local tolerability and irritation can be adequately assessed in general toxicity studies, whether by examination of the stomach and gastrointestinal tract after oral dosing or by examination of a site of injection. Where an agent is to be given intravenously, testing should include risk of inducing hemolysis and of protein precipitation in *in vitro* tests ideally conducted with human blood. For a product that is applied topically, dermal irritation and sensitization may need to be assessed in additional testing (EMA, 2000).

## GENOTOXICITY AND CARCINOGENICITY (ICH, 1997, 2008)

For Phase I studies, testing for carcinogenic risk is usually considered adequately addressed by genotoxicity testing (Jacobson-Kram and Jacobs, 2005). The short-term nature of use in most Phase I studies and the capacity of genotoxicity testing to identify agents that interact with the genome means that carcinogenicity testing is not required to support Phase I trials. An additional perspective is that *in vitro* genotoxicity tests may have very low specificity; that is, they commonly generate false positive results (Kirkland *et al.*, 2005). In these

circumstances, judgment is required to determine whether a positive finding indicates that there is a credible biological risk to trial subjects or not.

For certain biological products, *in vivo* data on risk of tumor formation are required prior to first human use, as discussed below.

Genotoxicity testing should comprise at least an assessment of gene mutation potential, and this, assuming no mutagenic potential is identified, is sufficient to support single human doses (ICH, 2011b). For multiple doses, a study to assess potential chromosomal damage is additionally expected. For studies in patients, an *in vivo* test is additionally expected; in summary, it is sufficient to have either:

- a test for gene mutation in bacteria, plus
- a cytogenetic test for chromosomal damage plus
- an *in vivo* test for genotoxicity, or
- a test for gene mutation in bacteria plus
- an *in vivo* test for genotoxicity that includes assessment of effects in two tissues (e.g., micronuclei formation in bone marrow and DNA breaks in liver).

For certain biological products, despite use as a single administration, there is long-term, perhaps lifelong, exposure to the test agent. This can apply in the development of cellular products or in the development of gene therapy, where the intent can be to deliver an agent that results in a permanent change in the recipient patient. In this circumstance, long-term follow up of animals dosed on one occasion to assess risk of cancer induction by the test agent may indeed be required prior to any human exposure (EMA, 2008).

#### REPRODUCTIVE TOXICITY (ICH S5)

Reproductive toxicity (ICH, 1995) testing in animals is not usually required prior to Phase I studies. This is because Phase I studies are usually conducted in healthy male volunteers and adequate information to assure safety can be provided from the combination of repeated-dose general toxicity studies of a sufficient duration and genotoxicity data. Even where the study is not limited to males, the potential risk to reproduction can be controlled to an acceptable degree by pregnancy testing and by use

of contraception. The design of most Phase I studies, however, is influenced by a desire to have a homogeneous population to reduce variability in response and most studies specify male subjects. Although not common, some Phase I protocols may specify inclusion of females in a separate cohort, especially if there is greater propensity of the disease in females with the expectation that the majority of those to be enrolled in future trials will be female.

Where repeated-dose general toxicity studies do not suggest any adverse effects on male reproductive organs and genotoxicity data suggest there is no risk, then male subjects can be included in trials in the absence of fertility studies in animals. The protocol should require that males agree to use barrier contraception to prevent transfer in the semen of drug or its metabolites. For women who are not of child-bearing potential (e.g., due to hysterectomy or because they are postmenopausal), no reproductive risk is identifiable and they can be included in trials without reproductive toxicity testing in animals. For women of child-bearing potential, their inclusion in Phase I trials can be accepted in the absence of teratogenicity data from animals where there is a requirement in the protocol for suitable pregnancy testing (e.g., at screening and prior to dosing, but on the same day as dosing) and a requirement to adhere to an effective contraceptive regimen. However, evidence has been cited that pregnancies do rarely still arise, even in later clinical trials where these stipulations are in place (ICH, 2009a); consequently, for later trials, risk assessment based on data from studies in animals is applied. Where nonclinical data suggest some risk, either expected due to the mechanism of action or following findings in pregnant animals, further measures may be required, either requiring further nonclinical data or more stringent pregnancy testing and contraceptive requirements.

#### OTHER TYPES OF STUDY

Studies of this type include those aiming to assess risks such as phototoxicity and dependence potential. Phototoxic risks can be minimized in Phase I trials by controlling the environment of the trial

subject to ensure there is limited exposure to direct sunlight (ICH, 2009a). Potential risks can be assessed by both *in vitro* and *in vivo* studies, but shortcomings in such testing have been recognized (EMA, 2010b). Immunotoxicity can initially be assessed as a component of general toxicity studies. Where there are hazards suggested, these can be followed up in dedicated studies (ICH, 2005b).

## APPROACHES TO SELECTION OF THE FIRST HUMAN DOSE

As noted above, one of the major objectives of nonclinical development, and specifically of toxicity studies is to determine the first dose that is to be given to humans. In all circumstances, evidence should be presented that justifies this as safe, and if there is no argument made, then the clinical trial application should be denied until such is presented. In some circumstances, it is also relevant to consider potential therapeutic activity.

Two regulatory guideline documents exist that address arguments for dose selection (FDA, 2005; EMA, 2007). In addition, there are publications that consider this issue from several perspectives (Reigner and Blesch, 2002; Jones and McBlane, 2011) and from those of predictive PK (Memo-Tetang and Lowe 2005; Lowe *et al.*, 2007; Mahmood, 2009; Sharma and McNeill, 2009), toxicology (Contrera *et al.* 2004; Dorato and Engelhardt, 2005) and as applied to biological products (Vischi and Prince, 2008; Agoram, 2009; Ling *et al.*, 2009; Muller and Brennan 2009; Muller *et al.* 2009; Mould and Green, 2010; Tibbitts *et al.*, 2010).

Justification of the FHD must take into account a range of different considerations. For instance, the test agent could have highly novel pharmacology and there may be no previous agents acting at the same pharmacological target – the perception of risk is different in this situation to one where there are many previous examples of drugs acting in a similar way. This difference can influence the starting dose because the expected toxicity can be more closely inferred by reference to the clinical data with agents acting by a similar pharmacological mechanism. Current practice is to rely on the determination of doses in animals that have no

major adverse effects. This is converted to an equivalent dose in humans by allometric scaling (FDA, 2005) and a safety factor, usually 10-fold, is applied. This suggested dose should be compared with those expected to have pharmacodynamic activity and the dose where minimum anticipated biological activity is estimated, usually by reference to primary pharmacology data. This can additionally include reference to activity of other drugs with the same pharmacological action and which have proven efficacy at known exposures – comparing primary pharmacodynamics of the two agents can allow some estimate of an active dose for the novel agent too. It is unusual to rely on prediction of human kinetic data to justify dose selection. This approach can have to make assumptions about unknown issues, so reducing their predictive utility. However, such an approach can generate estimates of human elimination and half-lives that can influence protocol designs in, for instance, duration of monitoring for cardiovascular effects.

## SPECIAL CIRCUMSTANCES: EXPLORATORY CLINICAL TRIALS, FIRST HUMAN TRIALS IN PATIENTS, VACCINES, GENERIC AND BIOSIMILAR PRODUCTS, CELLULAR PRODUCTS, AND GENE THERAPY

### EXPLORATORY CLINICAL TRIALS

Whereas most drugs will be suitable for conventional development, in some circumstances, it could be beneficial to test very low doses before committing to develop the drug more conventionally. This may be the case where a company has several candidates and wishes to obtain human kinetic data in order to decide on candidate prioritization, or where there is a wish to study interaction with a pharmacodynamic target, for instance one located in the brain, prior to deciding whether to commit to further development. In these circumstances, use of a very low dose in humans could support a decision on whether to continue or stop a development program. This approach applies the principle that use of a very low dose in the trial provides reasonable expectations of safety of trial subjects. This

Table 8.3 Summary of approaches to human microdose studies.

Approach	Limits on dose	General toxicity	Genotoxicity
1	Single dose; $\leq 100\text{ }\mu\text{g}$	Extended single dose study in one species	Not needed
2	$\leq 100\text{ }\mu\text{g}$ dosed $\leq 5$ times	7-day repeat dose study in one species	Not needed
3	Single dose; consider activity and toxicity; $\frac{1}{2}$ NOAEL	Extended single dose study in two species	Ames assay
4	14 days dosing; AUC 1/50th that at lower NOAEL or AUC 1/10th that at highest dose tested	2-week repeat dose study in two species	Ames assay
5	14 days dosing	2-week repeat dose study in rodent + shorter study in non-rodent	Ames assay

Note: see ICH (2009a; Section 7) for further details.

does, however, require quantitative justification of what constitutes a very low dose.

The ICH (2009a) guideline addresses this as summarized in Table 8.3. In brief, single human doses, as in Approaches 1 and 3, can be supported by a single-dose general toxicity study in one species, with or without genotoxicity data, depending on the dose. Repeated human exposure – that is, up to five single doses, each of which is not more than  $100\text{ }\mu\text{g}$  (Approach 2) – can be supported by a 7-day general toxicity study in one species without genotoxicity data. Approaches 4 and 5 represent greater human exposures, and a correspondingly greater amount of toxicity data is requested. However, in each case, the limitation on the clinical exposure, including that these studies are not intended to explore maximum tolerable doses in human subjects, contributes to the reduced amount of toxicological data needed to support this human dosing. Further explanations on exploratory clinical trials can be found in the ICH (2011a) document.

Two points are worth mentioning in relation to exploratory clinical studies. The toxicological data needed are the same regardless of whether the clinical trial subject is a healthy volunteer or is a patient – studies are not restricted to healthy volunteers, but can be conducted with patient volunteers. Second, the results from a clinical study in humans do not remove the need to conduct additional toxicity studies to support subsequent conventional development.

To support conventional Phase I studies subsequent to an exploratory clinical study requires com-

pletion of general toxicity and genotoxicity studies as summarized above. Thus, although such studies could reduce the use of animals in drug development, this is primarily by reducing subsequent development of drugs that would not reach a marketing authorization application stage and not by the clinical study replacing the toxicological studies needed to support conventional dosing. Exploratory clinical studies can contribute to earlier termination of projects, with consequent saving in both animal and human resources.

## FIRST HUMAN TRIALS IN PATIENTS

In this scenario, as well as ensuring the safety of the trial subject and exploring potential toxicity and kinetics of the test agent, there is an additional perspective that the individual patient who has volunteered for this trial either could, or should, receive some degree of personal therapeutic benefit, unlike where the volunteer is a healthy subject and there can be no expectation of therapeutic benefit to that individual. The type of test agent used in this setting usually is one that is perceived to be too toxic to give to healthy volunteers. If the product is being developed to treat cancer, the objective of treatment is to kill the abnormal, but not the healthy, cell. An alternative perspective is where there is expected to be sustained exposure to the test product, such as may occur with cellular therapies or with gene therapy. These are considered further below.

In general, where the first human trial is in patients, the starting dose needs also to give greater

weight to what might be construed as an effective dose. The principle is established that where there is great medical need, as there may well be in patients with cancer, development should aim to avoid exposing too many patients to doses that do not have pharmacological activity (Le Tourneau *et al.*, 2009). From any set of nonclinical data, there will likely be a range of possible doses that could reasonably be argued to be suggestive of clinical efficacy. Such data may take into account a range of different results from *in vitro* and *in vivo* pharmacodynamic testing, from pharmacokinetic data, including protein binding and bioavailability considerations, as well as data from toxicity studies. In this setting, the objective remains to ensure safety of the starting dose; but where dose setting based on toxicity study data would be expected to deliver a dose so low as to be ineffective, higher starting doses can be considered, if justified with reference to expected biological activity.

## VACCINES

Vaccines may be considered to be a special case in drug development because, for the most part, the intended population for product use and for inclusion into clinical trials is healthy, and if the vaccine is effective, then the healthy volunteer will derive some degree of clinical benefit from being treated in the clinical trial. This distinction can readily be recognized, but has little, if any, consequence in respect of the toxicity data needed to support dosing. Toxicity studies for vaccines typically comprise general toxicity studies and, in some cases, reproductive toxicity studies in species that show an immune response (CHMP, 2005; van der Laan *et al.*, 2009).

## GENERIC AND BIOSIMILAR PRODUCTS

Many Phase I studies are conducted for the purpose of establishing that a generic product does indeed have the same pharmacokinetic profile as an originator product. In this case, the trial is conducted by comparing the kinetics of the putative generic product with those of the licensed originator product. If there are no novel impurities at a level

of toxicological concern in the putative generic product, and if it contains only established excipients, then no toxicological data are needed.

The same principles cannot be directly applied to biological products owing to the fact that there is variability inherent in the active principles of such products. There is currently an ongoing debate about whether toxicological studies are needed, and if they are needed, then what they are needed for (Baldrick and Donninger, 2012; Jones *et al.*, 2012). If the principle is applied that the products should be shown to be comparable, whether kinetically or toxicologically, this implies that very large studies capable of detecting a difference of predefined size should be conducted. The numbers of animals required and the nature of the information derived invalidate this approach – clinical data will define whether comparability has been shown. Testing could be done to support clinical development of a putative biosimilar product, but even in this case, if the quality data suggest there are no differences considered to be of significance, then such testing may not be needed.

## CELLULAR PRODUCTS AND GENE THERAPY

These types of product will only be given to patients and it is possible that treatment in a clinical trial may result in life-long changes for each patient (Goldring *et al.*, 2011). Unlike with conventional chemical drugs and most biological products, once the product has been given, it may persist for the rest of the patient's life and be impossible to remove. Consequently, where this is anticipated, as is the case with some viral vectors, or where it could arise with a cellular product, the toxicological data need to be complete prior to the FHD. Toxicity evaluation can be included in combined toxicity and bio-distribution studies. and although the product may only be given at one time, follow up of animals may need to be for 1–2 years prior to starting human dosing.

## ANTICANCER AGENTS

A significant proportion of clinical trials conducted in the UK relate to oncology indications

(approximately 30% of all open UK trials – Jones and Jones, 2012). There are a number of regulatory guidelines available, international (ICH) and EU specific, many of which deal directly or indirectly with oncology products (e.g., ICH, 2009b). The Phase I clinical trials in the development of anticancer drugs usually involve cancer patients whose disease condition is progressive and are expected to have a short life expectancy. The dose levels in these studies are often close to or at the adverse effect dose levels. The design, timing, and flexibility of nonclinical studies for anticancer pharmaceuticals differ from those for most other therapeutic indications (Rosenfeldt *et al.*, 2010). The nonclinical data to support Phase I clinical trials, and the subsequent clinical data from those trials, would normally be sufficient for moving to Phase II and then into second- or first-line therapy in patients with advanced cancer. The primary objective of Phase I clinical trials in patients with advanced cancer is, as well as assessing the safety of the product, to identify a maximum tolerated dose (MTD) and dose limiting toxicity. Accordingly, nonclinical toxicology studies designed to determine an NOAEL, or no observed effect level (NOEL), are not considered essential to support clinical use of an anticancer pharmaceutical.

## PERSPECTIVES ON RISK

Some Phase I studies are typically done after there is evidence from Phase II or III studies to support the contention that the drug has therapeutic potential. Drug–drug interaction studies and detailed exploration of metabolic fate are in this class, and these studies would only be scheduled earlier in development if there are particular reasons for doing so. Dose and posology for these Phase I trials can be determined with reference to clinical data already generated; therefore, for these Phase I studies, no additional toxicological support is required.

The use of animals prior to humans in drug development is predicated on the supposition that information relevant to human safety can be identified by such testing. Where an animal study will

not generate useful information, it should not be done – examples include studies in animals that are not pharmacodynamically responsive to the drug and acute toxicity studies, where longer term general toxicity studies will provide sufficient information.

Studies in animals are incapable of predicting certain drug-induced changes, either because animals are not able to indicate the effect or because they cannot even experience the effect. Certain toxicities are only identifiable in humans – such things as nausea, blurred vision, headaches, feeling tired, rhinitis, or adverse changes in mental state such as asthenia, an increase in anxiety, or changes in sensations of temperature can be verbally reported by human subjects but are not amenable to identification in studies in animals. Many of these effects are reported by subjects in Phase I trials, and so some degree of discordance between toxicity identified in animals and dose-limiting toxicity in humans (Olson *et al.*, 2000) should be anticipated. Although changes in animal behavior or physiology can be detected that might arise from some of these types of changes, these largely subjective findings, which are fairly common in Phase I trials, are not detected by studies in animals.

## CONCLUSION

Toxicity studies generate data that are critical in assuring the safety of subjects that enroll in Phase I clinical trials. The starting dose in the first clinical trial of a new agent is based on results from different aspects of testing – both *in vitro* and *in vivo* data, with additional reliance on toxicokinetic data to ensure that doses proposed in the trial should be safe. Dose escalation should not be projected to above that at the NOEL from animal studies without extremely good cause; an exception to this is in the treatment of cancer. Most initial Phase I trials are of short duration and can be supported by toxicity studies of similarly short dosing duration. However, some products that have long exposures require longer term studies in animals. Finally, toxicity studies should indicate what may happen on dosing to humans and allow design of human

studies that ensure protection of subjects from significant adverse effects.

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# 9

## The Evaluation of Adverse Events in Clinical Trials (with a Particular Focus on the Use of Meta-Analysis)<sup>1</sup>

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### INTRODUCTION

Randomized controlled trials can provide estimates of how a treatment affects the risk of adverse events (AEs) free from the biases inherent in observational studies. The focus of this chapter is on evaluation of AEs in clinical trials during development, and stems from the premise that if potential harms are identified early in the drug development process, data collection strategies can be modified in time to collect additional data that are helpful for further understanding of a safety issue. Early assessment

of potential harms may increase the chances that the Phase III program, by virtue of providing a better understanding of the safety profile, allows postmarketing commitment needs to be better defined at the time of approval. The appropriate variety of post-approval activities will then permit ongoing refinement of the understanding of the benefit–risk profile of a new product. Although the emphasis in the chapter will be on drug development, the principles presented should also generally apply to trials conducted after approval.

It is critically important for sponsors to ensure that potential safety risks are identified and evaluated in a timely fashion, in order to minimize risks to study subjects (relative to potential benefits). In order to accomplish this, sponsors need to have a

<sup>1</sup>The views expressed in this manuscript are those of the authors and not necessarily of the institution or company at which they are employed.

well-defined and well-structured process in place. The Council for International Organizations of Medical Sciences (CIOMS) VI Working Group gave detailed recommendations for such a systematic approach to managing safety during drug development. They recommended that such a process start before initiating the first Phase I study and continue through post-approval use of the drug or biologic. They emphasized the need for early documentation of identified or potential risks along with plans for addressing them during development through the Development Risk Management Plan. They also recommended that Safety Management Teams be formed for each development program, to review all the available safety information on a regular basis so that decisions on safety can be made and risk minimization actions can be taken in a timely manner. We encourage readers to read their publication (CIOMS, 2005). The Safety Planning, Evaluation, and Reporting Team (SPERT) (Crowe *et al.*, 2009) expanded the CIOMS VI recommendations for a systematic approach and recommended that sponsors create a program safety analysis plan (PSAP), a complementary document to the development risk management plan that specifies the data collection and analysis of the safety data in more detail. The main point of both documents is the need to be proactive.

In this chapter we discuss important aspects of the systematic approach to clinical trial safety data evaluation. The approach calls for standardization of data collection methods, early and repeated safety assessments during development, including periodic meta-analyses of all the relevant available data at a given point in time, and review of safety data from all available sources at regular intervals during the lifecycle of a product. Much of the information we present is derived from the SPERT manuscript (Crowe *et al.*, 2009), though many of the ideas originated from the CIOMS VI report (CIOMS, 2005). In the next section we discuss important elements of planning, including the PSAP, and planning for meta-analysis. Then, in the third section, we discuss approaches to characterizing the product safety profile, including known or prespecified safety issues, and data sources for safety evaluation, including specific safety studies. The fourth section details specific planning for

clinical data collection and standardization. The fifth section addresses specific issues related to safety data analysis and reporting.

## ELEMENTS OF A SYSTEMATIC APPROACH TO CLINICAL TRIAL SAFETY DATA EVALUATION

As previously mentioned, there are several aspects to a systematic approach to managing clinical trial safety data in a drug development program. In this section we discuss two specific aspects: the PSAP and planning for meta-analysis.

### THE PROGRAM SAFETY ANALYSIS PLAN

The PSAP is a two-part program-level document; that is, it addresses analyses that will include multiple studies performed during clinical development. (Whether it is in the form of a formal, stand-alone PSAP or is incorporated in some other document is not crucial.) One part describes how data will be collected in a standard fashion for the development program. (Standardization of data collection and definitions are addressed in more detail in the “Planning for Clinical Data Collection and Standardization” section). The other part describes the analyses that will eventually be included in the Summary of Clinical Safety. The Summary of Clinical Safety is a component of new drug applications submitted to regulatory bodies. It contains summaries of all relevant safety data collected from multiple studies. (Note that, because the Summary of Clinical Safety, and thus, the PSAP, is at the program level, several indications for a given product might be included, either in series, or in parallel.) The analytical part of the PSAP should discuss events with or without a pre-specified hypothesis about an association with drug exposure, how safety data from studies are to be appropriately combined, and the statistical and graphical methodologies that will be employed during analysis and reporting of results. The analytical section should address issues such as missing data, multiplicity, analysis population, and so on, much like a single-trial statistical analysis plan does.

The PSAP is a living document, owing to the need to amend it as the safety profile emerges.

Typically, teams should start to consider how to collect data in a standard fashion by the beginning of Phase II, and the first version of the PSAP should be completed by the end of Phase II before pivotal Phase III studies embark. This timing allows for the PSAP to be discussed with the Food and Drug Administration (FDA), or other regulatory agencies, at the end-of-Phase II meeting and other subsequent milestone meetings as a drug development program evolves. Alternate timing may be considered if relevant to the product and the planned overall development program.

#### **FACILITATING COMBINING DATA ACROSS STUDIES, INCLUDING PLANNING META-ANALYSES (BE PREPARED)**

A central point made by CIOMS VI is that a systematic approach to safety data collection and analysis is essential during (and after) drug development. Part of this systematic approach is conducting reviews of all safety data on a regular basis. In many situations, safety data reviews may best be addressed by meta-analysis because individual studies usually are not sufficiently powered to address safety issues, especially for relatively uncommon events. Furthermore, meta-analysis has utility both for safety questions that are addressed retrospectively and for those that are prospectively defined and require additional information.

In the context of drug development in particular, meta-analyses should be prospectively planned. This point is a key message from The International Conference on Harmonisation E9 guideline (ICH, 1998). In their words, meta-analysis should be planned “so that the relevant trials are clearly identified and any necessary common features of their designs are specified in advance.” That document goes on to recommend common definitions of variables across studies in a program as an essential part of a planned meta-analysis. More specifically, they argue for defining, at the planning stage, the methods for measuring key efficacy variables, the timing of assessments relative to study entry, and even the definition of prognostic factors.

In an ideal setting, planning a meta-analysis should include not just planning the logistics, but

also specifying in advance the scientific questions to be addressed. Going beyond the logistics of defining endpoints and other variables, sponsors should be considering the design of “meta-experiments” rather than simply performing post hoc meta-analyses. In this regard, planning a meta-analysis, in principle, is similar to planning individual experiments, such as factorial designs or stratified randomization, with the purpose of avoiding confounding of study and patient characteristics across studies. As a simple example, if patient sex is being considered as a possible treatment effect modifier, one could argue in favor of conducting two studies, each including both men and women, and stratifying the analysis by sex, with or without stratified randomization, rather than conducting one study in men and a separate study in women. The drawback to conducting separate studies by sex is that doing so confounds sex and “study,” so any differences in study conduct between studies with otherwise “identical” designs will make it nearly impossible to determine whether differences in results stem from “study” effects or different effects by sex. In many situations, the designs of two studies will differ in more than one respect (e.g., they might use different doses of drug for men and women), further complicating interpretation of differences between study results.

We recognize that this lack of confounding may sometimes be impractical or even undesirable. The SPERT paper gives the example of anti-epileptic drugs. If a new anti-epileptic drug, already approved for epilepsy, is being developed for migraine prophylaxis, experience with existing drugs in the class might suggest that it would be more appropriate to perform studies in migraine at lower doses than those required for epilepsy. In this setting, confounding of dose and indication might be clinically necessary, and might require a separate assessment of the benefit-risk profile for the different populations.

#### **APPROACHES TO CHARACTERIZING THE PRODUCT SAFETY PROFILE**

In this section, we discuss various aspects of planning of safety analyses. Importantly, safety assessment should always include incorporation of newly

emerging safety information. For example, aspects of the data collection and the statistical analysis plan may need to change over the course of drug development as we accumulate more knowledge on the safety profile of the product.

Data to assess safety may come initially from preclinical and toxicology data, clinical trials, and meta-analysis of trials. As drugs move to the post-approval setting, where less common events may begin to be observed, and as a drug is used in patients with comorbidities who may not have been exposed during development, epidemiologic data may play more of a role. As noted, we focus this chapter on clinical trials and meta-analyses of clinical trials.

## KNOWN OR PRESPECIFIED SAFETY ISSUES

### Specific Safety Issues That Should Always Be Considered for All Products

Not all safety questions can be anticipated. However, when planning for the development of virtually any new medicinal product, certain toxicities should always be explicitly considered, because they are of recurring importance in the failure of new drugs to gain approval or in the withdrawal of drugs from the market. These events include, but are not limited to, QT prolongation (ICH, 2005), liver toxicity (FDA, 2009), nephrotoxicity, immunogenicity, and bone marrow toxicity (CIOMS, 2005). A comprehensive approach to assessing these events is needed. For example, to perform a comprehensive assessment of hepatotoxicity, liver damage may need to be looked at in several ways. This might include analysis of laboratory abnormalities defined using Hy's law, laboratory data in combination with AE data, and various combinations of AEs (such as liver damage requiring transplant, hepatitis, or jaundice).

### Product-specific Adverse Events of Special Interest

In addition to the standard items that should always be evaluated, early planning to assess safety should include consideration of how best to define and manage product-specific AEs of special interest

(AESIs). We will not replicate here the extensive discussion of AESIs presented by the CIOMS VI Working Group (CIOMS, 2005).

In addition to events that are actually observed in the clinical trials program during development, there are other sources of information that can inform subsequent plans for data collection and define events that may need special attention. Toxicology and other nonclinical data may suggest potential toxicities in humans. Sponsors may use this knowledge to specify certain events as AESIs that require special collection and/or reporting. It is also important to understand the epidemiology of the disease for which treatment is indicated and the characteristics of the population to be treated, including the prevalence of risk factors for potential or known adverse reactions associated with the product and the prevalence or incidence of the common major comorbidities and their associated mortality. For example, it is known that patients with rheumatoid arthritis have an increased incidence of cardiovascular diseases relative to the general population after adjusting for age and sex. The causes of this cardiovascular comorbidity are multifactorial, potentially including complications of rheumatoid arthritis, treatments used for rheumatoid arthritis, and other reasons not completely explained by traditional cardiovascular risk factors (Quyyumi, 2006). The knowledge of the epidemiology, in this case, would lead to more extensive (possibly adjudicated) assessment of cardiovascular events. It would also provide background rates of AESIs, which may permit an assessment of whether rates observed during development or after marketing are unexpectedly high, particularly in cases where there is no placebo control group. Caution is needed in comparisons with external reference groups, since the clinical trial participants may be drawn from a different (more selected) population than the reference group, and observation times, ascertainment, and many other elements may be different. Once a product moves to the postmarketing phase, data from spontaneous AE reporting systems (e.g., FDA AERS) can help in identifying safety signals. Under the FDA Sentinel Initiative (US DHHS, 2008, 2010; Platt *et al.*, 2009) we have seen more utility of using large

electronic health records and administrative claims databases for the purpose of further understanding and characterizing known risks (FDA, 2011) and potentially signal detection.

## PLANNING FOR CLINICAL DATA COLLECTION AND STANDARDIZATION

High-quality data and a comprehensive data collection scheme are crucial factors in providing the bases for thorough safety analyses. In contrast to the planning of efficacy analyses, more flexibility is required for safety analyses; therefore, appropriate approaches for routine collection of safety data need to be complemented by approaches that are aimed at specific events of interest identified earlier in the development program. As many safety questions are best addressed by aggregating information across studies, a high degree of standardization will further facilitate the safety assessments.

## DEFINITION OF SAFETY OUTCOMES AND ADJUDICATION

When available, standard medical definitions of AEs should be used. Such standards may not always exist, or multiple definitions might exist. In such situations, it is important to get regulatory agreement proactively on the operational definition to be adopted, including a clear specification of the adequate measurement of the important safety outcomes. Although the definitions may need to be modified as the program develops, safety outcomes should be defined in a transparent and reproducible manner, where possible, at a critical milestone in the drug development program (e.g., by the start of pivotal trials). It may sometimes be necessary to develop a definition retrospectively and apply it to completed clinical trials, but this situation is best avoided. Ideally, medical concepts should be predefined and independent of disease areas and products. If possible, it is preferable to establish a pool of AESI definitions (e.g., using well-established standardized MedDRA (Medical Dictionary for Regulatory Activities) queries) independent of the therapeutic area or product, so that having to define

an AESI retrospectively can be avoided. Having a “library” of AESI definitions also allows findings about the underlying events to be compared appropriately across trials and settings, or even across products within a class.

Some safety outcomes may require developing an event-specific case-report form. Protocols may require, for example, the collection of additional and more-detailed data for subjects with a suspected cardiac AE to facilitate the case identification and safety assessment. A specific definition of a venous thrombotic event (usually including deep vein thrombosis and pulmonary embolism) may require some form of diagnostic confirmation (e.g., venography). Routine AE reports of a venous thrombotic event, provided by an investigator, may not always include the requisite confirmatory evidence. Early identification of venous thrombotic events as AESIs should lead to generation of a specific case-report form designed to collect the results of the confirmatory test, avoiding the need to retrieve medical records, which may not be complete.

How broadly or narrowly to define AEs is another important consideration. It could be argued that broad searches for terms are more “conservative,” in the sense that they ensure that all relevant terms will be included in the definition of the safety endpoint. Defining events too narrowly might inappropriately reduce statistical power; for example, by separating events that might have the same pathophysiology. However, defining events too broadly can underestimate the true relative risk and potentially mask a safety signal (O’Neill, 1988) when the misclassification is “nondifferential”; that is, it is equally likely to occur in each treatment arm. A broad classification might include events that are either less likely to be related to the drug-induced mechanism of action or that, by their very nature, might just be more likely to be misclassified in clinical trials. When misclassification is nondifferential, the observed relative risk will generally be closer to the null for the broader classification than for the narrower classification. For a more detailed discussion, see Proschan *et al.* (2006, Sec. 9.2).

In some situations, adjudication may be considered necessary. For example, an excess of hepatic

events noted in Phase II could prompt denoting these as adjudicated events for Phase III. In such cases, an expert or group of experts (an adjudication committee) provides a medical classification and standardized evaluation of an AESI. Ideally, adjudication is done prospectively; pre-specification and keeping the committee blinded to treatment status greatly strengthen the quality and credibility of the adjudication. Retrospective adjudication is generally more challenging than prospective adjudication, as the detailed clinical information required for the adjudication committee is easier to capture completely when defined prospectively.

### STANDARDIZATION OF SAFETY DATA COLLECTION

Standardization can play a major role in facilitating the integration of information across studies. Standardization across companies, to the extent possible, could facilitate data integration and analysis within a program and, importantly, would allow regulatory reviewers to standardize methods to analyze the data and possibly conduct cross-company meta-analyses.

Standardization can be applied to:

- coding procedures for AEs, medical history, concomitant medications, and other areas;
- data collection procedures and definitions (using Clinical Data Acquisition Standards Harmonization where possible);
- case-report form design and instructions, including processes and procedures for eliciting safety outcomes (CIOMS, 2005: 79);
- definitions of AESIs;
- definitions of subgroups of patients (e.g., risk groups of special interest could be defined by using the same threshold value for a laboratory test);
- design aspects of the clinical studies (e.g., a common, or at least compatible, visit structure);
- statistical analysis of important safety outcomes;
- adjudication process.

### SAFETY DATA ANALYSIS AND REPORTING

The focus of safety analysis should be on the identification of potential harms, identification of risk factors or subgroups for potential and known harms, and the relationship between dose, duration of exposure, and safety outcomes.

We support the recommendation of CIOMS VI (2005) to conduct periodic aggregate safety data reviews. Though the focus of these reviews will likely be on unblinded data from completed trials, even the review of blinded data from ongoing trials can be useful to help identify unusual patterns that may be suggestive of a safety signal. If the event in question is potentially clinically important (e.g., a life-threatening AE) then a review of unblinded data (e.g., by a data monitoring committee or a select group of people internal to the sponsor, but independent of the people who are involved in the trial conduct) may be needed to determine if a safety signal is present and if steps are needed to ensure the safety of clinical trial subjects. Furthermore, as part of study planning, teams should consider if unblinded safety assessments need to be performed by a data monitoring committee and, if so, incorporate them into the data monitoring committee charter specifications.

Outcomes of an aggregate safety data review could include (but are not limited to) prompt communication to relevant parties (such as regulatory authorities or institutional review boards), changes to informed consent/data collection/monitoring procedures/conduct of trials/the development plan, or amendments to protocols.

These reviews can be enhanced by using graphical methods to review patient data, graphical approaches to complement statistical analyses, and more advanced methods, such as meta-analysis or competing risk analysis during development.

Safety data from clinical trials present analytical challenges, especially relative to efficacy data, because of the frequent lack of well-defined, pre-specified hypotheses. Multiplicity issues and low statistical power are related issues. Multiplicity can arise from both multiple looks at a specific endpoint, or from the large number of types of AEs (multiple endpoints) that are typically analyzed.

These issues are discussed in the FDA (2005) reviewer guidance.

## CONSIDERATIONS FOR INDIVIDUAL STUDIES

### Defining the Safety Analysis Set

Analytical principles that apply to individual studies are clearly relevant to the studies incorporated into meta-analyses. The Consolidated Standards of Reporting Trials group (Ioannidis *et al.*, 2004) recommended using the intention-to-treat (ITT) population for safety data analysis in general; however, we agree with the CIOMS VI Working Group (CIOMS, 2005), who suggested that ITT analyses are not always the most appropriate for analyzing safety data, as the results may have a tendency to underestimate the true differences between the groups. CIOMS VI suggested that other analysis populations, such as only those subjects who received a prespecified minimum number of doses of the study drug, might be more appropriate for analysis of safety data. As they noted, however, these analyses also may be biased, and the direction of the bias is unknown due to lack of knowledge about the relationship between the reasons for stopping treatment and the outcome of interest. Furthermore, teams might want to consider performing sensitivity analyses using populations other than the primary population.

### Accounting for Time On or Off Treatment

The length of time that each patient is “at risk” of having an AE has to be considered in any assessment of risk, particularly when the length of time for which a patient is followed varies by treatment group or across studies. Follow-up time may not be the same as the duration of treatment, when the trial protocol includes an on-treatment stage and a post-treatment follow-up period, or when the protocol allows subjects to remain in the study after treatment is discontinued. According to CIOMS VI (CIOMS, 2005: 150), this post-treatment follow-up is important and should normally extend to at least five half-lives once treatment is stopped, or even beyond that if an event with long latency is being investigated. The protocol should clearly define the

end of the study observation period for each individual patient.

Rates are often calculated per person-time, but such an approach typically assumes a constant hazard rate over time. In situations in which the hazard rate varies over time, it may be necessary to break the observation period into component periods (e.g., month 1, month 2) (FDA, 2005). Survival analysis techniques, such as the Kaplan–Meier, the Cox proportional hazards, piece-wise exponential models, and other time-to-event methods, are also useful for handling differential times on and off treatment. Survival analysis techniques can appropriately handle differing dropout rates between the treatment groups and may give less-biased estimates than an analysis that ignores person-time. However, neither survival analysis nor any other method will automatically adjust for differential dropout rates when the *reasons* for dropping out differ between the groups. For example, if placebo-treated patients tend to discontinue because of lack of efficacy and test drug-treated patients tend to discontinue because of AEs, then even similar dropout rates between groups will not exclude the possibility of a biased comparison.

For some events that tend to occur early in treatment if they are going to occur at all (such as hypersensitivity reactions), ignoring person-time will be most appropriate. For drugs taken on an as-needed basis, analyses using the number of doses taken may be helpful because time on study may not be highly correlated with exposure to the drug.

## META-ANALYSIS OF ADVERSE EVENT DATA

In general, meta-analysis in the context of assessing product safety can be used for the estimation of an average treatment effect and the exploration of reasons for heterogeneity among study-specific effects (Vanhonacker, 1996; Thompson *et al.*, 1997; Schmid, 1999; Thompson and Sharp, 1999; Greenland and O’Rourke, 2001; Higgins *et al.*, 2002; Sterne *et al.*, 2002). Combining results from multiple randomized studies will provide increased precision of treatment effect estimates and increased statistical power to test hypotheses relative to individual studies. As the size of the database increases,

one may be able to examine important subgroups with sufficient power, which individual studies may not have.

Crude pooling of AE numbers across different trials to compare treatment groups should be avoided if possible (especially when the randomization ratio varies among studies), as the results can be misleading (e.g., in the presence of confounding by "study"). It might also be useful in combined analyses of AE data across trials to preserve the stratification according to randomization factors (e.g., stratification by study, or by clinical subgroup and study simultaneously). If the randomization factors are potential modifiers of treatment effect, examining stratum-specific results will be important.

## MULTIPLICITY

As noted above, multiplicity can arise from both multiple looks over time at a specific endpoint and from the large number of types of AEs that are typically analyzed.

Cumulative meta-analysis involves performing a new meta-analysis as the data from a new clinical trial are available (Antman *et al.*, 1992; Lau *et al.*, 1992), or at prespecified decision points. Throughout the course of development, the principles of cumulative meta-analysis need to be applied to the repeated integrations of events for which there are prespecified hypotheses being tested. Some caution is advised in interpreting cumulative meta-analyses. Methods for addressing multiplicity (e.g., in analyses done at prespecified time points) have been developed in the context of cumulative meta-analysis (Berkey *et al.*, 1996; Lan *et al.*, 2003; Hu *et al.*, 2007). The concept of cumulative meta-analysis also seems to fit the Bayesian philosophy very well. We learn as we accumulate the data, and today's posterior becomes tomorrow's prior (Stangl and Berry, 2000).

Multiplicity generated by looking at many safety endpoints is perhaps an even thornier issue. The SPERT paper describes a three-tiered approach to safety endpoints: those for which a prior hypothesis is clearly defined (Tier 1); commonly occurring events for which there is no prior hypothesis (Tier 2); and uncommon events for which there is no

prior hypothesis (Tier 3). In general, that paper points toward adjustment for multiple looks for Tier 1 events and adjustments for multiple endpoints for Tier 2. For Tier 3, there may generally be too few events to make any meaningful statistical comparisons, with or without adjustment for multiplicity.

Any multiplicity adjustment must strike a reasonable balance between false positives and false negatives and assist in interpreting the safety findings. There are a number of multiplicity adjustment methods that have been proposed, including the "double false discovery rate" multiplicity-adjustment procedure of Mehrotra and Heyse (2004) and the Bayesian methods of Berry and Berry (2004). The distinction between Tier 2 and Tier 3 events is important for analysis using the double false discovery rate method, but is not necessary with the Bayesian approach. One of the advantages of the Bayesian approach is that the entire AE dataset is analyzed and the extremes are modulated through borrowing strength among different AEs under the hierarchical MedDRA coding structure. For example, if many AEs under the same system organ class (SOC) had AE counts of three events versus zero between the treatment and control arms, respectively, the Bayesian approach would strengthen the signal by borrowing strength among different AEs within the SOC. In this case, the signal would likely be missed with the double false discovery rate approach because those AEs would be removed in the first step due to their inability to reach statistical significance on their own. Xia *et al.* (2011) extended the work of Berry and Berry (2004) by accounting for various exposure or follow-up times among different subjects under the Poisson likelihood. They recommended using simulation studies to select a signal detection threshold, and demonstrated that the Bayesian approach outperformed other methods in the scenarios that they simulated.

## SIGNAL DETECTION FOR COMMON EVENTS

Signal generation is commonly implemented in the context of spontaneous reports of AEs in the post-approval setting. Similar methods to those used in that setting can also be incorporated into clinical

trials programs, including during development. A basic distinction between spontaneous reports and clinical trials is that, in the clinical trials setting, the number of exposed patients is known and hence there is a true denominator. Signal generation can be accomplished through a combination of inferential and descriptive statistics. It is possible, for example, to develop a hierarchy that is mainly based on *p*-values, the magnitude of relative risk estimates, and evidence of dose-response. It is used for *screening* only, not to make definitive assessments. Bayesian approaches could be used in this context as well, although they would not be based on *p*-values.

A next level of sophistication could involve data mining techniques, including visualization. Several such methods are presented in a paper by Southworth and O'Connell (2009). These include a so-called "inside-out" data mining method that treats AEs as explanatory variables, with treatment allocation as the "outcome" variable; a support method that fits separate regression models to each AE, with and without a term for the treatment effect, and a hierarchical Bayesian model for the analysis of counts of AEs. The basis for these methods is strength of evidence, rather than *p*-values. The methods can be implemented in conjunction with graphical methods, and links to individual-level laboratory or other data (e.g., concomitant medications) can be added to allow a deeper investigation into events and history in specific clinical trial subjects.

The aim of any methods for screening AEs in clinical trials is a thorough review of safety data that is statistically guided, but not dependent entirely on the results of formal criteria for making definitive decisions. Clinical judgment is always necessary so as to avoid basing decisions on what is likely to be artifact. Southworth and O'Connell (2009) cite an example in which the nonspecific event of "pain" appears statistically to be important. A close look at the data showed that the pain events included "tender inflamed nostrils," "toothache," "tenderness in big toe," and "pain in anterior lower part of leg when going to bed." The authors argued that there is no meaningful pattern or similarity to these events, suggesting (but not confirming) that the difference between treatment groups

is likely to be due to chance. They note that the *p*-value for this association would have been 0.002, which is a fairly compelling value, even after adjustment for multiplicity. Conversely, given the low frequency of some severe events, a real signal might miss a threshold of *p*-value or relative risk but still be important. Again, judgment needs to play a role; for example, bringing a perspective provided by knowledge of the class of drugs or the mechanism of action.

## DESCRIPTIVE ANALYSIS OF INFREQUENT ADVERSE EVENTS

For other AEs there will not likely be a prespecified hypothesis and they are infrequent. Clinical evaluation of these events is important for the overall benefit-risk profile of a product. Note that these events may be very important clinically, in terms of severity. Meta-analysis of rare events (particularly those with zero events being observed in one or more arms) is challenging. Preferred methods for rare events meta-analysis are addressed in a few recent papers (Sweeting *et al.*, 2004, 2006; Bradburn *et al.*, 2007).

When analyzing and reporting infrequent events, the relative risk and odds ratios could be misleading as they tend to exaggerate the perceived magnitude of the observed absolute difference between groups. Absolute risk should also be looked at in detail, and it is important to include clinical judgment in the assessment of any of these measures. (A change in event rate of 1 per 10 000 to 3 per 10 000 carries different implications from a tripling of a more common event.)

## REPORTING

As noted above, appropriate metrics of absolute risk should typically be reported (e.g., frequency, subject incidence, or incidence rate per person-time of exposure). An estimate of the risk difference, relative risk, or odds ratio should generally be reported, (at least for Tier 1 and Tier 2 events), together with corresponding confidence intervals or *p*-values (Chuang-Stein and Beltangady, 2011). The choice among these measures depends on the desired interpretation. For benefit-risk assessments,

risk differences are most useful, although, mathematically, odds ratios have some desirable properties. It is also possible to perform analyses on the odds ratio scale and then convert to risk differences (or relative risks) for presentation (Deeks, 2002; Localio *et al.*, 2007). Risk factors, such as age, sex, comorbidities, or other patient-level characteristics unique to the specific clinical situation, should be investigated as predictors of the event within each treatment group and overall. To assess whether particular subgroups of patients may be at differentially increased risk of the event due to treatment, compared with other subgroups, examination of a treatment by subgroup interaction is useful. To allow a proper assessment of the role of risk factors, the relevant risk factor information should be collected prospectively in all subjects or in those subjects who experienced the event and in a randomly selected sample of subjects who have not had the AE and thus can serve as controls in a nested case-control study. The description of the case-control approach is beyond the scope of this document.

## CONCLUSIONS

Recent years have seen an appropriate increase in emphasis by both industry and regulatory agencies on identifying safety issues for new compounds (or new indications for existing compounds) early in the drug development process. Identification of signals can be enhanced by using a well-defined, coordinated, program-wide approach to safety evaluation in new product development programs. Key elements in such programs should include the creation of a prospectively defined program-level data collection and analysis plan (the PSAP, as recommended by SPERT (Crowe *et al.*, 2009)) and regular reviews of aggregate data by a multidisciplinary safety management team (as recommended by CIOMS (2005)).

The value of a proactive approach is that potential harms may be identified early in the drug development process, which allows data collection strategies to be modified in time to collect additional data that are helpful for further understanding a safety issue. Developing a deeper understanding of the safety profile of a new drug during the Phase

III program will allow postmarketing commitment needs to be better defined. As described throughout the rest of this book, the appropriate variety of post-approval activities will encourage ongoing refinement of the understanding of the benefit-risk profile of a new product.

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# Case Reports as Evidence in Pharmacovigilance

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## INTRODUCTION

In recent years it has become increasingly appreciated that the hierarchy of clinical evidence, in which randomized controlled trials (RCTs) and systematic reviews and meta-analyses of trials have been regarded as the strongest forms of evidence, and case reports the least strong, distorts the true value of different forms of evidence in different circumstances.

This is particularly relevant to adverse reactions to drugs (or devices) (ADRs). Indeed, RCTs may not be the best sources of information about ADRs for several reasons:

- RCTs are primarily designed to detect a single beneficial outcome, whereas harms are secondary to the main interest and are usually multiple;
- beneficial outcomes are more readily detected than harms, which occur less commonly; RCTs

may therefore be too small and too short-lived to detect harms;

- information on harms is often poorly collected in RCTs;
- even when information on harms is well collected, it is often poorly reported;
- even when harms are well reported in the body of a report, they may not be mentioned in titles and abstracts and may be poorly indexed in large databases, making retrieval of information, and therefore systematic reviews, difficult.

These problems have been put into context by the demonstration, in a meta-analysis of meta-analyses, that the average odds ratios of ADRs are equally estimated in observational studies and RCTs (Golder *et al.*, 2011), suggesting that observational studies may be as good as RCTs in assessing the risks of proven harms. Indeed, there may be occasions on which they are better.

Nor should individual case reports of suspected adverse reactions be regarded as being necessarily evidentially poor, as discussed below.

#### **NOTE ON TERMINOLOGY: "SAFETY" VERSUS "HARM"**

The importance of defining terms clearly in all areas of science cannot be overstated. This is not the place for a detailed discussion of the many terms that are used in pharmacovigilance in relation to suspected ADRs (Aronson and Ferner, 2005; Hauben and Aronson, 2009; Ferner and Aronson, 2010; Aronson, 2011a; Aronson *et al.*, 2012). However, as will become clear, one term that is widely used but has not been widely discussed, deserves attention here: "safety."

"Safety," as defined by the *Oxford English Dictionary*, is "exemption from hurt or injury; . . . the quality of being unlikely to cause or occasion hurt or injury".

However, when people talk about "drug safety" they really mean "unsafety," or more accurately "harm". For example, the ICH E2B documents, discussed below, refer to "individual case safety reports" (ICSRs), when "individual case harm reports" (ICHRs) would be a better term. The term "drug safety" would be better avoided altogether. After all, it is the *patient's* safety about which we are primarily concerned. "Patient safety" has been defined as "the avoidance, prevention, and amelioration of adverse outcomes or injuries stemming from the processes of health care" (Vincent, 2005). However, there are three problems with this definition: (a) the phrase "adverse outcomes and injuries" (i.e., harms in general) excludes hazards that can, but do not always, lead to harms (Aronson, 2013); (b) the word "and" should be replaced by "or," since not all of these options will be possible in any one case; (c) "amelioration" means making something better, not reducing the harm – "mitigation" would be a better word to use. So, adapting this definition, patient safety in relation to the use of drugs or devices could be defined as "avoidance, prevention, or mitigation of the hazards posed by therapeutic interventions or the harms that arise from their use."

#### **THE ROLE OF CASE REPORTS IN PHARMACOVIGILANCE**

Anecdotal reports form a major source of information about suspected ADRs. Such reports come in many forms:

- 1 Reports to regulatory agencies (ICHRs; see above), usually from pharmaceutical companies, based on reports that they have received from patients via investigators, following the method laid down in the ICH E2B documents (see below).
- 2 Reports to regulatory agencies from prescribers, nurses, pharmacists, and non-health-care professionals, such as patients or their carers (for example, on Yellow Cards in the UK or Med-Watch forms in the USA).
- 3 Papers describing case reports published in journals in print form, online, or both.
- 4 Descriptions in registries or other databases.
- 5 Descriptions, often by patients themselves, on websites.

Of the published world literature on ADRs, published case reports (category 3) amount to about 30% (Aronson *et al.*, 2002).

Anecdotal reports of suspected ADRs have several uses (Table 10.1): to describe a newly recognized or suspected adverse reaction or interaction; to generate hypotheses; to test hypotheses; to demonstrate diagnostic techniques; to elucidate mechanisms; to elucidate or suggest methods of management; to remind or educate; and to add to the database of published and unpublished reports, thus enhancing signal detection. Sometimes a single anecdote, or a small number of such, can even provide definitive proof that a drug and an adverse event are causally associated (Table 10.2).

If enough case reports have been published it may be possible to make deductions about the nature of an ADR from a systematic review of its features. For example, a review of the features of cases of iodide mumps has confirmed that this reaction has two different time courses, suggesting that there may be two different mechanistic types: an immediate allergic reaction and a delayed toxic

Table 10.1 Uses of case reports of suspected ADRs.

Reasons for publishing anecdotes	Examples (for references see Aronson (2011a))
To describe a newly recognized or suspected adverse reaction or interaction	Oculomucocutaneous syndrome and practolol
To generate hypotheses	Teratogenicity of antihistamines
To test hypotheses	The loading dose of digoxin in severe renal insufficiency
To demonstrate diagnostic techniques	Serum KL-6 in diagnosing amiodarone induced lung damage
To elucidate mechanisms	Drug-induced torsade de pointes and prolongation of QT interval
To elucidate methods of management	Treatment of verapamil self-poisoning
To remind or educate	The adverse effects of liquorice
Signal detection in pharmacovigilance databases	Venous thromboembolism and mestranol
To enable systematic review	Iodide mumps

Table 10.2 Categories of definitive anecdotal ADRs (Aronson and Hauben, 2006; Hauben and Aronson, 2007).

Category	Event	Confirmatory tests/characteristics	Drug examples <sup>a</sup>
1a. Extracellular deposition of drug or metabolite (culprit caught at the scene of the crime)	Biliary lithiasis or pseudolithiasis Nephrolithiasis	Infrared spectroscopy  Infrared spectroscopy X-ray diffraction Mass spectroscopy	Ceftriaxone Sulindac Aciclovir, amoxicillin, ciprofloxacin, ephedrine/guaifenesin, felbamate, indinavir, magnesium trisilicate, methotrexate, primidone, sulfasalazine, sulfonamides, triamterene
	Conjunctival cysts Exogenous lipid pneumonia Pharmacobezoars	Wood's lamp Gas chromatography-mass spectrometry Visual inspection	Tetracycline Mineral oil  Colestyramine, sucralfate, modified-release formulations, guar gum, ion exchange resins
1b. Intracellular deposition of drug or metabolite (culprit caught at the scene of the crime)	Baroliths Corneal microprecipitates Crystalline retinopathy Crystal-storing histiocytosis  Intraglomerular crystal deposition Lymphadenopathy	X-ray and visual inspection Scanning EM and HPLC Confocal microscopy HPLC  Electron microprobe analysis Visual inspection Polarizing microscopy Fourier transform infrared spectroscopy Light and electron scanning microscopy	Barium Ciprofloxacin Gold Methoxyflurane Canthaxanthine Aluminium-containing vaccines Clofazimine Foscarnet  Gold

(Continued)

Table 10.2 (Continued)

Category	Event	Confirmatory tests/ characteristics	Drug examples <sup>a</sup>
2. Specific anatomical location or pattern of injury (culprit caught at the scene of the crime and seen committing it)	Deposition in nails or lunulae	Wood's lamp examination	Tetracycline
	Skin pigmentation	Microscopy HPLC Electron microscopy Energy dispersive X-ray microanalysis	Clofazimine Amiodarone
	Esophageal ulcers	Localization to areas of esophageal lesions	Bisphosphonates, potassium chloride, quinidine, tetracyclines
	Extravasation reactions	Anatomical contiguity to drug administration	Cancer chemotherapeutic agents
	Fulminant encephalomyelitis	Anatomical pattern of injury	Inadvertent intrathecal ionic contrast medium Inadvertent intrathecal vincristine
	Nodulosis	Anatomical contiguity to drug administration	Apomorphine
3. Physicochemical dysfunction or tissue damage (crime scene recreated)	Oral damage	Application site localization	Topical oral salicylates Topical ecstasy Topical cocaine
	Nasopalatal damage	Application site localization	Thorotrust
	Hemangiosarcoma	Anatomical localization in sites of drug accumulation or persistence	
	Oligohidrosis	Iontophoresis Acetylcholine loading test Heat loading test	Topirimate Zonisamide
4. Infection related (fingerprints found at the scene of the crime)	Photosensitivity	Phototesting Photo-patch testing	Carbamazepine, dapsone, fenofibrate, flutamide, NSAIDs, triflusal
	Taste disturbance	Gustatometry Electrogustatometry	NSAIDs
	Dry mouth	Meaurement of salivary flow	Omeprazole
	Sepsis unrelated to product contamination	Polymerase chain reaction	Bacille Calmette–Guérin (BCG) Lactobacillus Mumps vaccine
	Sepsis due to product contamination	DNA enzyme immunoassay electrophoresis Bacterial culture and strain typing DNA fingerprinting Endotoxin assay Plasmid and restriction-endonuclease analysis	Intravenous gentamicin Propofol

<sup>a</sup>For references, see Aronson *et al.* (2002) and Aronson and Hauben (2007).

reaction associated with renal impairment (Aronson, 2010).

Registries of patients receiving specific therapies for specific diseases are being increasingly used in postmarketing surveillance of medications (Willis *et al.*, 2012). Examples include the Prospective Immunogenicity Surveillance Registry, the Biologics Register of the British Society for Rheumatology, the Australian Rheumatology Association Database, the Haemostasis Registry, and the Bosen-tan Patient Registry. Such registries may improve the rates of reporting of adverse events (Hetland *et al.*, 2005). The controversy over breast implants manufactured in France (Holehouse *et al.*, 2012) demonstrated the potential value of such registries.

Finally, modern data mining methods of analysing large databases containing information about individual cases have proved powerful in detecting signals of previously undetected harms (Wilson *et al.*, 2004; Hauben *et al.*, 2005).

## **REPORTING SUSPECTED ADVERSE DRUG REACTIONS TO REGULATORY AGENCIES**

Various national and international agreements, rules, and regulations require individual case reports of adverse events and ADRs to be transmitted during drug development, as follows (ICH, 2001):

- from reporting sources to regulatory agencies and/or pharmaceutical companies;
- between regulatory agencies;
- between pharmaceutical companies and regulatory agencies;
- within regulatory agencies or pharmaceutical companies;
- from clinical investigators, via the sponsor, to ethics committees;
- from regulatory agencies to the WHO Collaborating Centre for International Drug Monitoring, in Uppsala, Sweden (the Uppsala Monitoring Centre, UMC).

With the introduction of electronic transmission of such data it became necessary to define the methods that would be used, specifying the common

data elements to be used. This has been done by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in the documents known as E2B (ICH, 2001). The standard transmission procedures have been specified by the ICH Electronic Standards for the Transfer of Regulatory Information (ESTRI) Expert Working Group (M2).

Opportunities are also available for submitting voluntary reports directly to individual regulatory agencies (using, for example, Yellow Cards for reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and MedWatch forms for reporting to the Food and Drug Administration (FDA) in the USA) and for publishing case reports in learned journals.

In some countries, mandatory reporting systems are in place; for example, in France (Albengres *et al.*, 1990; Daurat, 2010), Denmark (Viskum, 2011), and Korea (Park *et al.*, 2008). However, the benefit-to-harm balance of mandatory reporting is not clear. For example, in Japan, the proposed introduction of a mandatory system for reporting fatal adverse events led to widespread fear of prosecution and defensive medicine (Nagamatsu *et al.*, 2009); physicians started to refuse to see high-risk patients and referrals to other hospitals became widespread; medical school graduates began to avoid specialties that were perceived as being legally particularly vulnerable, and various hospitals and clinics had to close. In the UK, although reporting is not mandatory, the General Medical Council (2013) has ruled that, among their many duties, doctors “must inform the MHRA about serious suspected adverse reactions to all medicines”; the word “must” implies “an overriding duty or principle.”

## **E2B**

### **HISTORY**

E2B arose from a European TEDIS project called EuroSCaPe (European Single Case in Pharmacovigilance) (Moore *et al.*, 1994; Monteagudo, 1996; Montero *et al.*, 1998), which set down most

of its properties and defined an electronic message in the EDIFACT system. This was brought into ICH and became the first version of E2B, which, having been approved by the Steering Committee of the ICH, was released for public consultation in May 1996, and was finally approved and recommended for adoption in July 1997. The first revision, now labeled E2B(R1) (originally E2B(M)), was released in November 2000, and a second revision, E2B(R2), which contained only minor editorial corrections, was released without further consultation in February 2001. E2B was implemented during 2000–2002 by the three ICH regulatory bodies in the EU, the USA (the FDA), and Japan (the Ministry of Health, Labour and Welfare).

A third revision, E2B(R3) (the ICH Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs), Data Elements and Message Specification), was released for consultation in September 2011. This followed a decision by the ICH Steering Committee that technical specifications should no longer be developed solely by ICH, but should be created in collaboration with standards development organizations. ICH representatives have therefore been involved in a joint initiative, collaborating with experts from the International Organization for Standardization (ISO), Health Level 7 (HL7), the European Committee for Standardization (CEN), and the Clinical Data Interchange Standards Consortium (CDISC) to produce a single common standard for individual case harm reports. E2B(R3) was endorsed by the Steering Committee of ICH in July 2013 (ICH, 2013).

#### DEFINITION OF DATA ELEMENTS IN ICH 2EB

The data elements that are defined in E2B in assessing an individual case are designed to be sufficiently comprehensive to cover all types of cases, while acknowledging that not every data element will be available in every case. The minimum information should include at least one identifiable patient, one identifiable reporter, one reaction or event, and one suspected drug; the patient and the reporter can be the same individual. Information should also be given about the sender's identification, the case report unique identification number, and the date

of receipt of the most recent information. The structure of E2B is shown in Tables 10.3 and 10.4.

E2B allows the same information to be provided in different ways; for example, the patient's age can be sent as the date of birth, the age at time of onset of the reaction or event, or the patient's age group (for example, neonate, child, adult, elderly); it is preferred that the most appropriate set of data elements should be provided, rather than including multiple elements or redundant data.

Besides structured information, E2B allows transmission of some free-text items, including a narrative summary of the case. Medical information in reports under E2B is coded using MedDRA terms. In addition, the following terms are specifically defined:

- *receiver* – the intended recipient of the transmission;
- *reporter* – the primary source of the information (i.e., a person who first reports the facts);
- *sender* – the person or entity that creates the message for transmission.

Although the reporter and sender may be the same person, the function of the sender should not be confused with that of the reporter; if the two individuals are different, the reporter should be distinguished from the sender.

#### JOURNALS THAT PUBLISH CASE REPORTS OF SUSPECTED ADVERSE DRUG REACTIONS

The numbers of case reports published in bio-science journals have been increasing gradually over the years (Figure 10.1), and the numbers of case reports of adverse events have been increasing at a greater rate than other types of case reports. In part, these increases have been due to the overall increase over this time in scientific activity as a whole. However, after correcting for that, there was an absolute 37% increase in the numbers of all published case reports (i.e., corrected for total numbers of publications in each year) between 1966 and 2010 and a 100% increase in the numbers of case reports of adverse events. The divergence

Table 10.3 The structure of ICH E2B – Section A: Administrative and Identification Information.

Subsection	Sub-subsection	Notes <sup>a</sup>
A.1: Identification of the case safety report	A.1.0.1	Sender's (case) safety report unique identifier. This should remain constant in subsequent transmissions by the same sender. Retransmitters should replace it with their own unique identifier.
	A.1.1	Identification of the country of the primary source. Usually a single country, but can include other countries visited or in which products may have been manufactured.
	A.1.2	Identification of the country where the reaction/event occurred.
	A.1.3	Date of the report.
	A.1.4	Type of report (spontaneous report, report from a study, other, or unknown); see also A.2.2 and A.2.3.
	A.1.5	Seriousness – for definitions see Aronson (2011a).
	A.1.6	Date report was first received from the primary source.
	A.1.7	Date of receipt of the most recent information.
	A.1.8	Additional available documents held by sender (listed).
	A.1.9	Does this case fulfill local criteria for an expedited report? See also E2A (ICH, 1994).
	A.1.10	Worldwide unique case identification number (the regulatory agency's case report number or a sender's case report number).
	A.1.11	Other case identifiers in previous transmissions.
	A.1.12	Identification number of a report linked to this report (to identify cases that warrant being evaluated together, such as a mother-child pair, siblings with common exposure, several reports involving the same patient, and several similar reports from the same reporter).
	A.1.13	Report nullification (to retract a previous report; for example, because it was erroneous), giving the reason.
A.2: Primary source(s) of the information	A.1.14	Was the case medically confirmed, if not initially from a health professional?
	A.2.1.1	Reporter identifier (name or initials).
	A.2.1.2	Reporter's address.
	A.2.1.3	Country.
	A.2.1.4	Qualification (physician, pharmacist, other health professional, lawyer, consumer or other non-health professional).
	A.2.2	Literature reference(s).
	A.2.3	Study identification (study name, sponsor study number, study type in which the reaction(s)/event(s) were observed – clinical trial, individual patient use, other).
A.3: Information on the sender and receiver of the case safety report	A.3.1	Sender (pharmaceutical company, regulatory agency, health professional, regional pharmacovigilance center, UMC, other); sender's identifier; person responsible for sending the report; sender's address, fax, telephone, and e-mail address.
	A.3.2	Receiver (pharmaceutical company, regulatory agency, health professional, regional pharmacovigilance center, UMC, other); receiver's identifier; receiver's address, fax, telephone, and e-mail address.

<sup>a</sup>For more detailed information see ICH (2001).

Table 10.4 The structure of ISH E2B – Section B: Information on the Case.

Subsection	Sub-subsection	Notes <sup>a</sup>
B.1: Patient characteristics	B.1.1	Patient (including, in the case of a fetus or suckling infant, information on both the parent and the child/fetus); medical record number(s) and the source(s) of the record number (if allowable).
	B.1.2	Age information: date of birth; age at time of onset of reaction/event; gestation of the fetus; patient age group (neonate, infant, child, adolescent, adult, elderly).
	B.1.3	Weight (kg).
	B.1.4	Height (cm).
	B.1.5	Sex.
	B.1.6	Last menstrual period date.
	B.1.7	Relevant medical history and concurrent conditions.
	B.1.8	Relevant past drug history.
	B.1.9	In case of death: date of death, reported cause(s) of death, whether an autopsy was done, autopsy-determined cause(s) of death.
	B.1.10	For a parent-child/fetus report, information concerning the parent: parent's age, last menstrual period date, weight (kg) of parent, height (cm) of parent, sex of parent, relevant medical history and concurrent conditions of parent, relevant past drug history of parent.
B.2: Reaction(s)/event(s)	B.2.i.0	Reaction/event as reported by the primary source.
	B.2.i.1	Reaction/event in MedDRA terminology (lowest level term).
	B.2.i.2	Reaction/event MedDRA term (preferred term).
	B.2.i.3	Whether term is highlighted by the reporter.
	B.2.i.4	Date of start of reaction/event.
	B.2.i.5	Date of end of reaction/event.
	B.2.i.6	Duration of reaction/event.
	B.2.i.7	Time intervals between suspect drug administration and start of reaction/event.
	B.2.i.8	Outcome of reaction/event at the time of last observation (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown).
B.3: Results of tests and procedures	B.3.1	Structured information about tests (date, test, result, units, reference range).
B.4: Drug(s) information	B.3.2	Results of tests and procedures relevant to the investigation.
	B.4.k.1	Characterization of drug role (suspect/concomitant/interacting).
	B.4.k.2	Drug identification (proprietary medicinal product name, active substance name(s), the country where the drug was obtained).
	B.4.k.3	Batch/lot number.
	B.4.k.4	Holder and authorization/application number of drug.
	B.4.k.5	Structured dosage information (dose (number), dose (units), number of separate doses, number of units in the interval, definition of the interval unit, cumulative dose to first reaction (number), cumulative dose to first reaction (units)).
	B.4.k.6	Dosage text (if structured dosage information is not available).
	B.4.k.7	Pharmaceutical form (dosage form).
	B.4.k.8	Route of administration.
	B.4.k.9	Parent route of administration (in case of a parent child/fetus report).
	B.4.k.10	Gestation period at time of exposure.
	B.4.k.11	Indication for use in the case.
	B.4.k.12	Date of start of drug.
	B.4.k.13	Time intervals between drug administration and start of reaction/event.
	B.4.k.14	Date of last administration.
	B.4.k.15	Duration of drug administration.

Table 10.4 (Continued)

Subsection	Sub-subsection	Notes <sup>a</sup>
	B.4.k.16	Action(s) taken (drug withdrawn, dose reduced, dose increased, dose not changed, unknown, not applicable).
	B.4.k.17	Effect of rechallenge (or re-exposure), for suspect drug(s) only.
	B.4.k.18	Suspected relatedness of drug to reaction(s)/event(s).
	B.4.k.19	Additional information on drug.
B.5: Narrative case summary and further information	B.5.1	Case narrative including clinical course, therapeutic measures, outcome and additional relevant information.
	B.5.2	Reporter's comments.
	B.5.3	Sender's diagnosis/syndrome and/or reclassification of reaction/event.
	B.5.4	Sender's comments.

<sup>a</sup>For more detailed information see ICH (2001).

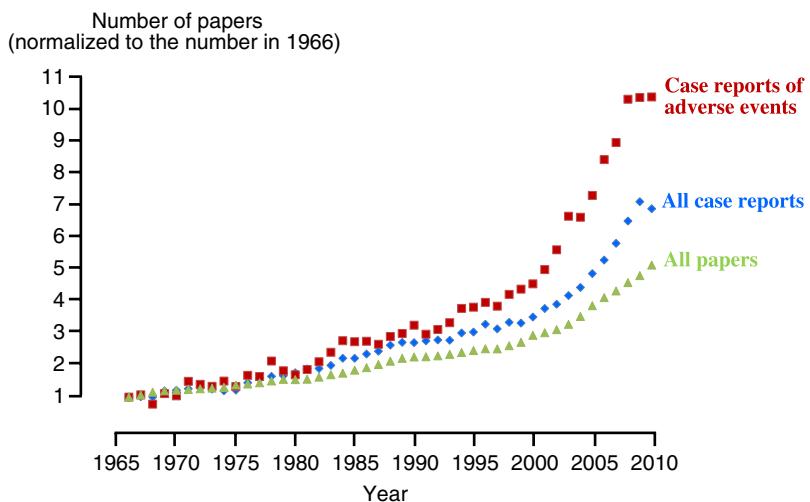


Figure 10.1 The numbers of papers containing the words "case report" or "report of a case" in the title, normalized to the number published in 1966; diamonds: all reports; squares: reports of adverse events. For comparison, the total numbers of papers published in each year are also shown (triangles). Source of data: Pubmed 1966 to 2010 inclusive.

between the increases in the numbers of all reports and reports of adverse events started in the mid 1990s, coinciding with increased pharmacovigilance activities at that time, as shown in Figure 10.2, in which the numbers of papers indexed in Pubmed under the term "pharmacovigilance"

(excluding authors' addresses) are shown over time. As the figure shows, the term pharmacovigilance emerged somewhat before its first indexed instance (OMS, 1969).

Many journals publish case reports of suspected ADRs from time to time, but in most of these

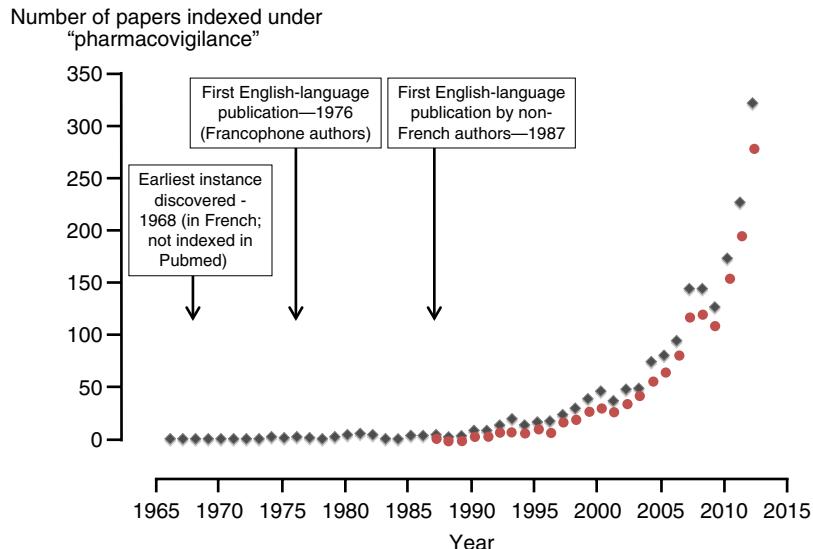


Figure 10.2 The numbers of papers indexed under “pharmacovigilance” (excluding authors’ addresses) in Pubmed from 1966 to 2012 inclusive (diamonds: all papers,  $n = 1763$ ; circles: English-language papers, 1989–2012,  $n = 1401$ ).

journals the case reports are greatly outnumbered by other types of articles. An important exception is the journal *Contact Dermatitis*, which publishes large numbers of case reports besides reports of original research. For example, in the 12 issues that appeared during 2011 the journal published 7 review articles, 69 original articles, and 77 so-called “Contact Points”; many of the latter dealt with individual case reports.

A few journals specialize in publishing case reports only. These include the following:

- *Journal of Medical Case Reports* ([www.jmedicalcasereports.com](http://www.jmedicalcasereports.com)) is “an open access, peer-reviewed online journal that will consider any original case report that expands the field of general medical knowledge, and original research relating to case reports”; it was launched in 2007 (Kidd and Hubbard, 2007) and its articles are archived at [www.ncbi.nlm.nih.gov/pmc/journals/476](http://www.ncbi.nlm.nih.gov/pmc/journals/476), where they are freely available.
- *Journal of Clinical Case Reports* ([www.omicsgroup.org/journals/jccrhome.php](http://www.omicsgroup.org/journals/jccrhome.php)) “explicates the complicated aspects of unusual disease symptoms followed by progression of the chronic disease, diagnosis of which leads to the detection of new aspects or mechanisms in the pathology

of that disease”; it was launched online in December 2011 (Rehman, 2011) and its articles are archived at [www.omicsgroup.org/journals/archiveJCCR.php](http://www.omicsgroup.org/journals/archiveJCCR.php), where they are freely available.

- *BMJ Case Reports* (<http://casereports.bmjjournals.com>) “delivers a focused, peer-reviewed, valuable collection of cases in all disciplines so that health-care professionals, researchers and others can easily find clinically important information on common and rare conditions”; it was launched in 2008 and its published articles are archived at [www.casesjournal.com/content](http://www.casesjournal.com/content), where the abstract/extract views are free, but access to the full texts in most cases requires a subscription or payment.
- *Cases Journal* ([www.casesjournal.com](http://www.casesjournal.com)), published “any case report that is authentic, understandable, and ethical” (Smith, 2008); it was launched in 2008 but ceased accepting articles in 2010; its published articles are archived at [www.casesjournal.com/content](http://www.casesjournal.com/content), where they are freely available.

However, these journals publish relatively few case reports of suspected ADRs (22 out of about 1400 reports in *BMJ Case Reports* and 73 out of

about 2000 reports in *Journal of Medical Case Reports* at the time of writing); most such reports appear in many other journals.

At the time of searching (April 2013), Pubmed listed 62 journals under the rubric “Case reports,” of which all but nine contained the words “case” or “cases” in their titles. However, only three (*BMJ Case Reports*, *Journal of Radiology Case Reports*, and *Neurocase*) were marked as being “currently indexed for MEDLINE” (National Library of Medicine, [www.ncbi.nlm.nih.gov/nlmcatalog/journals](http://www.ncbi.nlm.nih.gov/nlmcatalog/journals)), although many are indexed in EMBASE and a few in CINAHL and Psychinfo. In addition to these, five other case reports journals were indexed in other databases (see Appendix). Other journals that publish summaries of reports published in other journals (e.g., *Reactions Weekly* and *Adverse Reactions Titles*) were not indexed or even listed. This illustrates that many reports are not available for searching.

It also illustrates that, for journals that are included in databases, one needs to search several databases when looking for reports. For example,

when I combined the hits for the journal *Neurocase* from Embase ( $n = 817$ ), MEDLINE ( $n = 615$ ), and PsycINFO ( $n = 748$ ), after removing duplicates I was left with 868 reports, more than were found in any one of the databases alone. There is a case for having a separate database of case reports.

In order to determine which journals are publishing case reports of suspected adverse drug reactions, I have surveyed the reports that were cited in the *Side Effects of Drugs Annual*, Volume 33 (SEDA-33), in which papers on ADRs that were published in 2008 and the first half of 2009 were reviewed (Aronson, 2011b). Of over 5000 citations, 1881 referred to anecdotal reports, usually of single cases. In all, 708 different journals were represented and most of them (519) published only one or two papers. The topics of journals in which most of the reports appeared are listed in Table 10.5. About 50% of the papers were published in 100 journals (Figure 10.3). These data conform to Bradford’s law of scattering (Garfield, 1971), which states that “articles of interest to a specialist must occur not only in the periodicals specializing in his subject,

Table 10.5 Journals that published the most case reports of suspected ADRs during 2008 and the first half of 2009.

Main topic of journal	No.	%	Citations in SEDA-33 (Aronson, 2011b)	Top journal (number of papers published)
Medicine <sup>a</sup>	286	15.2	American Journal of Emergency Medicine (23)	
Pharmacotherapeutics <sup>b</sup>	276	14.7	Annals of Pharmacotherapy (54)	
Dermatology	206	11.0	Contact Dermatitis (29)	
Neurology	130	6.9	Journal of Neurology (12)	
Movement Disorders (12)				
Cardiology	126	6.7	International Journal of Cardiology (24)	
Gastroenterology <sup>c</sup>	104	5.5	European Journal of Gastroenterology & Hepatology (8)	
Anesthetics <sup>d</sup>	95	5.1	Anesthesia and Analgesia (19)	
Pediatrics <sup>e</sup>	91	4.8	Pediatric Blood & Cancer (8)	
Infectious diseases <sup>f</sup>	72	3.8	AIDS (10)	
Ophthalmology	60	3.2	American Journal of Ophthalmology (10)	
All journals	1881	100	Annals of Pharmacotherapy (54)	

<sup>a</sup>Medicine includes community medicine, emergency medicine, and critical care.

<sup>b</sup>Pharmacotherapeutics includes adverse drug reactions, clinical pharmacology, pharmacy, pharmacology, substance-related disorders, therapeutics, and toxicology.

<sup>c</sup>Gastroenterology includes studies of the liver, biliary tract, and pancreas.

<sup>d</sup>Anesthetics includes pain.

<sup>e</sup>Pediatrics includes all pediatric subspecialties and fetal and neonatal medicine.

<sup>f</sup>Infectious diseases includes microbiology, sexually transmitted diseases, and tropical medicine.

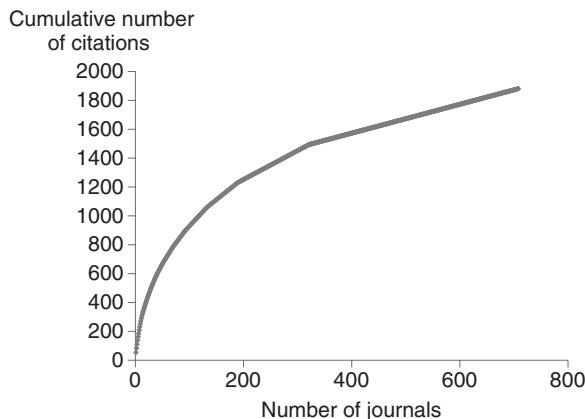


Figure 10.3 Cumulative number of case reports ( $n = 1881$ ) published in 708 journals, cited in *Side Effects of Drugs Annual* 33 (SEDA-33). Source: National Library of Medicine. NLM Catalog. [www.ncbi.nlm.nih.gov/nlmcatalog/journals](http://www.ncbi.nlm.nih.gov/nlmcatalog/journals).

but also, from time to time, in other periodicals, which grow in number as the relation of their fields to that of his subject lessens and the number of articles on his subject in each periodical diminishes" (Bradford, 1950). A corollary of this law (Garfield's law of concentration) is that most citations in any subject will be covered by a relatively small number of journals, as here.

For comparison, 258 systematic reviews and/or meta-analyses of all kinds were cited in the same volume of SEDA – only about 5% of the total. The most common source, unsurprisingly, was the *Cochrane Database* ( $n = 20$ ), with *Annals of Pharmacotherapy* second ( $n = 11$ ).

These data demonstrate the difficulty of keeping up with individual case reports and stress the importance of systematic reviews and database collections.

## REPORTING SUSPECTED ADVERSE DRUG REACTIONS IN JOURNALS

Methods of reporting suspected ADRs to journals have not been well described, apart from rudimentary lists of desiderata, without extended annotation or formal structure (Berneker *et al.*, 1983; Venulet, 1985; Auriche *et al.*, 1997), none of which has been further developed or adopted. The prob-

lems have been highlighted intermittently for over 30 years. Laganiere and Biron (1979) surveyed 23 papers on ADRs and discussed their shortcomings. Venulet *et al.* (1982) did likewise with a series of 5737 articles from 80 countries published between 1972 and 1979. Others have pointed to problems with the reporting of harms in clinical trials (Bradford, 1950; Hemminki, 1980; Hibberd and Meadows, 1980) and the need for systematic reviews. However, none of these studies has highlighted anecdotal reports in journals.

In 2003 I surveyed 35 *BMJ* reports concerning 48 patients; the median number of items mentioned was 9 (range 5–12) of a proposed set of 19 essential items, 9 (4–12) of the 14 items required by the MHRA on its Yellow Cards, and 8 (3–11) of 14 MedWatch items; and this analysis omitted other desirable features of anecdotal reports, such as formal causality assessment, possible mechanisms, and review of previous cases (Aronson, 2003a). Subsequently, Kelly (2003) published similar findings from a larger study. He found that in 1520 published case reports only three patient variables were reported more than 90% of the time, while 12 others were reported under 25% of the time; only one drug variable was reported more than 90% of the time and six others were reported 14–74% of the time. Other pieces of information (drug interactions, medication errors, and allergic drug reactions) were reported 61–99% of the time.

These observations led to two complementary sets of guidelines: PHARMA (Aronson, 2003b) and the ISPE/ISoP guidelines (Kelly *et al.*, 2007a,b, 2009). The former includes guidance about aspects of four important items that the latter omits (the nature of the title of the report, the inclusion of a structured summary, and some aspects of the introduction and the discussion). The latter includes a structure that allows a selection of items according to whether they are required, desirable, or [expected to be included] if relevant; it also includes herbal preparations. A checklist of compulsory, desirable, and optional items based on a synthesis of these two systems is given in Table 10.6. It is hoped that journals that publish case reports of suspected ADRs will ask authors to use this checklist in preparing their accounts, and it is supplied here,

Table 10.6 Checklist of items for inclusion in an anecdotal report of a suspected ADR: C, compulsory; D, desirable; O, optional (if relevant to the case).

C	D	O	Item	Comments
■			Title	<input type="checkbox"/> Non-declarative; should specify, when relevant: the suspected adverse event, the suspected drug, the age and sex of the patient, and important susceptibility factors, if known
■			Structured summary (headings italicized; up to 250 words)	<input type="checkbox"/> The adverse event <input type="checkbox"/> The suspected drug <input type="checkbox"/> Details of the patient(s) <input type="checkbox"/> Evidence that links the drug to the event <input type="checkbox"/> The management used <input type="checkbox"/> The mechanism, if known <input type="checkbox"/> The implications for therapy <input type="checkbox"/> Hypotheses that arise (if any)
■			Introduction	<input type="checkbox"/> The suspected drug and the associated adverse event <input type="checkbox"/> Previous similar reports <input type="checkbox"/> The purpose of the report
■			Demographics	<input type="checkbox"/> Age <input type="checkbox"/> Sex
■	■		Demographics	<input type="checkbox"/> Weight, height, ethnic background, occupation
■	■		Demographics	<input type="checkbox"/> Obstetric status
■			Premorbid condition	<input type="checkbox"/> All diagnoses, especially those for which drug therapy was indicated (could be matched to the list of current medicines); specify allergies (present or absent)
■	■		Premorbid condition	<input type="checkbox"/> Previous diagnoses, including duration and severity
■			The suspected drug	<input type="checkbox"/> International non-proprietary name (or other generic name); proprietary name; synonyms <input type="checkbox"/> Indication <input type="checkbox"/> Dosage regimen (dose, frequency, route, other instructions) <input type="checkbox"/> Duration For herbal products: <input type="checkbox"/> The family and Latin binomial name, the ingredients of the formulation, the plant part(s), and the type of preparation (e.g., crude herb or extract) <input type="checkbox"/> The dosage unit
■			The suspected drug	<input type="checkbox"/> Prior exposure to the suspected drug or another in its class <input type="checkbox"/> Plasma concentrations (parent compound and main metabolites) <input type="checkbox"/> For herbal extracts: standardization, the solvent used, the drug:extract ratio, and actual contents, if assayed <input type="checkbox"/> Reason for off-label use
■			The suspected drug	<input type="checkbox"/> All current drug therapy, including dosage, duration, and indication <input type="checkbox"/> Other recent drug therapy, if relevant [Include prescription, non-prescription, herbal, and complementary medicines, if known]
■			Other drug therapy	
■			Other relevant history	<input type="checkbox"/> Relevant family history (including relevant negatives) <input type="checkbox"/> Relevant social history (e.g., smoking, alcohol, recreational drugs)
■			The adverse event	<input type="checkbox"/> Case definition <input type="checkbox"/> Assessment of severity (intensity) and seriousness <input type="checkbox"/> The time-course in relation to administration of the suspected drug <input type="checkbox"/> The effect of withdrawal, including time-course (dechallenge) <input type="checkbox"/> The effect of rechallenge, including time-course; state reasons for non-rechallenge <input type="checkbox"/> The final outcome (e.g., recovered completely, recovered with sequelae, died) <input type="checkbox"/> Post-mortem findings, if relevant

(Continued)

Table 10.6 (Continued)

free of all copyright restrictions. A set of guidelines on publishing case reports in general has also been published (Gagnier *et al.*, 2013; Gagnier *et al.*, 2014).

## ACKNOWLEDGMENTS

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## APPENDIX

Case reports journals listed in Pubmed ( $n = 62$ ) but mostly marked as “Not currently indexed for MEDLINE”; X marks those indexed in different databases with, in parentheses, the number of hits on the day of searching (8 April 2013); five other journals\*, found in other databases but not listed in Pubmed, are also listed.

Journal	Pubmed	Embase	Medline	CINAHL	PsycINFO
AHRQ WebM&M: Morbidity & Mortality Rounds on the Web					
American Journal of Case Reports	X (395)				
APSP Journal of Case Reports					
Archivos de Neurología y Psiquiatría de México: Órgano de la Sociedad Mexicana de Neurología y Psiquiatría			X (4)		X (12)
BMJ Case Reports	X (5435)	X (2836)	X (5493)		
Case Reports	*		X (58)		
Case Reports and Clinical Practice Review	*	X (255)			
Case Reports Chicago Children's Memorial Hospital		X (14)			
Case Reports in Anesthesiology					
Case Reports in Clinical Psychology	*				X (67)
Case Reports in Dentistry					
Case Reports in Dermatological Medicine					
Case Reports in Dermatology		X (135)			
Case Reports in Emergency Medicine					

Journal	Pubmed	Embase	Medline	CINAHL	PsycINFO
<i>Case Reports in Endocrinology</i>					
<i>Case Reports in Gastroenterology</i>		X (321)			
<i>Case Reports in Gastrointestinal Medicine</i>					
<i>Case Reports in Genetics</i>					
<i>Case Reports in Hematology</i>					
<i>Case Reports in Infectious Diseases</i>					
<i>Case Reports in Medicine</i>		X (604)			
<i>Case Reports in Nephrology and Urology</i>					
<i>Case Reports in Neurological Medicine</i>					
<i>Case Reports in Neurology</i>		X (86)			
<i>Case Reports in Obstetrics and Gynecology</i>					
<i>Case Reports in Oncological Medicine</i>					
<i>Case Reports in Oncology</i>		X (271)			
<i>Case Reports in Ophthalmological Medicine</i>					
<i>Case Reports in Ophthalmology</i>		X (125)			
<i>Case Reports in Orthopedics</i>					
<i>Case Reports in Otolaryngology</i>					
<i>Case Reports in Pathology</i>					
<i>Case Reports in Pediatrics</i>					
<i>Case Reports in Psychiatry</i>					
<i>Case Reports in Pulmonology</i>					
<i>Case Reports in Radiology</i>					
<i>Case Reports in Rheumatology</i>					
<i>Case Reports in Surgery</i>					
<i>Case Reports in Transplantation</i>					
<i>Case Reports in Urology</i>					
<i>Case Reports in Vascular Medicine</i>					
<i>Case Reports. Chicago. Children's Memorial Hospital Cases Journal</i>		X (1145)			
<i>Clinical Case Studies</i>		X (275)			X (330)
<i>Clinical Cases in Mineral and Bone Metabolism</i>	*	X (260)			
<i>Clinical Medicine. Case Reports</i>		X (16)			
<i>Clinical Medicine Insights. Case Reports</i>		X (65)			
<i>Clinics and Practice</i>					
<i>Infectious Disease Reports</i>		X (65)			
<i>International Journal of Surgery Case Reports</i>		X (424)			
<i>International Medical Case Reports Journal</i>		X (36)			
<i>Journal of Cardiology Cases</i>		X (301)			
<i>Journal of Dermatological Case Reports</i>		X (84)			
<i>Journal of Medical Case Reports</i>		X (2285)			
<i>Journal of Medical Cases</i>					
<i>Journal of Participatory Medicine</i>					
<i>Journal of Radiology Case Reports</i>	X (301)	X (202)	X (202)		
<i>Journal of Surgical Case Reports</i>					
<i>Medical Ethics (Burlington, Mass.)</i>		X (55)			
<i>Medical Mycology Case Reports</i>		X (18)			
<i>Neurocase</i>	X (693)	X (817)	X (615)	X (636)	X (748)
<i>Pediatric Case Reviews</i>		X <sup>a</sup> (33)	X (71)		
<i>Periodontal Case Reports</i>		X (94)			
<i>Periodontal Clinical Investigations</i>		X (104)			
<i>Physical Therapy Case Reports</i>	*			X (154)	
<i>Rare Tumors</i>		X (125)	X (233)		
<i>Retinal Cases &amp; Brief Reports</i>					
<i>Urologic Radiology</i>		X (699)	X (669)		

<sup>a</sup>Print version only.

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# 11

## Periodic Safety Update Reports

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### INTRODUCTION

The periodic safety update report (PSUR) is a document that allows a periodic, comprehensive assessment of the worldwide safety data of a marketed drug or biological product. The concept evolved from the Council for International Organizations of Medical Sciences (CIOMS) Working Group II report (CIOMS, 1992). The process that culminated in the publication of that report was initiated in 1989, at a time when several countries had requirements for periodic safety updates. Individual local regulatory authorities were requesting that both foreign and domestic data be presented according to different inclusion criteria, formats and time intervals, and the number of reports that had to be produced was placing a high administrative burden on manufacturers. The purpose of CIOMS II was to explore the possibility of developing a harmonized approach to preparing PSURs

that would meet most existing needs and forestall any diversity in future requirements. CIOMS II formed the basis for the International Conference on Harmonization E2C Guidance for Industry (ICH, 1996), which defined the format and content for PSURs and introduced the concept of an international birth date (IBD) – the date of first approval in the world. ICH E2C set the period for review of interval (rather than cumulative) safety data as 6 months. After it was adopted, practical considerations regarding the content and preparation of the report were addressed in the CIOMS Working Group V report (CIOMS, 2001), and many of the recommendations in that report formed the basis of an addendum to ICH E2C (ICH, 2003). The addendum introduced to the PSUR new concepts that were not in E2C but that reflect current pharmacovigilance practices. These include confidentiality of proprietary information, risk management programs and benefit–risk analyses. All these

regulations are now in Section 6 (for PSURs) of Volume 9A of the Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human use (updated in September 2008).

The PSUR has now been adopted in many European countries, Japan and the USA. It is emerging as a gold standard of safety evaluation for marketed drugs and an important pharmacovigilance tool. The new EU pharmacovigilance legislation (Regulation no. 1235/2010 and Directive 2010/84/EC (amending Regulations 726/2004 and 1394/2007, and Directive 2001/83/EC)) published in the *Official Journal* on 31 December 2010 and that applied from July 2, 2012, proposes a number of changes that strengthen the way the safety of medicines for human use is monitored in the EU and impact the format and content of many documents, including PSURs.

## PURPOSE OF THE PERIODIC SAFETY UPDATE REPORT

The PSUR creates the opportunity for a periodic overall safety evaluation to show whether a product's safety profile has remained the same or has undergone change since it was authorized and to indicate whether changes should be made to product information to optimize the use of a product. The reason such a review is needed periodically is because clinical trials tend to be of short duration and to include a limited number of patients. Moreover, clinical trials have inclusion and exclusion criteria. After a product is launched, it may be used by patients not studied in clinical trials; for example, children, the elderly, pregnant or breastfeeding women, or patients with comorbidities, such as hepatic or renal disease, or co-prescriptions that were forbidden during the clinical trials. After approval, a drug becomes available for immediate use in large populations, so rare adverse drug reactions (ADRs) can be more easily identified. The drugs also become available for indefinite use (unless prescribing information indicates otherwise), and delayed-onset ADRs become easier to identify.

## PERIODIC SAFETY UPDATE REPORT: GENERAL PRINCIPLES

### ONE REPORT FOR PRODUCTS CONTAINING ONE ACTIVE SUBSTANCE AUTHORIZED TO ONE MARKETING AUTHORIZATION HOLDER

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance for medicinal products authorized to one marketing authorization holder (MAH) may be covered in one PSUR. Within the single PSUR, separate presentations of data for different dosage forms, indications, or populations (e.g., children versus adults) may be appropriate.

### PRODUCTS AUTHORIZED TO MORE THAN ONE MARKETING AUTHORIZATION HOLDER

Each MAH is responsible for submitting PSURs, even if different companies market the same product in the same country. When companies are involved in contractual relationships (e.g., licensor- licensee), arrangements for sharing safety information should be clearly set out. To ensure that all relevant data are reported to the regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

### COMBINATION PRODUCTS

For combinations of substances that are also authorized individually, safety information for the fixed combination may be reported either in a separate PSUR or included as separate presentations in the report for one of the separate components, depending on the circumstances. Cross-referencing all relevant PSURs is essential.

### GENERAL SCOPE OF INFORMATION

All relevant clinical and nonclinical safety data should cover only the period of the report (interval data), with the exception of regulatory status information on authorization applications and renewals and data on serious, unlisted ADRs, which should be provided for both the period in question and as

cumulative summary tabulations starting from the IBD. A listed ADR is one whose nature, severity, specificity, and outcome are consistent with the company core safety information (CCSI) (ICH, 1996). A serious ADR is defined as any untoward medical occurrence that at any dose results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital abnormality/birth defect (ICH, 1994).

The safety information contained within the PSUR comes from a variety of different sources. These include spontaneous reports of adverse events from different countries, the literature, clinical trials, registries, regulatory ADR databases, and important animal findings. The main focus of the report should, however, be ADRs. For spontaneous reports, unless indicated otherwise by the reporting healthcare professional, all adverse experiences should be assumed to be ADRs; for clinical trial and literature cases, only those judged not related to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Reports of lack of efficacy specifically for drugs used in the treatment of life-threatening conditions and for certain other medicinal products, such as contraceptives and vaccines, may represent a significant hazard, and in that sense may be a safety issue. These types of cases should be discussed in the PSUR.

#### **PREPARATION OF PERIODIC SAFETY UPDATE REPORTS ACCORDING TO THE INTERNATIONAL BIRTH DATE**

Each medicinal product should have as an IBD the date of the first marketing authorization for the product granted to any company in any country in the world. When the CIOMS II proposals were first incorporated into European regulations, they were modified to include the concept of a European birth date rather than an IBD. This effectively implied that PSURs currently scheduled to the IBD had to be rescheduled to the first European approval date – which seemed to run counter to the drive for harmonization. Fortunately, ICH E2C reverted to the IBD for scheduling reports, so now the Euro-

pean birth date is the same as the IBD for medicinal products first authorized in the EU, and the MAH may use the IBD to determine data-lock points (DLPs) in Europe. The DLP is the date designated as the cut-off for data to be included in a PSUR.

#### **FREQUENCY OF REPORTING**

Each PSUR should cover the period since the last update report and should be submitted within 60 days of the last DLP. An additional 30-day delay may be provided in exceptional circumstances, such as a large number of case reports, additional safety analyses required, or request considered on a “one-off” individual basis. The need for a report and the frequency of report submission to authorities are subject to local regulatory requirements. The age of a medicinal product on the market may influence this process. Moreover, during the initial years of marketing, a medicinal product will ordinarily receive authorizations at different times in different countries. It is during this early period that harmonization of reporting is particularly important. Once a product has been marketed for several years, the need for a comprehensive PSUR and the frequency of reporting may be reviewed, depending on local regulations or requests while maintaining one IBD for all regulatory authorities. In Europe, for example, the last 6-month PSUR should be provided at the first renewal, while for subsequent renewals either a single 5-year PSUR or a separate 6-month or yearly PSUR covering 5 years, together with a PSUR bridging summary report, are required.

The new EU pharmacovigilance regulation that came into force in July 2012 also introduces requirements for the PSUR to be proportionated to the risks; then, it may not be necessary to submit a PSUR with the usual timeframe for low-risk products (e.g., generic drug, well-established use, traditional herbal products) unless there are specific safety concerns.

#### **RESTARTING THE CLOCK**

Approvals beyond the initial approval for the active substance may be granted for reasons including new indications, dosage forms, and routes of

administration or populations beyond those for which the active substance was initially authorized. The potential consequences for the safety profile of new types and extent of population exposure should be discussed between the regulatory authorities and the MAH because they may influence the requirements for periodic reporting. When an amendment is proposed to the PSUR submission cycle, the applicant should submit a reasoned request for the amendment as part of the application for a marketing authorization.

#### REFERENCE SAFETY INFORMATION

The CCSI is derived from the company core data sheet (CCDS), which contains all relevant safety information, which the company requires to be listed for the drug in all countries where it is marketed. The CCSI forms the basis for determining whether an ADR is listed or unlisted, as opposed to labeled or unlabeled. If the ADR reported is found in the approved product information for a given country, the event is considered labeled. If not, it is unlabeled. The locally approved product information (e.g., the European Summary of Product Characteristics (SPC) in Europe) continues to be the reference document upon which labeledness (or expectedness) is based for the purpose of local expedited post-authorization safety reporting, so labeledness is country specific. Listedness, by contrast, is uniform across all countries, and it is listedness that must be determined for the PSUR.

#### DESCRIPTION OF THE REACTION

The reaction terms used in the PSUR will generally be derived from whatever standard terminology ("controlled vocabulary" or "coding dictionary") is used by the reporting MAH. In many cases, this will be the Medical Dictionary for Regulatory Activities (MedDRA). It is now widely used in the preparation of PSURs. In November 1997, the US Food and Drug Administration (FDA) replaced its spontaneous reporting system and its conventional dictionary, the Coding Symbols for a Thesaurus of Adverse Reaction Terms, with the new adverse events reporting system and the MedDRA termi-

nology. MedDRA is also a key part of the electronic database systems used by European and Japanese authorities. MedDRA is not perfect, however, and there are still issues regarding its implementation that need to be resolved. For example, there are important differences in the ways that safety databases interface with the dictionary and uncertainty about the most appropriate way to manage version changes (Brown, 2004).

#### REGULATORY REQUIREMENTS

ICH E2C, in conjunction with its addendum, has been adopted by the Japanese Ministry of Health, Labour and Welfare and included in Volume 9 of the Rules Governing Medicinal Products in the European Union, on pharmacovigilance (EC, 2004a). The US FDA has also introduced periodic reporting requirements based on ICH E2C, and in its published guidance for industry in February 2004 (FDA, 2004). ICH E2C has therefore made its mark in all three ICH regions. However, the reporting requirements in those regions differ:

- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require that reports be submitted every 6 months for the first 2 years after authorization, annually for the two following years, and then three-yearly after the first renewal;
- In the USA, the FDA requires quarterly reports during the first 3 years, and then annual reports.
- In Japan, the authorities require PSURs covering global experience plus periodic reports summarizing "clinical experience investigations" and "special investigation" experience every 6 months for the first 2 years, then on an annual basis during the "re-examination" period (4, 6 or 10 years), and finally five-yearly following of the "re-examination" period.
- In other countries, the periodicity has not been really harmonized; for example, annual reports for 3 years in Australia, annual reports or produced upon demand in Canada, 6-monthly for 2 years and then annually for 2 years in India.

The ICH steering committee should revise soon the guidelines E2C (R2) (on PSUR template),

E2E and E2F. The idea is to optimize the lifecycle benefit–risk of medicines for the promotion of public health by establishing a modular and improved approach to avoid redundant work between PSURs, development safety update reports, and risk management plans (RMPs). This should form the basis for detailed guidance in the EU Good Vigilance Practices guidelines.

## PERIODIC SAFETY UPDATE REPORT CONTENT

The amendment to ICH E2C stipulates that the MAH should submit a PSUR to the competent authority of the country or region in question with succinct summary information and a benefit–risk analysis in the light of new or changing post-authorization information. Specifically, the contents of the PSUR should be as laid out in Table 11.1. The rest of this section describes an overview of a model PSUR.

Table 11.1 Contents of the PSUR.

Section number	Section title
Executive summary	
1.1	Introduction
1.2	Worldwide market authorization
1.3	Update on regulatory authority or marketing authorization holder actions taken for safety reasons
1.4	Changes in reference safety information
1.5	Patient exposure
1.6	Presentation of individual case histories
1.7	Studies
1.8	Other information
1.9	Overall safety evaluation
1.10	Conclusion
Appendix 1	Company core data sheet
Appendix 2	Marketing authorization status
Appendix 3	Line listings of case reports
Appendix 4	Summary tabulations of events (complement to Appendix 3)

## TITLE

PSURs contain proprietary information, so the title page should contain a statement on the confidentiality of the data and conclusions included in the report.

## EXECUTIVE SUMMARY

The executive summary should consist of a brief overview and a summary of the key messages, providing the reader with a description of the most important information. An example can be found on page 333 of the CIOMS V report (CIOMS, 2001).

## INTRODUCTION

The introduction sets the scene and puts the report in context, cross-referencing it to previous reports, describing those products/formulations that are included and excluded, outlining the pharmacology of the product, its indications (both marketed and in clinical trials) and any co-licensing agreements.

## WORLDWIDE MARKETING AUTHORISATION STATUS

The PSUR should include a short summary of the worldwide marketing authorization status and cross-reference this to an appendix in which the cumulative approvals (and renewal dates) should be tabulated in chronological sequence. This table should also include lack of approval, relevant explanations from regulatory authorities, and withdrawals by the company for efficacy or safety reasons.

## UPDATE ON REGULATORY AUTHORITY OR MARKETING AUTHORIZATION HOLDER ACTIONS TAKEN FOR SAFETY REASONS

The update on regulatory authority or MAH actions taken for safety reasons during the reporting period refers to:

- marketing authorization, withdrawal or suspension;

- failure to obtain a marketing authorization renewal;
- restrictions on distribution;
- clinical trial suspension;
- dosage modification/formulation changes, and
- changes in target population or indications.

The update should discuss the safety-related reasons that led to the actions described and append the appropriate documentation including any communication with healthcare professionals (e.g., Direct Healthcare Professional Communications).

#### **CHANGES IN REFERENCE SAFETY INFORMATION**

The changes in reference safety information section refers to changes in the CCSI during the reporting period. The CCDS, which incorporates the CCSI, should be included as an appendix. If no CCDS is available, a national SPC can be used. A covering letter should discuss meaningful differences between the CCSI and local datasheets and comment on the consequences for safety evaluations and for actions proposed or initiated.

#### **PATIENT EXPOSURE**

Patient exposure refers to both market exposure and clinical trials (if relevant). Estimates of patient exposure for marketed drugs often rely on gross approximations of in-house or purchased sales data or volume. This information is not always reliable or available for all products. For example, hospital-based statistics from the major use-monitoring sources are frequently unavailable. It is also difficult to obtain accurate data for generics, non-prescription drugs, or multiple drug regimens. The MAH should use a consistent method of calculation across PSURs for the same product. If a change in the method is appropriate, both previous and current methods and calculations should be shown in the PSUR introducing the change. When exposure data are based on information from a period that does not fully cover the period of the PSUR, the MAH can make extrapolations using the available data. When this is done, it should be clearly indicated what data were used and why it is

valid to extrapolate for the PSUR period in question (for example, stable sales over a long period and seasonality of use of the product). In addition, when possible and relevant, data should be broken down by age and gender. The CIOMS V report contains examples of patient exposure estimations (CIOMS, 2001).

#### **PRESENTATION OF INDIVIDUAL CASE HISTORIES**

There is no specific guidance in E2C on the presentation of individual case histories; but because it is impractical to present all case reports for the reporting period, a brief description of the criteria used to select cases for presentation should be given. This section of the PSUR should contain a description and analysis of selected cases, including fatalities, presenting new and relevant safety information and grouped by medically relevant headings or system organ classes (SOCs). Depending on their type or source, available ADR cases should be presented as line listings and/or as summary tabulations. A line listing provides key information but not necessarily all the details customarily collected on individual cases. However, it does serve to help regulatory authorities identify cases that they might wish to examine more closely by requesting full case reports. In addition to individual case line listings, summary tabulations of ADR terms for signs, symptoms, and diagnoses across all patients should usually be presented. Such tabulations should be based on the data in line listings (e.g., all serious ADRs and all non-serious unlisted ADRs), but also on other sources for which line listings are not requested (e.g., non-serious listed ADRs).

#### **STUDIES**

Studies refer to only those company-sponsored studies and published safety studies, including epidemiology studies, that produce findings with potential impact on product safety information. These should be included along with a discussion of any final or interim results. The MAH should not routinely catalog or describe all the studies.

## OTHER INFORMATION

Other information may include risk management programs the MAH has put in place and/or a benefit–risk analysis report. If such an analysis has been conducted separately, a summary of the analysis should be included in this section. This section can also include important information received after the DLP; for example, significant follow-up on cases included in the PSUR and changes to the CCSI agreed after the DLP.

## OVERALL SAFETY EVALUATION

The overall safety evaluation should highlight new information on serious and non-serious unlisted ADRs. For listed ADRs, it should describe any reported changes in the characteristics of the reaction (e.g., severity, outcome and target population) as well as increases in frequency of reporting of reactions. For emerging safety issues, the information received during the period under review should be discussed from the perspective of cumulative experience. For new safety issues, the current action should be stated (e.g., under active review). If there are no new safety issues, this should be stated with a note that the information is in keeping with the established safety profile. All evaluations should be concise, and the discussion and analysis should be organized by SOC rather than by listedness or seriousness. Although related terms might be found in different SOCs, they should be reviewed together for clinical relevance. This section should also review reports of:

- drug interactions;
- overdose – deliberate or accidental and treatment;
- abuse or misuse;
- pregnancy or lactation: positive and negative experiences;
- special patient groups (e.g., children, elderly, organ impaired); and
- effects of long-term treatment.

## CONCLUSION

The conclusion should indicate safety data that are not in accordance with previous experience and/or

with the CCSI and specify and justify any action recommended or initiated.

## APPENDICES

Although the intent of the PSUR initiative is to have a standard PSUR format and content, individual countries may require additional information. For example, the PSUR is designed to contain information reported or confirmed by a healthcare professional, but regulatory agencies in some countries, including the US, also require consumer reports of ADRs. This is accommodated by including consumer information in an appendix to the PSUR.

But the content of the PSUR changed with the new EU pharmacovigilance regulation in 2012. Indeed, a concept paper from the European Commission (on implementing measures in order to harmonize the performance of the pharmacovigilance activities provided in Directive 2001/83/EC and regulation (EC) No. 726/2004) was submitted for public consultation in September 2011 (EC, 2011). This document proposed amending the content of the PSUR to include more clearly:

- cumulative data starting from the granting of the marketing authorization while retaining a focus on new information emerging in the period since the last submission;
- results of assessments of the effectiveness of risk minimization activities relevant to the risk–benefit assessment;
- an accurate estimation of the population exposed to the medicinal product including all data relating to the volume of sales and volume of prescriptions, accompanied by a qualitative and quantitative analysis of actual use, including how it may differ from indicated use, based on all data available to the MAH, including the results of observational or drug utilization studies;
- summaries of data relevant to the benefit–risk assessment of the product (including studies results) and scientific evaluation of this benefit–risk balance from all available data, including data from clinical trials in unauthorized indications and populations.

In contrast, detailed listings of individual cases shall not be included routinely. Case narratives shall, however, be provided where relevant to the scientific analysis of a signal or safety concern in the relevant risk evaluation section of the PSUR.

The structure of the document should then be changed to include sections on:

- lack of efficacy in controlled clinical trials;
- overview of signals ongoing and closed;
- signal and risk evaluation;
- benefit evaluation; and
- integrated benefit-risk analysis for approved indications.

All these proposed changes have been implemented into the Guidelines on good Pharmacovigilance practices (GVP) 3 – Module VII (EMA/816292/2011 Rev 1\*).

## SUMMARY BRIDGING REPORTS

The different frequency and periodicity requirements of different regulatory authorities in different countries create potential problems for the production of PSURs. Under ICH E2C provisions, regulators who do not wish to receive 6-month report are expected to accept two 6-month reports as an annual report or the appropriate series of reports as a 5-year report. CIOMS V therefore proposed the use of the summary bridging report to facilitate the review of a series of reports. This is a concise document integrating the information presented in two or more PSURs that is submitted to a regulatory authority to cover a specified period over which a single report is required. It should not contain new data or repeat the information already included in the PSURs, but it should cross-reference those other reports. The format/outline should be identical to the format of the usual PSUR, but the content should consist of summary highlights. The summary bridging report ordinarily should not contain line listings; however, a summary tabulation of serious, unlisted ADRs should be included if the regulatory authority requests it.

## ADDENDUM REPORTS

The concept and use of the IBD for PSURs have not been fully accepted by all regulators. Some require that PSURs be scheduled according to the local approval date. Moreover, not all companies will have synchronized their renewal dates by bringing them forward to the IBD in those countries where this is permissible. To avoid producing additional reports for those countries perceiving that any report with a DLP more than 60 days before submission is out of date, CIOMS V recommended the use of an addendum report. This is an update to the most recently completed, scheduled PSUR that is produced when a regulator requires a safety update outside the usual reporting cycle, and more than a brief amount of time has elapsed since the DLP of the most recent PSUR. A brief amount of time here refers to 3 months for a 6-month report and more than 6 months for an annual or longer interval report. The addendum report, therefore, supplements annual or five-yearly reports. CIOMS V proposed that the addendum report should follow the PSUR format, but that it should contain the minimum of information.

## THE PERIODIC SAFETY UPDATE REPORT PROCESS

The PSUR process comprises the following steps:

- intake of ADR information;
- case processing;
- data retrieval;
- data analysis; and
- medical review and risk assessment.

Once an ADR has been reported (usually spontaneously to a company representative), the case is entered into a safety database, a narrative is prepared, and a MedDRA term assigned to ADRs described in the case. Seriousness and labeledness are assigned, and these determine whether or not the event needs to be processed as an expedited report. Data retrieval from the DLP and generation of line listings and summary tabulations are typically the most time-consuming parts of the PSUR

process, but they are the key to a thorough medical review and risk assessment. The sections of the PSUR that lend it its value as a pharmacovigilance tool, the presentation of individual case histories and the overall safety evaluation, depend critically on the data retrieval step. Data analysis is based on the traditional method of medical review carried out by trained healthcare professionals and increasingly supplemented by data mining methods that are emerging as useful tools in signal detection. Finally, the medical review and risk assessment steps force the MAH to take a critical look at its data to determine whether the risk for the marketed product has changed and whether changes to the product label have to be made or other risk management initiatives need to be implemented. Once finalized, the PSUR is submitted electronically (most of the time) to the competent authorities.

## BEST METHODS OF COMPLIANCE

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for the evaluation of medicinal products has published a position paper on compliance with pharmacovigilance regulatory obligations (CPMP, 2001). This paper, which came into effect in January 2002, emphasizes the importance of compliance with periodic reporting and lists the forms that noncompliance may take:

- *Submission:* complete non-submission of PSURs, submission outside the correct cycle or outside the correct timeframes and non-restart of the cycle of submission when necessary.
- *Format of the document:* report not in accordance with ICH E2C.
- *Concealment of information,* particularly in the following sections of the report: update of regulatory authority or MAH actions taken for safety reasons, changes to reference safety information, patient exposure and presentation of individual case histories.
- *Poor-quality reports:* poor documentation of ADR reports or insufficient information provided to perform a thorough assessment in the presentation of individual case histories section,

new safety signals not or poorly assessed in the overall safety information section, misuse not highlighted and absence of standardized medical terminology.

- *CCDS:* where changes have been made to the CCDS since the submission of the last PSUR and submission of a report where the covering letter does not highlight the differences between the CCDS and the EU or national SPC.
- *Previous requests from competent authorities not addressed:* submission of a report where previous requests from competent authorities have not been addressed (e.g., close monitoring of specific safety issues).

## PRAGMATIC SOLUTIONS

In a paper published in 2004, Michael J. Klepper of North Carolina based Integrated Safety Systems, Inc., a safety surveillance and consulting firm for pharmaceutical, biological, and medical device companies, outlined some of the ways that companies could maximize the efficiency of their procedures for producing PSURs, avoid potential pitfalls, and ensure full compliance (Klepper, 2004). Some of these elements have also been considered in a recent paper by Brian D. Edwards and Giovanni Furlan that describes how to apply the human factor to PSURs (Edwards and Furlan, 2010).

## RESOURCE PLANNING

The PSUR process relies heavily on the availability of adequate resources, particularly since CIOMS V introduced the concept of PSURs covering periods longer than 6 months (including the five-yearly reports for local product renewals in Europe) that still have to be submitted within 60 days of the DLP. The resources needed depend on factors including the size of the company, the number of marketed products, when these products were approved, the number of countries where these medical products are marketed, the volume of ADRs, and the complexity of the medical condition for which the medical product is indicated. For example, the process of producing a PSUR for a newly approved AIDS drug that is marketed in

many countries will require considerably more resources than the same process for a 15-year-old topical formulation that is only approved in a few countries worldwide for the treatment of athlete's foot. Those resources are not solely restricted to the product safety department. Contributions are also required from regulatory departments, which provide information regarding the status of worldwide approval and any regulatory action taken anywhere in the world, clinical research departments, which provide data on any important safety issues emerging from ongoing clinical trials, and marketing/financial services departments, which hold the sales/prescriptions data needed to estimate patient exposure.

Over a given period, say a year, the MAH should know the number of PSURs due in that year, including the DLPs and submission dates of these reports. It should also factor in an estimate of volume and complexity of cases. The MAH can then allocate its resources accordingly and put in place a contingency plan in case new work arises; for example, an unexpected regulatory query. If there are too few resources available, the MAH may consider outsourcing the work, hiring more people, providing more training, or re-prioritizing projects. It is also essential that communication between departments is good, so that all the personnel involved in producing the PSUR are aware of expectations, deliverables, and dates of completion.

#### DEFINITIONS AND SCRIPTS FOR MEDICALLY IMPORTANT ADVERSE DRUG REACTIONS

Reported ADR data are, in general, incomplete and of poor quality (Venulet, 1986). Although most suspected ADRs are reported by physicians trained in what is called Western (biological) medicine, there are considerable cultural differences in the use and interpretation of certain medical terms. *Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use* (CIOMS, 1999) is one attempt to cross those cultural differences by establishing standard definitions for selected terms for ADRs and minimum requirements for the use of those terms in international reporting. In an introductory chapter to the former version of that

book, Ronald Mann, former director of the University of Southampton's Drug Safety Research Unit, emphasized the importance of keeping the patient's own words when reporting complaints, so as not to corrupt the data at source. At the next stage of the communication process – when the physician-reporter passes the information on to a company representative – Klepper suggests that scripts should be developed that are designed to extract the critical information from the reporter. Those responsible for the intake of ADR information should be thoroughly trained in the use of these scripts. A script dealing with liver necrosis, for example, would guide the representative to ask specific questions, such as the basis of the diagnosis (e.g., viral serologies and needle biopsy). Examples of some medically important ADRs (FDA, 2003; Mann, 2005) are summarized in Table 11.2. The World Health Organization Critical Term list provides an even more extensive list of such ADRs (WHO, 1998).

#### TRAINING

The personnel involved in the PSUR process require training in four broad areas:

Table 11.2 Some medically important ADRs.

Acute liver failure
Acute renal failure
Acute respiratory failure
Agranulocytosis anaphylaxis
Aplastic anemia
Cardiac valvular disease
Congenital anomalies
Liver necrosis
Lyell's syndrome
Malignant hypertension
Pulmonary fibrosis
Pulmonary hypertension
QT prolongation
Rhabdomyolysis
Sclerosing syndromes
Seizure
Stevens–Johnson syndrome
Torsades de pointe
Toxic epidermal necrolysis
Ventricular fibrillation

- *product training* – to fully understand a product’s pharmacology or biological activity, mechanism of action, and the known risks associated with its use;
- *clinical training* – to fully understand the characteristics of the targeted patient population likely to take the product, with respect to underlying comorbidities and concomitant medications;
- *pharmacovigilance training* – to fully understand the critical concepts, disciplines, and components associated with pharmacovigilance, the methods used with key considerations affecting risk versus benefits analysis, and the medical significance of the most important ADRs; and
- *MedDRA training* – to fully understand the dictionary, its hierarchy, and the implications of its granularity.

### ONGOING MEDICAL REVIEW

Because the presentation of individual case histories and the overall safety evaluation are the most time-consuming parts of the PSUR process, companies should commit themselves to an ongoing review process, regardless of when a PSUR falls due. Indeed, safety assessment should be done independently of PSUR timelines, and in the PSUR you should then be able to provide the conclusion on what safety issue was identified and the measures that had been taken as a consequence. It is also advisable to set up an in-house safety review committee. The medical reviewer/physician responsible for a given medical product in the company may become too close to the data to judge it objectively and may end up overlooking signals. The safety review committee should be composed of senior, experienced individuals who are not directly involved in the safety evaluation of the medical product. This committee should meet regularly, say quarterly, to take a fresh look at the data and to bring to the review process a broader medical expertise than was available in the initial evaluation.

### METRICS

Measures should be put in place to monitor existing processes to ensure that they remain effective

Table 11.3 Examples of metrics of the PSUR process.

Number of late PSUR submissions
Number of active queries per month
Number of case misclassifications per month
Number of coding errors/inconsistencies per month
Proportion of verbatim terms that auto-encoded per month
Number of duplicate cases per month
Number/type of audit observations
Number of avoidable ADRs after label change
Number of medication errors since product name change

Source: Adapted from Klepper (2004).

and efficient and that corrective actions are having the intended effect. An example of such a metric would be looking at the number of avoidable ADRs that were due to a newly identified drug–drug interaction. Risk management initiatives could be put in place to address such a finding, such as a label change or patient education. The results of these initiatives should be reflected in subsequent PSURs. Other examples of PSUR metrics are summarized in Table 11.3.

### DEVELOPMENT SAFETY UPDATE REPORTS

Development safety update reports are a requirement of the 2001 European Union Clinical Trials Directive which came into effect on May 1, 2004. Once a year throughout the clinical trial, the manufacturer or sponsor is required to report a line listing of all suspected serious adverse reactions that have occurred over the period and a report of the subject’s safety both to the competent authority (in the member state in whose territory the clinical trial is being conducted) and to the ethics committee in each member state, as set out in a detailed guidance published by the European Commission (EC, 2004b). This guidance applies to all clinical trials on medicinal products for human use conducted within the European Community. Importantly, it applies to all investigational medicinal products for human use, regardless of their marketing authorization status in any member

state or whether they are used under the conditions of marketing authorization. It provides detailed guidance on the collection, verification, and presentation of adverse event/reaction reports arising from clinical trials. Although it does not cover spontaneous postmarketing ADRs, the introduction of this European directive, along with the proposed regulations in the USA regarding safety reporting for human drugs and biological products (FDA, 2003), is indicative of a global trend towards more rigorous regulation of product safety, which will inevitably have implications for PSURs and the resources that companies devote to producing them.

## **PERIODIC SAFETY UPDATE REPORT AND RISK MANAGEMENT**

The “Guideline on risk management systems for medicinal products for human use” (EMA, 2005), adopted in November 2005, clearly states that the RMP and its updates should be submitted at the same time as the PSURs unless other requirements have been laid down as a condition of the marketing authorization. This RMP is now requested from health authorities for all new applications. In general, safety issues should be identified at early stages in the development of a compound, and these issues be approached in an RMP. This RMP can then propose different actions to counteract or better understand these issues: education (physicians, patients, sales representatives, etc.), step-wise market approach, use of utilization and/or safety databases, specific studies targeting defined issues, and so on. The RMP will serve as a guiding document, and assessment of the plan will be reported in the PSUR. The PSUR is thus now the document in which all the available information on safety of a given product is gathered from all sources, such as clinical trials, observational studies, spontaneous reports, and also pre-clinical experiments, and put into perspective. The consistency of a potential signal/issue across all the sources is of very high value. The PSUR will help in that analysis because it is a unique document assembling all the information from multiple sources.

## **CHANGES FOLLOWING THE NEW PHARMACOVIGILANCE EU REGULATION (REGULATION NO. 1235/2010 AND DIRECTIVE 2010/84/EU)**

A new scientific committee within the EMA with a key role in the pharmacovigilance assessments has replaced the CHMP Pharmacovigilance Working Party. This Pharmacovigilance Risk Assessment Committee (PRAC) is at the same level as the CHMP, and the members are representatives from EU member states with competence in the pharmacovigilance and risk assessment of medicines, independent scientific experts appointed by the EU Commission, and representatives from healthcare professionals and patient associations. The scope of activities concerns all medicinal products and pharmacovigilance areas (RMP, PSUR, Post-Authorisation Safety Studies [PASS], signal detection, urgent union procedure). For the PSURs, the PRAC is involved in the assessments and recommendations.

The content of the PSURs has changed also with an increased emphasis on the benefit. Indeed, new sections are included to detail the benefit evaluation (including important efficacy/effectiveness information, with the strength of the evidence and limitations of the data) and the integrated benefit–risk analysis for approved indications.

Finally, to increase transparency and communication in Europe, the frequency of PSUR submission and PSUR final assessment conclusions should be available on medicine web-portals at the EMA and each member state levels. The publication of PSUR assessment reports may, in the near future, have important business implications for Pharma companies, due to the availability of such information on all marketed products.

## **CONCLUSION**

The PSUR can be an important source for the identification of new safety signals, a means of determining changes in the benefit–risk profile, an effective means of risk communication to regulatory authorities, an indicator for the need for risk management initiatives, as well as a tracking mechanism to monitor the effectiveness of such initiatives (Klepper,

2004). It is a useful tool for the MAH and not simply a document for submission to regulatory authorities. One of the major strengths of the PSUR is the unique opportunity it provides to review aggregate data. If a drug is marketed in many countries, for example, a finding of an ADR of interest across several countries has greater clinical weight than the same finding made in isolated countries. More generally, it is a chance to view all the available information on the safety of a given product – from clinical trials, observational studies, and spontaneous reporting, as well as from pre-clinical studies. The consistency (or lack of it) of a potential signal across all these information sources can be extremely valuable to an MAH. The PSUR is also a chance to detect potential problems as patient exposure increases in response to promotional efforts. For example, it may reveal ADRs in elderly people on multiple drug regimes. Such patients may be excluded from clinical trials, but their number may increase very quickly after the product has been launched, and the PSUR provides a means of reviewing the relevant safety data in a regular and intelligent manner. Similarly, it is a tool for monitoring the unpromoted use of a drug in sub-populations, such as children, the very old, and those with multiple diseases, and it can alert manufacturers or sponsors to long-latency ADRs or explosive ADRs (when a handful of reports is quickly followed by dozens). The company is then in a position to respond proactively if and when such an event is reported. With the implementation of the new pharmacovigilance regulation in Europe, the PSUR will consequently become a real postmarketing evaluation tool of the benefits and risks, based on all available data at defined time points in the product lifecycle.

In short, rather than considering the PSUR a tedious piece of compliance with regulatory authorities, companies should regard it as a valuable exercise in which the manufacturer or sponsor thoughtfully assesses benefit and risks, and seeks to protect its patients and products.

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# 12

## The Principles behind Risk Management in the European Union<sup>1</sup>

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### INTRODUCTION

We may not realize it, but we are all acquainted with risk management and practice it! From basic survival techniques, such as looking for traffic before crossing the road and cooking raw food properly, to insurance to cover us for life's mishaps, risk management is part of our lives. It is also a critical area for many industries, including aviation, nuclear power, and oil, where any accident has the potential for catastrophic effects.

Most people will not think of taking a medicine in the same context as flying or living near a nuclear reactor, but the huge range of medicines taken daily by tens of millions of people means that the poten-

tial for harm and the numbers affected is probably greater. In realization of this, medicines are strictly regulated, and before a pharmaceutical company can market a medicine it has to satisfy regulators of its quality, safety, and efficacy. However, this does not mean that adverse drug reactions (ADRs) will not happen. Authorization of a medicine means that, at the time of licensing, for the average patient, the potential benefits of the medicine outweigh the potential risks in the approved indication. Risk management is all about trying to increase further the odds in favor of the patient (i.e., improving the benefit–risk balance) by anticipating the risks and trying to prevent them.

Pharmacovigilance (PhV) has been an evolving process – largely driven by high-profile drug withdrawals. In the early days, post-thalidomide, it relied solely on healthcare professionals submitting reports of suspected adverse reactions to the regulatory authorities. Although some companies continued research into the safety profile of their

<sup>1</sup>The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of, the European Medicines Agency or one of its committees or working parties or the MHRA.

medicines post-authorization, this was not the norm, and the general consensus was that authorization marked the end of the research process – except for that into new indications. A small number of very public suspensions and withdrawals of medicines from the market due to serious adverse reactions led to the realization that this “wait, watch, and react” scenario was not adequate. PhV needed to be proactive as well as reactive.

In 2003, Waller and Evans published “A model for the future conduct of pharmacovigilance.” One of the conclusions was that: “there should be a clear starting point or ‘specification’ of what is already known at the time of licensing a medicine and what is required to extend safety knowledge post-authorisation” (Waller and Evans, 2003). This concept was taken up by the International Council on Harmonisation (ICH), whose expert working group produced a guidance, known as E2E, on PhV planning (ICH, 2004). This was a tri-regional agreement on the content of a two-part document: the first part, the safety specification, stated what was known and not known about the safety profile of a medicine, and the second part, the PhV plan, detailed the PhV activities that would be taken to provide further information on known risks and identify new ones. Risk minimization was deliberately not included in this planning document owing to the complexity of trying to agree a process and format which would fit the multitude of different healthcare systems, indications, and medical practices. Although Japan and the USA were also signatories to this document, the EU was for many years the only region formally to ratify ICH E2E and make it a requirement. The ICH E2E guideline was adopted by the Committee for Medicinal Products for Human Use (CHMP) in December 2004.

In parallel with the ICH process, Europe had also been looking at other ways of improving PhV. In 2004, following a lengthy consultation exercise, the legislation was amended to strengthen PhV, and risk management for medicinal products officially came into being in the EU in November 2005. Although medicines have had risk management in the form of the summary of product characteristics (SmPC) and patient information leaflets (PILs – also known as package leaflets) for many years prior to this, 2005 was the first time that companies

were required, where appropriate, to provide a formal risk management plan (RMP) with an application for some marketing authorizations.

Directive 2004/27/EC, which amended Directive 2001/83/EC, included a new requirement in the dossier accompanying applications for a marketing authorization. Article 8 3(i) of Directive 2001/83/EC required the applicant to submit “a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce.” The legislation, at that time, did not define what a PhV system or a risk management system was, so a series of guidelines were written to provide the details and finally published by the European Commission (EC) on its website. EC (2006) provided an interpretation of what was meant by this legislation. The detailed description of the PhV system (DDPS) was defined as the documents proving that the marketing authorization holder (MAH) has: “the services of a Qualified Person Responsible for Pharmacovigilance (QPPV) and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country” (EC, 2006: Part I, Chapter 2). A risk management system was defined as: “a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions” (EC, 2006: Part I, Chapter 3). It also stated that the requirement to submit a detailed description of a risk management system could be fulfilled by the provision of a RMP. And thus the EU RMP was born.

In its original format, the EU RMP closely followed ICH E2E, in that the first two parts were the safety specification and PhV plan. A third part was an evaluation of the need for risk minimization activities and, if thought necessary, a risk minimization plan. The risk minimization plan was only required if the evaluation suggested that risk minimization beyond that of the SmPC and PILs was required. An RMP was not normally required for generic medicines unless the reference medicinal product had additional risk minimization activities.

A further independent review of the strengths and weaknesses of PhV in the EU, carried out at

<b>Part I</b>	Product(s) overview
<b>Part II</b>	Safety specification
<b>Module SII</b>	Epidemiology of the indication(s) and target population
<b>Module SII</b>	Non-clinical part of the safety specification
<b>Module SIII</b>	Clinical trial exposure
<b>Module SIV</b>	Populations not studied in clinical trials
<b>Module SV</b>	Post-authorisation experience
<b>Module SVI</b>	Additional EU requirements for the safety specification
<b>Module SVII</b>	Identified and potential risks
<b>Module SVIII</b>	Summary of the safety concerns
<b>Part III</b>	Pharmacovigilance plan
<b>Part IV</b>	Plans for post-authorisation efficacy studies
<b>Part V</b>	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
<b>Part VI</b>	Summary of the risk management plan
<b>Part VII</b>	Annexes

Figure 12.1 Structure of the EU RMP. Source: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129134.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf). © European Medicines Agency (EMA).

the request of the EC, concluded that further enhancement was necessary. The result was the publication of Directive 2010/84/EU (EC, 2010a) and Regulation (EU) 1235/2010 (EC, 2010b) in December 2010. This revision of the legislation has been described as the most fundamental change to medicines regulation in Europe since the formation of the European Medicines Agency. Although dubbed the “New Pharmacovigilance Legislation,” its effect went much wider than pure PhV, and risk management was a significant part of it. All applications for a new marketing authorization now had to come complete with an RMP. Also prominent in the new legislation was a move to much greater transparency about medicines and the basis for the actions taken by regulatory authorities. For risk management this meant the publication of a summary of the RMP on competent authorities’ web portals. This new legislation also required new guidances and the much relied upon Volume 9A gave way to Good Pharmacovigilance Practices (GVP).

GVP is a modular structure, with each module, or chapter, providing guidance and interpretation of a particular aspect of the PhV legislation. Module V on risk management systems ([www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129134.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf)) and Module XVI on risk minimization and the

measurement of effectiveness ([www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2013/06/WC500144010.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144010.pdf)) are the GVP modules that cover risk management. There are also separately published guidances on the document format for RMPs.

The new legislation provided an opportunity to update the format for the RMP. Recognizing that risk management is a global activity, the EU RMP is now divided into seven parts with the aim of facilitating submission to different regulatory authorities. Some parts may be common to all authorities – for example, Part II: Safety Specification – whereas others, such as Part V: Risk Minimization Measures, may need to be region specific. Figure 12.1 shows the new structure of the EU RMP.

Part II: Safety Specification is also divided into modules. Although ordered differently, the modules in the new Part II reflect the content of the original ICH E2E safety specification – but reordered and categorized based on the experience gained since 2005. The presentation of the content was also updated and clarified with the aim of making the RMP a more thoughtful document reflecting the experience of what worked well and what worked less well in the previous version.

As a medicine matures in its life cycle, some modules may no longer require updating – for

example, clinical trials and the generation of pre-clinical data may no longer be undertaken for a product that has been on the market for many years. The modular structure allows these modules to be “locked,” with the eventual aim that, when IT systems permit, only those modules that have changed when an RMP is updated will need to be resubmitted. However, once locked, a module does not have to remain locked. For example, if an MAH (which is the EU name for the pharmaceutical company that holds the license to market the drug in the EU) does more clinical trials in a new indication, the clinical trial exposure module can be “unlocked” to add the new information.

## THE PURPOSE OF RISK MANAGEMENT

A somewhat cynical definition of a lecture is “the transfer of information from the notes of the lecturer to the notebook of the student without going through the minds of either.” A similarly disparaging interpretation is sometimes applied to the provision of the RMP – treating it as a pointless bureaucratic formality that needs to be complied with before a license is granted! However, to do that is to miss an opportunity.

For the vast majority of medicines, the benefit–risk balance is probably at its most favorable at the time a medicine is licensed. This is because the clinical trial program is optimized to show benefit, but the numbers involved mean that only the most frequent adverse reactions will be detected. The efficacy shown under the “ideal” situation of a clinical trial may not be achieved in “real life” use, whereas as more and more patients are exposed, the less frequent adverse reactions will gradually be identified. Therefore, theoretically, the benefit may decline whereas the risks known to be associated with the medicine will increase over the lifetime of a product. As a result, the benefit–risk balance is on a continuous downward slope – and this will happen with virtually all medicines. For those medicines where the balance is strongly in favor of benefit, this will probably not have a major impact on the marketing authorization, but for those products where this is not the case – that is, where there is a narrow therapeutic window or where the benefits are limited or

where other products have a more favorable profile – then the prospects are not so good. However, by reducing the risks through risk minimization and/or increasing the benefits by selecting those patients who can gain most, the benefit–risk balance can be improved.

## MAXIMIZING THE BENEFITS

The clinical trial program is designed to show benefit. The patients entering into them are carefully selected by the judicious use of inclusion and exclusion criteria to reflect a relatively homogeneous patient pool. Some of these criteria are to protect study patients, by removing those most likely to suffer harm, but others are to provide the optimal conditions to show the efficacy of the product. As the clinical trial program continues, the criteria are gradually relaxed to get a more representative sample of patients – that is, who more closely resemble the future target population; but inevitably, the trial conditions will almost never be truly representative of the sort of patients who will receive the product in “real life.” An exception to this may be field trials of vaccines, which tend to replicate more closely actual conditions of use.

Unless the efficacy is marginal, companies do not routinely perform sub-group analyses to identify patients most likely to benefit from the medicine. In many cases this may not matter greatly, but if it were done, it is a way of improving the benefit part of the equation. By removing those least likely to benefit, the “unit benefit” per patient will increase. If one thinks of a bell curve reflecting benefit, by removing part of the left-hand side, the median and mean are shifted to the right.

With the arrival of cheap genetic testing, it may be possible in future to select those patients most likely to benefit. We may not know what all the individual genes do, but it could be possible to identify those which predict a more successful outcome and those which indicate a likely lack of success. This is already occurring with some oncology treatments that target a specific receptor, but it could be extended to those areas where the stakes are not so high (Figure 12.2).

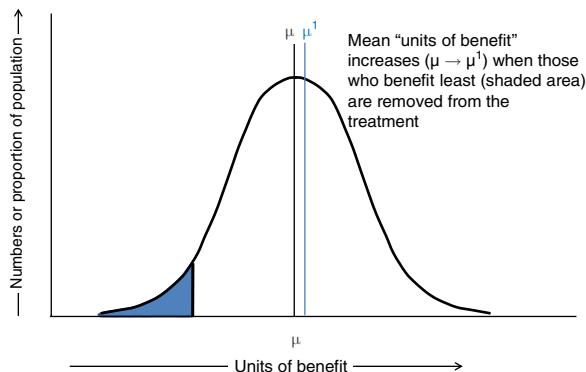


Figure 12.2 Illustration of the effect of removing patients least likely to benefit from drug treatment. Source: Stella Blackburn. Reproduced with permission of Stella Blackburn.

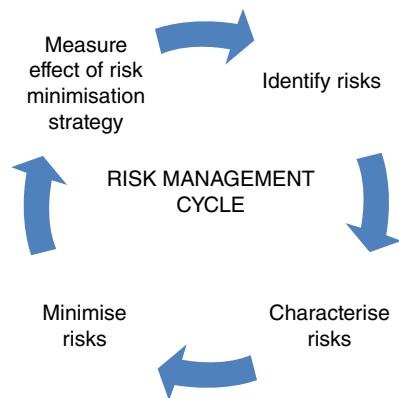


Figure 12.3 Risk management cycle. Source: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/06/WC500129134.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf). © European Medicines Agency (EMA).

The new EU RMP looks towards this future with a section, notable currently by its emptiness, on post-authorization efficacy trials. In fact, this section will probably be populated by effectiveness trials. Despite the legislation only mentioning efficacy, from the accompanying description, it is clear that effectiveness is really what is being discussed.

## REDUCING THE RISKS

The aim of risk management ultimately is to reduce risks. This can be divided into four basic stages:

- 1 risk identification;
- 2 risk characterization;
- 3 risk minimization;
- 4 measurement of the effectiveness of risk minimization.

The four stages do not run in isolation but are part of a continuing circle, illustrated by Figure 12.3.

The two parts of the RMP that contribute most to risk identification and characterization are the safety specification and the PhV plan. The safety specification is a précis of all the available data about risks, whilst the PhV plan states how more information will be gained. The two go hand in hand. In the early stages of a product's life not a huge amount will be known about the risks of a

product, so there will be a need for more investigation, which will be described in the PhV plan, whereas later, much more will be known and there will be less need for further investigation.

Figure 12.3 also illustrates that risk management is a reiterative process. Having identified a risk, planned how to investigate risk factors, and put in place risk minimization, it is essential to measure the effectiveness of the risk minimization. New risks will continue to arise during the product lifecycle and require analysis and steps to minimize them, so although the process may be most intense during the early stages of a medicine, it is a foolhardy company (and regulator) who ceases a regime of perpetual vigilance!

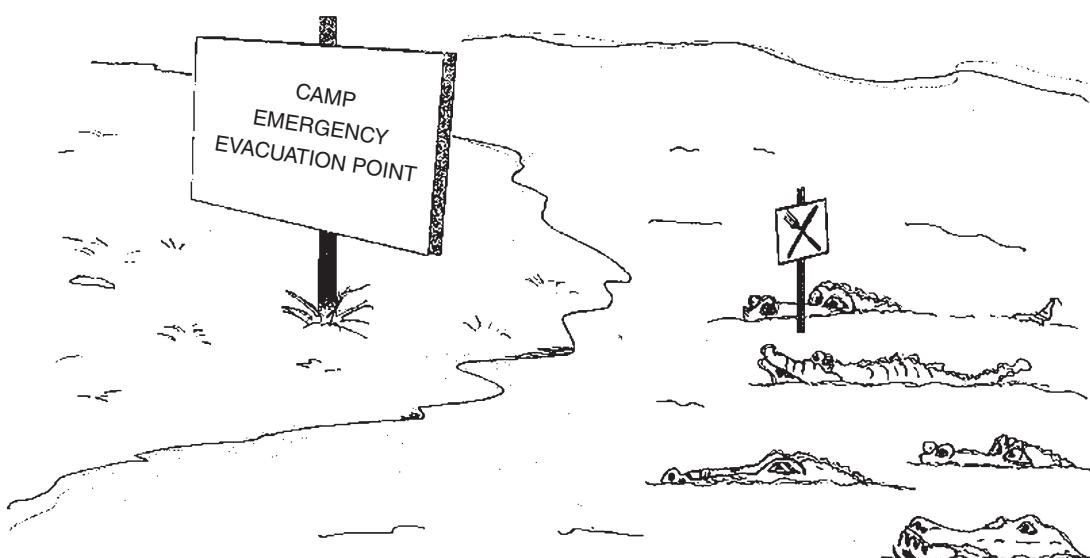
Having said this, the key to a good RMP is the safety specification. A poor safety specification means that risk minimization will, at best, be patchy, whereas a good safety specification improves the chances of a good plan.

## THE SAFETY SPECIFICATION

This is the core of the RMP. It is a summary of the dossier – what is known and not known about the product. To be useful it must examine the data critically and reflect the potential risks and

uncertainties. No-one expects that everything will be known about a medicine at the time of its application for a license. The fact that the safety specification contains potential risks and missing information is paradoxically reassuring, as it means that there has been a critical appraisal of the evidence rather than an attempt to gloss over perceived deficiencies. As an example, imagine planning an RMP for a safari camp. The safety specification might identify lions and monkeys as the main identified risks, with snakes a potential risk. Risk minimization might be to ensure that there was a good fence around the camp (to keep lions out), avoid overhanging branches (to keep monkeys out), and have guards patrolling the perimeter (to deter and detect both lions and monkeys). In the extreme, if the camp were actually invaded by lions or packs of monkeys, the risk minimization plan could specify that the inhabitants could retreat to the nearby river and wait there until the danger had passed. However, if the safety specification failed to mention that the nearby large river had not been surveyed, the missing information could turn out to be very important if there were 20 hungry crocodiles that were just waiting for the lions to drive supper into the river!

The missing information should reflect the likely usage of the medicine. It is not realistic to include every possible population subgroup who might possibly be exposed. Use in populations outside of the likely indication is a difficult area and needs to be balanced between encouraging off-label use and a pragmatic view of what is likely to happen. For example, if a medicine is initially authorized only for use in adults, but there is no equally effective medicine available for the pediatric population, it is highly likely that there will be use in the pediatric age groups and it would be sensible to include use in the pediatric population as missing information and a safety concern. Equally, it would probably not be helpful to include use in the pediatric population as missing information in a drug for the treatment of benign prostatic hyperplasia, although the medicine would not have been studied in that population. Oncology medicines are particularly difficult, and off-label use may itself sometimes be a safety concern. An obvious area where missing information on use outside the authorized indication may be particularly relevant as a safety concern is where the medicine is authorized for a particular sub-population; for example, tumors expressing a particular characteristic or with a specific chromo-



some deletion. Use in the wider population may be important missing information – particularly where the test to identify the sub-population is not readily available or is expensive and there is a high likelihood of off-label use.

## **DESCRIPTION OF SPECIFIC MODULES AND PARTS OF THE RISK MANAGEMENT PLAN**

GVP Module V, along with the published guidelines on the format and content of the EU RMP, provides detailed guidance on the entire RMP and can be found on the EMA website ([http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000258.jsp&mid=WC0b01ac05800241de](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp&mid=WC0b01ac05800241de)). What the following sections below aim to do is highlight some of the key principles behind specific modules and parts of the RMP.

### **PART II. MODULE S1: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION**

The safety specification follows the development of the medicine. The idea of the epidemiology module is to set the scene. Who are the patients who get the disease, what is the natural course of the disease, and what happens as a consequence of the disease? This is actually very important as it provides a lot more information than is at first apparent.

Everyone has adverse events in their life. What PhV is trying to do is to assess which ones are causally related to the drug and which are due to some other factor in the patient's life and environment. It is analogous to a good detective novel where the hero is trying to ascertain who was responsible for the crime. Epidemiology provides a lot of the supporting evidence to help with assessing the likelihood that a particular event is caused by a particular drug. By understanding who are the patients with the disease, one can also identify on a population basis what other factors may be significant. For example, if the drug of interest was for the treatment of prostate cancer, epidemiology can provide a lot of useful information (<http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/incidence/uk-prostate-cancer-incidence-statistics>):

- the crude incidence rate is 133.7 per 100 000 males in the UK;
- 75% of cases are diagnosed in men over the age of 65, with only 1% in men under the age of 50 years;
- the incidence in African Americans is 60% higher than among whites, which is in turn higher than in Hispanics and Asians (Crawford, 2004).

From these three very basic facts, important information about the target population and what is expected can be derived. The fact that the population is male, with a substantial majority over the age of 65 years old, means that events due to cardiovascular disease are highly likely. Since cardiovascular disease is correlated with age, an estimate of the expected number of myocardial infarcts and deaths in the prostate cancer population can be done. The fact that cardiovascular disease is commoner in African Americans than in white Americans suggest that an upward adjustment is needed given that prostate cancer incidence is higher in this population as well. This is very useful information to have, as it prevents widespread alarm when the first few cases of fatal myocardial infarction are reported. Equally important is that it facilitates attempts to assess whether the observed events exceed expected. This is hard to do with spontaneous reports because of the known issues with underreporting, but it gives a benchmark for clinical trial data. It is also important not to assume that all reported events are due to other underlying diseases, so an observed rate close to or above the expected rate should lead to a much closer evaluation of the data.

The epidemiology information also gives pointers to concomitant medication that may be important for interactions, which are examined in a later module.

### **PART II. MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION**

The nonclinical module is one where expert toxicological advice is usually required. This is because it

needs to be a summary of the important findings and the relevance to use in humans. Most clinicians – and many PhV people – will not be familiar with the specifics of, for example, Sprague-Dawley or Wistar rats or the significance of particular carcinogenicity findings in one or other strain, and so interpretation of what the results actually mean is essential. Similarly, explanation is needed where results are positive in one species and negative in another.

Negative results may also be important to mention in the nonclinical module. For instance, negative reproductive toxicity is important if the medicine is intended for use in women of child-bearing potential. This is one example where negative results are really important to report in an RMP.

Many issues or unknowns arising from toxicology studies may be subsequently resolved from clinical data. However, the reverse is also true, and use in humans may give rise to toxicity that was unexpected from the animal models. This is of particular concern with humanized monoclonal antibodies, where the development of anti-human antibodies in animal models prevents much of the predictive value of pre-clinical work.

## PART II. MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

The importance of the module on “populations not studied in clinical trials” has been highlighted earlier in this chapter. However, it is not solely related to the population, but also to the trial setting compared with the expected post-authorization use. Many medicines are developed in hospital clinics with specialists in the disease of interest treating the patients. Post-authorization, the setting may move from hospital outpatient to community care with also a change in the prescriber from specialist to generalist. This may have important consequences for risk minimization. Easy and rapid access to diagnostic tools in a hospital may not reflect what is available in the community, and resources such as magnetic resonance imaging (MRI) may be common in hospitals in some EU countries and less so in others. Therefore, patients may have to travel quite a distance to have some

tests, and treatment algorithms easily manageable in a research setting may also not travel well.

## PART II. MODULE SV: POST-AUTHORIZATION EXPERIENCE

The post-authorization experience module is very useful because it gives an opportunity to provide data that were/are unavailable at the time of licensing. The much wider usage post-authorization should provide answers to many of the uncertainties present at the time of initial authorization. It can also be very useful to know what has happened in one market when the medicine is being licensed later in another market. For example, there may be a concern that medicines with a narrow indication may be used off-label in populations where the benefit-risk is much less positive or even negative. Data from another country where the drug is already marketed may provide reassurance or alternatively suggestions as to where risk minimization should be targeted. This post-marketing drug utilization ties in with the module on additional EU requirements.

## PART II. MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Two important elements of this EU-specific module are off-label use and use in the pediatric population. Frequently, companies will put statements such as “X is only indicated for treatment in Y and we will only promote its use in this area so off-label use is unlikely to happen.” The only use of this statement is to indicate that either the writer is a fool or they think that regulators are. Neither is conducive to progressing the process of authorization! It is much better to accept that off-label use could happen and take a serious look at the situations where this might occur, whether any off-label use could pose particular problems, and what needs to be done to minimize the risks of this happening.

The pediatric population is a specific population where off-label use is likely to occur. Until the pediatric regulation, there was no requirement for companies either to research the use of a product in the

pediatric population or develop child-friendly formulations. As a result, many of the medicines used in the pediatric population are not licensed for this age group. Although the pediatric regulation requires companies to submit (and carry out) a pediatric investigation plan (PIP), there is frequently a delay between authorization for the adult population and that for the pediatric population. In disease areas where there are limited treatments available, it is therefore likely that some pediatric off-label use may occur.

Medication error is another key area in this module of the RMP. Despite research suggesting that medication errors accounts for between 30.3 and 47.0% of all adverse drug events among hospital patients, companies seem curiously loathe to examine this area critically in the RMP (Council of Europe, 2006). Since many of these errors are entirely preventable, companies are missing a major opportunity of reducing the burden of adverse reactions on patients. During the early stages of product development, companies should think about the common causes of medication error: wrong drug, wrong dose, wrong administration route, and wrong patient and think whether any of these are likely with their medicine. As a minimum during clinical trials, companies should record and investigate all medication errors (or “near misses”) that have occurred and perform an analysis of the causes and suggest possible remedies in the RMP. This review and analysis should be continued post-authorization and should be a routine part of risk management. Obviously, for certain advanced therapy medicinal products (ATMPs) where source material is taken from a patient, engineered, or processed in a laboratory and returned to the patient, there is a chance of administration to the wrong patient. For these products, stringent traceability would be an important form of risk minimization. In the past, some companies liked to have the same color scheme on the cartons of all their products. Products for vastly different indications would be packed in very similar boxes with only the printed name on the outside to identify the actual product. This would now be discouraged as being likely to increase the risk of medication error during dispensing of the drug. Concomitant use of drugs with different routes of administration is another

risk where thoughtful design could help minimize risks of maladministration. In the oncology field there have been tragic cases where syringes have been mixed up and drugs intended for intravenous use have been given intrathecally and vice versa. Different strengths of adrenaline is another classic, where vials of the 1 in 1000 strength looked very similar to 1 in 10 000. Potassium chloride being used to flush cannulae instead of normal saline is another oft-reported form of medication error. In a bright sunny room in the middle of the afternoon, it may be easy to distinguish small differences in color and read minute text, but in the middle of the night in a dark room with a patient in extremis the situation is likely to be very different.

By thinking of the situations of where and how their drugs will be used in practice, companies can prevent many of these relatively predictable medication errors. However, certain aspects, such as size, color, and shape of pills need to start early when different formulations are being tried.

## PART II. MODULE VII: IDENTIFIED AND POTENTIAL RISKS

There are two different versions of the module on identified and potential risks, and which needs to be used depends on whether the medicine is what is known as an ATMP or not. The concept of what constitutes an ATMP is defined in Regulation (EC) 1394/2007 (<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32007R1394:en:NOT>), but practically this means either gene therapy, somatic cell therapy, or a tissue-engineered product. Because of the complexities of manufacture, the opportunities for risks not commonly or cumulatively found in non-ATMP products (such as risks to donors, risks to the environment, risks due to surgical procedures, or conditioning of the recipient, etc.), there is a need for a more exhaustive “checklist” of headings and topics. Similarly, the “risks common to the pharmacological class” are not likely to be of importance with an ATMP, whilst they are with a non-ATMP.

The module on identified and potential risks also provides an opportunity to look more closely at the potential for interactions – both from a theoretical analysis of the mode of action, and from

nonclinical and clinical studies. It is impossible to look at every interaction, but based on the action of the medicine and what is known of the epidemiology of the population (and likely concomitant diseases and medications), the most likely interactions can be predicted and classified as to their significance. A classic example is sildenafil, which has an important interaction with nitrates. Because erectile dysfunction is a consequence of cardiovascular disease and many patients with cardiovascular disease have angina which is frequently treated with nitrates, this was a major safety concern – not notwithstanding that the conditions of use could increase the likelihood of angina and hence use of nitrates!

## PART II. MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

The final module of the safety specification is really the summary and final conclusions of the preceding ones. A safety concern is defined as an important identified risk, an important potential risk, and missing information, and this module sets out which risks from the preceding modules remain and are significant enough to be regarded as safety concerns. The ICH definition of a safety issue includes important identified risks, important potential risks, and important missing information. Until July 2013, the EU used the same definition for what constituted a safety concern – safety concern being the preferred term as it was thought to be less alarming to the public than safety issue. However, Article 12 of Regulation 726/2004 states that a marketing authorization should be refused if “... it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product.” To avoid any impression that the competent authorities were not complying with the legislation and issuing premature authorizations, it was decided to remove the word “important” from “important missing information.” The concept has not changed; neither has its interpretation or implementation, in that it is still missing information that could be clinically important that should be included as a safety concern; however, how it is phrased has changed!

A frequently asked question is what is important or what is significant, but although some suggestions are provided in Module V of GVP, it remains one of clinical judgment and will depend upon the indication, the patient population, and intended prescriber. The intended criterion is what really matters to the patient and what information is essential for a clinician to know when deciding on the benefit–risk balance for an individual patient – that is, moving from the population-based benefit–risk on which licensing is based to that at the patient level and actually treating a patient. Probably much of the information in the potential Sections 4.3, 4.4, and 4.6 of the SmPC should be considered as the types of issues which warrant inclusion as safety concerns. What is definitely not wanted is the complete line listing of adverse reactions that make up Section 4.8 of the SmPC.

Those safety concerns, which make it into the summary of safety concerns, form the basis for the rest of the RMP, which is why the safety specification is possibly the most important part of the plan.

## PARTS III AND IV OF THE RISK MANAGEMENT PLAN

The familiar “PhV plan” and the less familiar “plans for post-authorization efficacy studies” are, as the names suggest, the planning parts of the RMP. The PhV plan (Part III of the RMP) is primarily concerned with investigating the safety concerns identified in the safety specification. In Europe, the regulations and directives relating to medicines specify many PhV requirements which are legal obligations. These relate to the qualified person in PhV (QPPV) and reporting of suspected adverse reactions. For the purposes of the PhV plan, these are referred to as routine PhV, since they are a legal obligation for the pharmaceutical company who is the MAH of the particular medicine. Many medicines will only require routine PhV to investigate the safety concerns. For others, such as innovative medicines, or those with newly identified risks or areas of missing information, there may be a need to undertake what are known as additional PhV activities. Both routine and additional PhV activities are activities designed to identify and/or characterize safety concerns.

Studies to *assess* the effectiveness of risk minimization measures may also be included in the PhV plan, but the risk minimization measures themselves should not be. Studies intended to develop new, or extensions of, indications are not normally part of the PhV plan since they are not designed to investigate safety concerns but new areas of efficacy. However, some of the data from trials in new patient populations will eventually be included in the safety specification since they will form part of the overall clinical trial population and there could be important findings relevant to the current indications.

Most people assume that additional activities in the PhV plan will be either phase IV clinical trials or noninterventional studies of some form, such as drug utilization studies. Although pharmacoepidemiology is the mainstay of the PhV plan, other types of studies are frequently required by regulators. These may include nonclinical studies (e.g., to develop a diagnostic test, test further interactions, or even additional animal studies) or can be pharmacokinetic or pharmacodynamics studies. Rarely, environmental or quality issues may be safety concerns which require study and hence become part of the PhV plan.

What is required in the PhV plan will depend on the product, the indication, and the knowledge about the active substance. A medicine for an orphan disease, or one which has been subject to an accelerated development or a conditional authorization due to an unmet medical need, will likely have a much smaller knowledge base and so will require more post-authorization study. At the opposite end of the spectrum, a generic version of the 10th drug in the same pharmaceutical class will probably not need any additional PhV studies.

If there is a need for a formal study to measure the effectiveness of risk minimization measures, then this will also be included as part of the PhV plan.

Part IV of the RMP, “Plans for post-authorisation efficacy studies,” is much less well developed as a concept. The legal basis comes from two new articles in the 2010 PhV legislation that gave regulators the ability to impose what the legislators termed post-authorization efficacy studies (EC, 2006: Chapter 3; EC, 2010a). The two situations described

where this might occur are described in the legislation:

- Where concerns relating to some aspects of the efficacy of the medicinal product are identified and be resolved only after the product has been marketed.
- When the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly.

However, in the same way that the majority of studies in the PhV plan are not imposed by the competent authority, MAHs may start to make use of this section to study positive or negative “benefit factors” that predict the likelihood of successful treatment.

## PART V OF THE RISK MANAGEMENT PLAN

Risk minimization is probably what most people think of when they hear the term “RMP.” In Europe, risk minimization measures are divided into “routine” and “additional” measures. Every licensed medicine will have routine risk minimization measures, since these form part of the marketing authorization and so are assessed and assigned at authorization. These routine risk minimization measures are:

- the SmPC;
- the PIL;
- the labeling (what is on the packaging and actual medicine container);
- the pack size;
- The legal status.

It is a legal requirement in Europe that each medicine is accompanied by a PIL. This is a summary, written in lay language, of the information given to healthcare practitioners in the SmPC. It is also a requirement that it is tested for readability and comprehensibility by users.

Good labeling is probably key to avoiding medication errors. The main causes of medication error are wrong patient, wrong drug, wrong dose, and wrong route. In Europe, all medicines being

authorized via the centralized procedure are required to have their proposed brand name assessed by the Name Review Group of the EMA, who review whether the name is similar to one currently in use in any of the EU member states, or whether the name is likely to cause confusion, is inappropriate, or likely to mislead as to its purpose. Aside from the name issue, intelligently applied labeling can help avoid mistakes in drug, dose, and route. Historically, many companies used the same color and design in the packs of all their medicines – presumably to indicate that they came from the same “trusted” company. When the only differentiating factor is the name, mistakes are easy. Similarly, if a medicine comes in different strengths and/or different formulations for different routes, then packs need to be clearly distinguishable so that a tired healthcare professional in the middle of the night can easily tell one from another. Glass vials also need to be clearly labeled and distinguishable from each other, as known mistakes in the past were flushing cannulas with potassium instead of normal saline or using adrenaline 1:1000 instead of 1:10 000.

The use of the pack size as a risk minimization measure is not immediately obvious, as pack sizes were usually determined by usage predictions – for example, course or monthly packs for patients and larger sizes for institutional use. However, if the safe use of a medicine requires monthly testing of the patient, use of a single pack size of 28 or 30 days can help remind patients to go for tests.

The legal status of a medicine is not standardized throughout Europe. What is standardized are two criteria: whether a medicine is required to be prescribed by a doctor or whether it is available without prescription. However, for older medicines, which category a medicine falls into is not harmonized throughout Europe. For example, sumatriptan for migraine is available without prescription in some European countries but not in others. Some countries also subdivide the “available without prescription” category further into whether a medicine can only be bought from a pharmacist or whether it is available from other outlets – for example, in a pharmacy where it is not directly supervised by the pharmacist or even supermarket shelves.

There is a refinement of the “subject to medical prescription” requirement, in that it is possible to designate a drug as available under special medical prescription or restricted medical prescription. Special medical prescription is used for drugs capable of misuse or abuse as categorized by the United Nations Conventions of 1961 or 1971, whereas restricted medical prescription can be used to suggest categories of physician who can prescribe, or the setting where it can be used. The only difficulty with using the “restricted use” category is that the definition of a specialist is not harmonized across Europe. To overcome this, the phraseology used in marketing authorizations tends to be: “use by a physician experienced in the treatment and diagnosis of X.” Similarly “hospital” or “clinic” can mean different things in different countries, so again it is better to specify what needs to be available – for example, “in a setting where full resuscitation equipment is immediately available.”

It may sound obvious, but additional risk minimization measures are those that are not routine. For the most part they tend to be additional communication tools in some form or other. Educational materials for physicians and/or patients are used when it is particularly important to ensure that particular messages are communicated. Typically these take the format of brochures giving information, but sometimes other formats can be useful. Most physicians will be familiar with the “I am a patient on steroids” card that is given to patients on long-term steroid treatment, but this “patient alert” card format can be used also to warn physicians unfamiliar with the patient that they are taking a particular medication that has multiple interactions or to watch out for particular signs and symptoms – for example, those suggestive of progressive multifocal leucoencephalopathy (PML) for patients on biological immunosuppressants. Checklists of tests needed prior to prescription, or diagnostic algorithms, are also frequently used as means of risk minimization, as are patient reminder cards where blood test results and dates of next tests can be recorded.

What is essential when planning risk minimization measures is to think of how the drug will be used and by whom. This means that sometimes an extension of indication may lead to a requirement

for educational material when none was needed previously. For example, a drug used commonly by cardiologists that has the potential for QT prolongation will probably not need additional educational materials since cardiologists are familiar with QT intervals, how to measure them, what precautions to take with QT prolongation, and possible interactions, and therefore the information on the risk in the SmPC will usually be sufficient. However, an extension of indication to either a general practice setting or even another specialist, such as a dermatologist, could lead to the need for educational material to warn of this risk, how to manage it, and which interacting substances to avoid, since these aspects may not be quite so familiar to these healthcare practitioners.

Additional risk minimization measures can be used consecutively or concurrently when the need arises. A pregnancy prevention plan for a major teratogen will have many facets. There will usually be educational material for both patients and physicians warning of the risk and the need for appropriate contraception in women of child-bearing potential. This may be augmented by an algorithm for patient selection and determining whether a woman is actually of child-bearing potential, since this is not quite as straightforward as it might seem. There could be a patient reminder card if regular pregnancy tests are required prior to each prescription, and also there could be advice on immediate actions to take if the patient suspects she might be pregnant.

The use of risk minimization measures needs to be balanced between the need to avoid a particular outcome and the increase in burden to both patient and doctor. In the above example of a major teratogen, the prospect of a seriously deformed child is horrifying enough to justify putting in place major preventative measures, but in other cases it may be less clear cut. For example what level of risk of PML requires a patient to have regular MRI? In a country where there is an MRI scanner in every hospital the level of acceptable risk might be lower than in a country where there is limited MRI resource and a patient may have to travel 100 miles to reach one. But is this pragmatic differentiation on the basis of scarce resource and inconvenience to the patient justifiable since the risk of PML is

the same regardless of the proximity of the scanner? This is one of the challenges facing regulators and why consultation with healthcare practitioners and patients is increasingly seen as an important part of the regulatory process.

## MEASURING EFFECTIVENESS

The legal definition of a risk management system contains the phrase “including the assessment of the effectiveness of those interventions.” This is to ensure that what has been put in place to minimize risks works – both on the grounds of minimizing risk and also because many additional risk minimization measures are expensive and also cause inconvenience to patients and/or doctors, and this is only justifiable if the benefits outweigh the harm. It is also bad science not to measure whether the assumption that measure x will reduce risk y is correct. Module XVI of GVP and the Council for International Organizations of Medical Sciences IX publication provide guidance on both risk minimization measures and how to measure effectiveness. However, in practice, there are two main paths for this: one can either measure the implementation of the measure or the achievement of the result.

A risk of hepatic failure might be managed by educational material informing the doctor of the risk and advising monthly liver function tests. If one were to measure implementation, there are a number of steps where this could occur:

- 1 Did the doctor receive the material?
- 2 Did the doctor read the material?
- 3 Did the doctor understand the material?
- 4 Did the doctor implement what was required?

Each of these steps is subtly different and requires different measurement tools. But even if these are all positive, there is still the need for three further steps, which are more problematic to measure:

- 1 Did the doctor review the results from the tests?
- 2 Did the doctor act on them to prevent harm?
- 3 Was harm prevented?

Measuring the actual achievement of risk minimization might appear to be simpler, but it can also

be difficult. To measure reduction implies that one knows a level before a risk minimization measure is implemented and the level afterwards. This may not always be the case. Measuring can itself also be problematic – how do you measure? Spontaneous adverse reaction reports are well known to underestimate the frequency of occurrence, but it is unlikely that the degree of underestimation is constant across the range of adverse reactions. There are many factors that influence reporting, so in the majority of cases it is probably not advisable to use spontaneous adverse reaction reports as a measure of effectiveness. Even a true absence of reports may not be due to the risk minimization measure itself but be due to another effect whose influence is not measured. A simplistic example of the above could be risk minimization measures in the prevention of drowning. In response to a media campaign, a council might employ a lifeguard on a beach and put lots of life rings in accessible places and congratulate itself on its risk minimization because no-one swimming in that particular bay drowned. However, if no-one in the adjacent bay without those precautions drowned, what conclusions can be drawn? It might be that the measures were effective, but the lack of drownings in the adjacent bay makes it difficult to be sure. The currents in the other bay might be weaker or the beach very stony so fewer people use it; in either case, this suggests that the two risks are not comparable, making the results difficult to interpret. It could also be due to the fact that no-one swam in either place because the weather was lousy and the sea freezing – both highly effective risk minimization measures but not what had been put in place! This illustrates the importance of anticipating how the results could be interpreted before instituting measures of effectiveness.

Another question is what constitutes success and what should be measured? In the example of risk minimization measures to prevent teratogenesis, no children born with deformities is one important measure of success and is easy to measure. However, if there were 100 terminations of pregnancy then one might be considerably less confident in proclaiming that the pregnancy prevention plan was a success. A better outcome measure of success might be no exposed fetuses; in which case, ensuring all

reports of pregnancies are collected would be a better, if more difficult, endpoint.

Regardless of whether routine or additional risk minimization measures are put in place, there should always be a description of how the effectiveness will be measured in Part V of the RMP. If it is decided that a study is needed, then this should be included in the PhV plan (see Figure 12.4).

## PART VI OF THE RISK MANAGEMENT PLAN AND PUBLICATION OF THE SUMMARY

Part VI is the Summary of the RMP and is the other completely new part of the RMP and is a result of the legislation which now requires that a summary of the RMP should be published. Part VI contains several tables and also summaries, in lay language, of the other parts and modules of the RMP to facilitate implementation of the legislation. It is not intended to publish Part VI in the exact form it is submitted, but to incorporate tables and text from it in a public summary. Exactly what form publication of a public summary will take was still under discussion in 2013, but it is most likely at present (2013) that there will be a stepwise approach with flexibility in the implementation in different member states of the EU.

The current publication possibilities in order of detail are:

- statements in the Summary of the (European) public assessment report ((E)PAR);
- tables in the (E)PAR;
- stand-alone public summary of the RMP.

For products authorized through the centralized procedure, there is already an EPAR and a Summary of the EPAR. The former is a detailed scientific assessment of the data provided to the CHMP and the conclusions drawn by that committee. This already contained an overview table summarizing the RMP, but this is being expanded to include more tables from Part VI of the RMP. The concept of a PAR for products authorized via other routes has been agreed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).

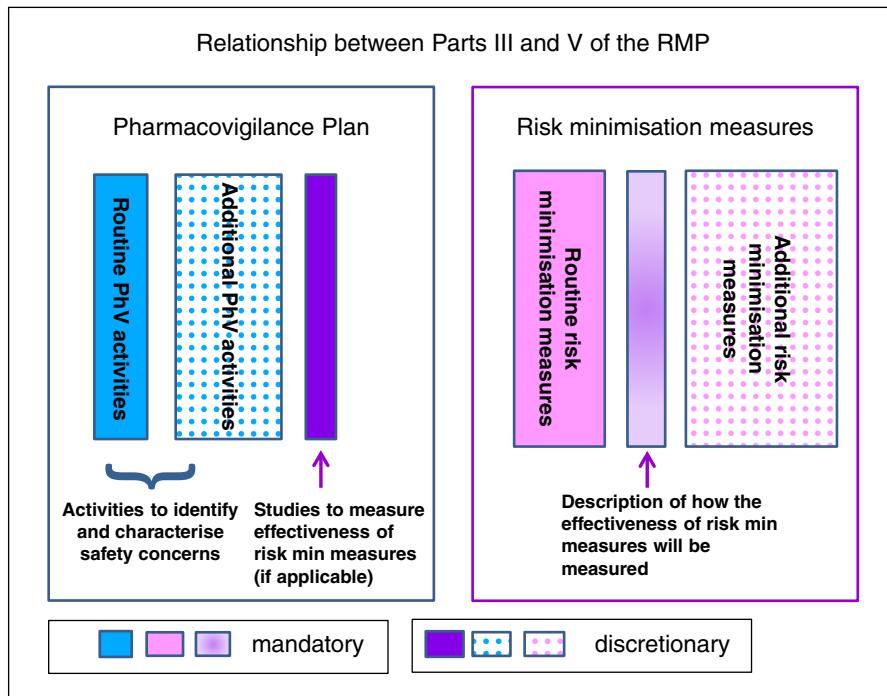


Figure 12.4 Relationship between Parts III and V of the RMP. Source: Stella Blackburn. Reproduced with permission of Stella Blackburn.

The Summary of the EPAR is a concise one- to two-page summary written in lay language that includes two brief paragraphs on the RMP.

The stand-alone public summary as currently proposed provides a more detailed explanation of what is in the RMP written in lay language. Anecdotal evidence suggests that patients are sometimes deterred from taking a medicine by the PIL which details the possible adverse reactions to the medicine. For patients to be able to make informed choices on whether to take a medicine or not, they need to understand the risks associated with the disease and its natural history without treatment (or prevention). The stand-alone summary includes a brief overview of the epidemiology of the disease to give context to the benefits of the medicine in reducing the risks of the disease as well as more information on the risks of the medicine and how they can be prevented. It will also provide details of how the MAH intends to further investigate the safety concerns and state whether any studies

have been formally imposed by the regulatory authorities.

It maybe that flexibility in the format of the public summary could also relate to the type of medicine. It seems less useful to provide a detailed public summary of the RMP for medicines where the patient has little involvement in which particular product is used or whether it is used (e.g., anesthetics or diagnostic agents). The one current certainty is that the format, utility, benefit-risk, and effectiveness of use of resource relating to the summary of the RMP will be debated for many years to come.

## UPDATES TO THE RISK MANAGEMENT PLAN

In the past, the RMP had defined timelines when it was required to be updated. These followed the time schedule of the periodic safety update reports. These

“routine” updates were in addition to the requirement to update the RMP whenever there was:

- an application for a significant change to a marketing application;
- within 60 days of an important PhV or risk minimization milestone being reached;
- or when there was new information that could have a significant impact on the benefit–risk balance of the product.

A milestone was considered to include final or interim study reports or some form of evaluation of the effectiveness of a risk minimization measure. Milestones could also include a set number of patients prescribed a medicine or a period of time after the medicine was first marketed.

In the light of experience, the transition of the RMP to focus on risk management planning and a desire to rationalize the use of scarce PhV resources whilst still protecting public health, submission at fixed time points seems less useful. Updates will now only be required when a risk management system is updated or at the request of a competent authority. It is likely that changes to the risk minimization system will occur because of an application for a significant change to the marketing authorization (e.g., new indication and hence a new target population or a new route of administration), a milestone in a PhV study being reached, or when data suggest that the benefit–risk has changed and a change to risk minimization measures should be evaluated. This change may at first appear negligible, but in fact it marks a major change in concept and places the onus on the MAH to decide when there is sufficient change to the risk management system to warrant the submission of an updated RMP. Of course, the competent authority can always request the submission of an RMP if it has concerns. This change in concept to a risk-based approach also emphasizes that the RMP is not a bureaucratic document but has a key role in protecting patients.

## CONCLUSIONS

The choice of the chapter title as “the principles behind risk management in the EU” was deliberate.

Risk management as a science is continuously evolving. Since its formal inception in November 2005, there has been a massive change in perception of the importance of risk management and the role it has to play in protecting both public health and the well-being of individual patients. There is also a growing realization that planning of research in the post-authorization period should not be an afterthought but an integral part of lifecycle management. This is just the start, and there will be a continuous evolution for many years to come. For this reason, although there is a description of the current status and requirements relating to the RMP in this chapter, the focus is much more on the principles behind risk management, what needs to be achieved, and a discussion of the way things may evolve. It seems likely that we will move from risk management alone to the concept that maximizing the benefit–risk balance can be better achieved by attacking both sides of the equation.

A marketing authorization implies that, at the time of licensing, for the average patient the potential benefits of treatment outweigh the potential risks in the approved indication. However, there is no such thing as an average patient. The complex interplay between genetics, the environment, and individual lifestyle choices mean that every person will have different risk factors and also different “benefit factors.” Medicine will become more complex, but possibly the results of treatment will also become more predictable. Our ability to diagnose and treat disease is expanding, people are living longer, and so the costs of healthcare are increasing. Cost effectiveness is the new paradigm for health economists, and comparative effectiveness is increasingly required as the fourth criterion after quality, safety, and efficacy. Post-authorization research is no longer an option but an essential part of lifecycle management. Risk management is just the first step on the path.

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**Part II**

**PHARMACOVIGILANCE SYSTEMS**



## **Part II: PHARMACOVIGILANCE SYSTEMS**

### **Pharmacovigilance in Europe**

**13a**

# **Regulatory Pharmacovigilance in the European Union<sup>1</sup>**

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## **INTRODUCTION, HISTORICAL PERSPECTIVE AND CURRENT DEVELOPMENTS**

Modern regulation of medicines in Europe began in the 1960s in the wake of the occurrence of several thousand cases of phocomelia, a congenital limb abnormality, which was caused by exposure to thalidomide during pregnancy (Stephens and Brynner, 2001). In response to this tragedy, spontaneous adverse reaction reporting schemes were developed with the aim of providing signals of unexpected hazards. Also, legislation was passed to provide regulatory controls on quality, safety, and efficacy of medicines through systems of standards for

development and manufacturing, authorization, pharmacovigilance, and inspection. In the European Union (EU), the first Community Directive on medicines was enacted in 1965, Council Directive 65/65/EEC (EEC, 1965), and laid down basic principles relating to these systems, which are still operational early in the third millennium. In particular, quality, safety and efficacy are the criteria through which medicines are regulated, and other factors, such as cost, are not taken into account in decisions relating to the granting of a marketing authorization.

Despite the extensive requirements for evidence on quality, safety, and efficacy which are necessary to gain a marketing authorization, pharmacovigilance during the post-authorization phase is a high priority for regulatory authorities in the EU. Although the quality and efficacy of a medicine are generally well described at the time of authorization, conclusions on the adverse effect profiles of medicines from clinical trials are limited by the

<sup>1</sup> Disclaimer: The views expressed in this chapter are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Table 13a.1 Objectives of regulatory pharmacovigilance.

- |    |  |
|----|--|
| 1. | Long-term monitoring of safety in clinical practice to identify previously unrecognized safety hazards or changes in the adverse effect profiles |
| 2. | Assessment of the risks and benefits of authorized medicines to take action to improve safety  |
| 3. | Provision of information to users to optimize safe and effective use of their medicines  |
| 4. | Monitoring the impact of any action taken  |

numbers and selection of patients included in such trials, their duration, and the relatively controlled conditions under which they are conducted. Safety in practice can only be fully assessed after marketing, and it is well recognized that hazards may emerge at any time during the life of a product. Hence, there is a need to monitor continuously the safety of all marketed medicines indefinitely. The overall objectives of regulatory pharmacovigilance (Waller *et al.*, 1996) are summarized in Table 13a.1. Spontaneous reporting schemes continue to underpin such monitoring throughout the EU and have proved successful in identifying many important safety hazards. However, both false positives and false negatives have occurred, one of the most striking examples of the latter being the failure to identify the oculomucocutaneous syndrome induced by propranolol at an early stage (Felix *et al.*, 1974). Specific limitations of spontaneous reporting schemes include underreporting and uncertainty about causality and frequency. Thus, many other sources of information are also used. There is increasing emphasis on epidemiological studies and the use of databases in the EU to evaluate the safety of marketed medicines.

During the early 1990s, closer cooperation between EU member states developed as proposals for a more closely integrated regulatory system were formulated. Ultimately, this led in 1995 to the establishment of the European Agency for the Evaluation of Medicinal Products (EMEA), since 2004 called the European Medicines Agency (now abbreviated EMA), and to a new regulatory system that includes procedures for a centralized authori-

zation and multiple identical authorizations through decentralized and mutual recognition procedures. These procedures have had a considerable impact on the operation of pharmacovigilance in the EU. Although pharmacovigilance continues to be embedded in national systems, particularly in terms of data collection and expertise, there is central coordination through the EMA and, until July 2012, through the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP, previously called CPMP). This involves agreed standards and procedures as well as systems for exchanging information and decision-making.

In this millennium, legal provisions for pharmacovigilance in the EU have already been enhanced twice, first in 2004, when *inter alia* the risk management approach was introduced, and in 2010, when specific legislation was passed to strengthen pharmacovigilance in the EU. This new legislation presents major changes, resulting from the culmination of a process which had been started by the European Commission several years earlier and has been applicable from July 2012 subject to some transitional provisions. The "recitals" of the legislation explain the reasoning behind these changes, namely the identified need, on the basis of experience and an assessment by the Commission, to take measures to (1) strengthen post-authorization regulation of medicines, in particular through EU-wide procedures with binding outcomes, (2) improve efficiency, both within the pharmaceutical industry and through reduced duplication of effort between the member states and central coordination by the EMA, and (3) to increase transparency and public participation. An additional piece of legislation, a Commission Implementing Regulation, deals with technical and operational aspects of major pharmacovigilance processes, including quality management for marketing authorization holders, national competent authorities, and the EMA.

## **LEGAL BASIS, PRINCIPLES, AND ORGANIZATION**

The concept of pharmacovigilance was introduced into the legislation at EU level in 1993 through

Council Directive 93/39/EEC (EEC, 1993a) amending Council Directive 75/319/EEC (EC, 1998). Later, EU medicines legislation was codified into a single directive (EC, 2001) in which pharmacovigilance was covered in Title IX and revised in 2004 and 2010. Directives of the European Parliament and the Council have the objective of harmonizing the national legislation of member states, which are bound to implement these legal provisions into their national legislations. However, pharmacovigilance systems already existed in most countries which were member states in 1993 and also in many of those joining the EU through the enlargement processes thereafter. These systems vary according to differences in historical development and the organization of healthcare at national level. All are an integral part of the respective national competent authority. Through the EU legislation, their activities are specified with regard to medicinal products authorized for use on their territory as follows:

- to collect information about suspected adverse reactions that occur with use inside or outside the terms of the marketing authorization;
- to obtain information on consumption data;
- to collate information on misuse and abuse;
- to evaluate this information scientifically;
- to inspect marketing authorization holders' pharmacovigilance systems; and
- to ensure the adoption of appropriate regulatory decisions and public communication.

Practice has shown that pharmacovigilance needs to be conducted with a view to how the product is used in ordinary clinical practice. Experience gained during the post-authorization phase may also provide valuable input into the evaluation of medicinal products at the stage of application for marketing authorization, if there are chemical or pharmacological similarities with authorized products.

The national pharmacovigilance systems of the member states, together with the European Commission and the EMA, form the regulatory pharmacovigilance system of the EU, cooperating in a network structure under the coordination of the EMA. Also included are Norway, Iceland, and Liechtenstein, which are not members of the EU

but are part of the European Economic Area (EEA, 2000). Within this network structure, all parties have their roles and responsibilities for the surveillance of medicinal products. These roles and responsibilities vary depending on the route of marketing authorization of the product in the EU and were initially defined through Council Directive 93/39/EEC (EEC, 1993a), and Council Regulation (EEC) No. 2309/93 (EEC, 1993b). In 2004, as a result of an intensive legislative review process, the directive was amended and the regulation was replaced as of 20 November 2005, by Regulation (EC) No. 726/2004 (EC, 2004). Both the directive and the new regulation were amended on 31 December 2010 through Directive 2010/84/EU (EU, 2010a) and Regulation (EU) No 1235/2010 (EU, 2010b) as a result of an assessment of the current EU pharmacovigilance system and the political commitment to strengthen it. They are supplemented by Commission Implementing Regulation (EU) No 520/2012 (EU, 2012b) on the performance of selected pharmacovigilance activities. Directive 2012/26/EU (EU, 2012c) and Regulation (EU) No 1027/2012 (EU, 2012d) of 25 October 2012 added some further amendments to the EU legislation for pharmacovigilance.

Guidance documents for the practical implementation of the legislation were developed at EU level for the first time during the 1990s for the national competent authorities, the EMA, and marketing authorization holders in consultation with member states and interested parties in accordance with recommendations agreed at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). They were made available in a compiled format first as Volume 9, later as Volume 9A of the *Rules Governing Medicinal Products in the European Union*, published in its last revision in 2008 (EC, 2008a). Under the new legislation, Volume 9A has, since 2012, been replaced by a new set of guidelines, called good pharmacovigilance practices (GVP) (EMA, 2013c).

The EMA is a Community agency: a public authority of the EU set up by a Community act of secondary legislation (EEC, 1993b) with its own legal personality (EU, 2012e). The objective of the EMA is the protection and promotion of human

and animal health in the EU by fulfilling, *inter alia*, the following tasks with respect to human medicines:

- the coordination of the scientific evaluation of quality, safety, and efficacy of medicinal products that have been applied for a central marketing authorization with the aim of facilitating the access to effective and safe innovative medicinal products throughout the EU; and
- the coordination of post-authorization safety of medicinal products through the pharmacovigilance network.

The EMA pools scientific expertise from the authorities and also from academic and healthcare institutions in member states as well as from European patient organizations and health professional bodies for the evaluation of medicinal products, and to provide advice on drug research and development programs ([www.ema.europa.eu](http://www.ema.europa.eu)). More specific to pharmacovigilance, the tasks of the EMA include the following:

- overall coordination of pharmacovigilance activities of medicinal products authorized in the EU;
- maintenance of EudraVigilance as the database and data-processing network of suspected adverse reactions reported for medicinal products marketed in the EU and provision of public access to related information;
- coordination of signal and incidence management;
- risk assessment, including assessment of signals, periodic safety update reports (PSURs), and risk management plans (RMPs) to be dealt with by the Pharmacovigilance Risk Assessment Committee (PRAC);
- oversight of post-authorization safety studies through the PRAC;
- maintenance of and variations to the terms of the marketing authorization for centrally authorized products;
- management of referral procedures for nationally authorized products leading to decisions binding in all member states when there is a safety concern that impacts on public health in the Community; and
- coordination of safety announcements to the public.

EudraVigilance was put in place by the EMA from December 2001 (EMA, 2013a), enabling the electronic transmission, management, and analysis of suspected adverse reaction case reports to a central point accessible by all competent authorities in the EU and exchange of pharmacovigilance information between all stakeholders (marketing authorization holders, national competent authorities, and EMA). In addition to the case reports arising worldwide post-authorization, EudraVigilance was extended to include clinical trials data as of May 2004. These developments were in line with international developments at ICH level (Tsintis and LaMache, 2004) and proactive pharmacovigilance and risk management (Waller and Evans, 2003). Guidance for the electronic submission of case reports in relation to medicinal products authorized in the EU is provided (EMA, 2013a).

Much of the work of the EMA is done within its scientific committees. With regard to pharmacovigilance, a new committee, PRAC, came into operation in July 2012 and meets 11 times per year at the EMA.

It supersedes the PhVWP which had operated relatively informally under the auspices of the CPMP/CHMP since 1995 to provide advice on the safety of medicinal products and the investigation of adverse reactions and to enable effective risk identification, assessment, and management, in the pre- and post-authorization phases, leading to non-binding recommendations on harmonized and synchronized action to the CHMP and the competent authorities in member states.

In contrast, the main purpose of PRAC is to provide the necessary expertise and resources for post-authorization assessment of pharmacovigilance data and recommendations on any such EU-wide assessment as well as on risk management systems and monitoring their effectiveness. Its mandate covers detection, assessment, minimization and communication of risks of adverse reactions, design and evaluation of post-authorization studies, and pharmacovigilance audits. PRAC is composed of one member and alternate from each member state plus one member and alternate to

represent each of the following stakeholders: health professionals and patient organizations. Additionally, there are six members appointed by the European Commission on the basis of relevant expertise. PRAC provides its recommendations to CHMP for active substances or classes of medicines contained in centrally authorized products and to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for nationally authorized products. The PRAC recommendations are ultimately implemented either by the European Commission following a CHMP Opinion or through a position of the CMDh (followed up by a Commission Decision in the case of CMD(h) not reaching consensus). Both CHMP and CMDh are legally obliged to *rely* on the PRAC recommendations; however, final responsibility for risk–benefit assessment remains with the CHMP or the national competent authorities responsible for granting the marketing authorization. If the CHMP or the CMDh do not follow PRAC recommendations, they are legally bound to publish a justification.

Prior to 2012, some referral procedures, initiated for nationally authorized products with a safety concern relevant across the EU, often took many months to resolve. The new legislation imposes a tighter timetable: 60 days for PRAC to make a recommendation and then 30 days for CHMP to reach an opinion, followed by 15 days for the European Commission to reach a decision. PRAC may shorten its timetable in urgent cases and may recommend interim measures directly to the Commission. The legislation specifies the circumstances under which the procedure may be invoked – essentially in the case of a potential need to withdraw or restrict a product on grounds of safety. PRAC may recommend further evaluation, new studies, and new risk minimization measures, as well as suspend, revoke, vary or not renew the authorization.

PRAC also contributes to the development of pharmacovigilance guidelines by the EMA.

To facilitate a continuous exchange of information between regulators in the EU, in particular with regard to changes in the benefit–risk balance possibly requiring major regulatory action, but also for signal evaluation, the so-called rapid alert–non-urgent information system has been established. This is supported by an electronic database, the

European Pharmacovigilance Issues Tracking Tool (EPITT) that is maintained centrally by the EMA for recording the information flow and tracking the ongoing work. The principles and procedures of this system are presented in guidance (EMA, 2013c).

Pharmaceutical companies holding marketing authorizations in the EU have various obligations in the area of pharmacovigilance that are laid down in Title IX of Directive 2001/83/EC as amended (European Commission, 2012) and Regulation (EC) No 726/2004 as amended (European Commission, 2013) and elaborated further in the GVP (EMA, 2013c). A new obligation under the 2010 legislation is for marketing authorization holders to create a pharmacovigilance system master file (PSMF) documenting their pharmacovigilance system, which can be inspected at any time. In particular, marketing authorization holders must employ a qualified person who is *inter alia* responsible for:

- overseeing the marketing authorization holder's pharmacovigilance system;
- establishing and maintaining a system that collects and collates all suspected adverse reactions and investigates signals;
- the preparation of RMPs, post-authorization safety studies, and PSURs;
- responding to requests for additional information from competent authorities; and
- provision to competent authorities of any other information relevant to the risk–benefit evaluation.

Marketing authorization holders are obliged to report serious suspected adverse reactions in accordance with the legislation and guidance cited above to competent authorities within 15 days ("expedited reports") and to implement requests issued by the competent authorities.

Penalties may be applied in order to enforce the legal provisions relating to pharmacovigilance.

## THE PROCESS OF REGULATORY PHARMACOVIGILANCE IN THE EUROPEAN UNION

Regulatory pharmacovigilance is dependent on the availability of information on the clinical effects of

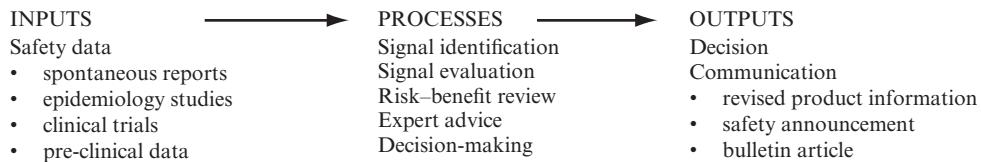


Figure 13a.1 Regulatory pharmacovigilance.

medicines in representative populations as used in normal clinical practice. In addition to systems for collecting and handling suspected adverse reactions, processes for identifying and investigating signals are necessary. All potentially important hazards are investigated with a view to taking appropriate action based on the available scientific evidence. The most important outputs of the process are actions to promote safer use of medicines. These include introducing warnings, contraindications, information on adverse reactions, or changes to dosing recommendations. Indications or methods of supply may also be restricted, although withdrawal of a medicinal product from the market on safety grounds is relatively unusual. Informing users and explaining the reasons for the action taken is a critical determinant of the effectiveness of these measures. The process of regulatory pharmacovigilance is summarized in Figure 13a.1.

## RISK MANAGEMENT, PERIODIC SAFETY UPDATE REPORTS, POST-AUTHORIZATION SAFETY STUDIES, AND THE EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE

With a view to increase proactivity, the 2004 revision of the legislation introduced the concept of risk management, which is defined in the EU as a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions. Some of its elements had already been agreed by ICH in guideline E2E on pharmacovigilance planning and incorporated a “best evidence” approach of the excellence model

in pharmacovigilance (Waller and Evans, 2003). In terms of risk management, there is a need for use of best expertise and methods in safety studies and epidemiology to take this forward by means of RMPs to be submitted by marketing authorization holders. With the 2010 legislation, RMPs are at the heart of the pharmacovigilance process and required for all new marketing applications, as well as for new indications and major changes or emerging safety concerns to existing products. Notably, monitoring the effectiveness of risk minimization measures has become one of the tasks for the EMA, the national competent authorities, and also for PRAC (Prieto *et al.*, 2012).

Post-authorization safety studies may be requested by the authorities as part of risk management. Previously, competent authorities in the EU lacked the power to impose on marketing authorization holders to conduct post-authorization studies, and practice in this field was almost entirely defined by guidance (Volume 9A) rather than law. This produced a major imbalance in regulatory powers before and after authorization, since, pre-authorization, the authorities could simply refuse to grant an authorization until further studies had been done. The 2010 legislation has empowered competent authorities to impose on applicants or marketing authorization holders the obligation to conduct post-authorization studies when justified by concerns or missing information. Both safety and efficacy studies may be required, and the obligation may be imposed at the time of authorization or subsequently if an important concern emerges. The imposition of such obligations will need to be justified by the authorities, who will define the objectives and timeframe for the study. In addition to these new powers, much of what was previously included in Volume 9A is now included in legislation; for example, that studies shall not be per-

formed where the act of conducting the study promotes use of a medicinal product. Also, competent authorities now supervise noninterventional post-authorization studies (not only those which are clinical trials) Another important change is the legal obligation of marketing authorization holders to provide safety information to competent authorities from clinical trials, including those conducted outside the terms of the authorization, promptly.

In order to facilitate research in the EU at an academic level, the EMA established the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) in 2006. Its goal is to further strengthen the post-authorization monitoring of medicinal products in the EU by facilitating the conduct of multicentre, independent, post-authorization studies focusing on safety and on the benefit–risk balance, using available expertise and research experience across the EU. This network comprises relevant research centers, medical care centers, healthcare databases, electronic registries, and existing European networks covering certain rare diseases, therapeutic fields, and adverse events of interest (EMA, 2013b).

While RMPs are documents for planning pharmacovigilance data collection and risk minimization, PSURs summarize the available worldwide data at defined points in time, evaluate the benefit–risk balance and whether new risk minimization measures or more data are needed. PSURs have to be prepared by the marketing authorization holders and submitted to the competent authorities in member states and the EMA in accordance with the GVP for coordinated assessment within the EU (EMA, 2013c). PSURs must now be submitted electronically to the EMA, where they will be managed in a repository and made available to member states and the relevant committees, including PRAC. The PSUR concept was originally proposed by CIOMS in 1992, put into EU legislation in 1993, and subject to the ICH process in 1996. The 2010 legislation changed the emphasis of PSURs considerably by requiring them to evaluate benefits and risks based on all available data with consideration of the potential impact of the evaluation on the marketing authorization. A new format for a periodic benefit–risk evaluation report (PBRER) has been developed by the ICH

([www.ich.org](http://www.ich.org)) and incorporated in the GVP (EMA, 2013c).

## DETECTION OF ADVERSE REACTIONS AND SIGNAL MANAGEMENT

Potentially important safety issues can be identified at any stage of product development. In the post-authorization phase, they are particularly likely to be identified in the first few years after marketing, although new issues also arise with long-established medicines. To ensure that safety problems which have not been recognized or fully understood pre-marketing are handled promptly, proactive processes are used for screening emerging data for potential issues and bringing together all the available information from multiple sources. A signal has been defined as information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify confirmatory action. For the purpose of monitoring data in the EudraVigilance database, only signals related to an adverse reaction shall be considered (EU, 2012b).

The commonest source for identification of significant safety concerns arising with marketed medicines is spontaneous adverse reaction reporting. These are individual case reports from health professionals or patients of adverse events which the reporter considers may be related to the medicine(s) being taken. Reporters are not asked to provide all adverse events that follow administration of the medicine but to selectively report those which they suspect were adverse reactions. So-called direct patient reporting schemes have been established increasingly in member states over the last decade and have become an EU-wide requirement by means of the 2010 legislation.

There is frequently confusion between the terms “adverse event” and “adverse reaction,” which can be avoided by using the term “*suspected* adverse reaction” when referring to a case or series of cases reported through a spontaneous reporting scheme.

The term “adverse event” should be used in the context of studies where all events are being collected regardless of whether or not they are suspected to be related to a product. This approach is underpinned by definitions given in EU legislation (EC, 2001) and is also consistent with definitions proposed by ICH in guidelines E2A and E2D ([www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html](http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html)).

A new tool introduced by the 2010 legislation to stimulate reporting of adverse reactions by patients and health professionals to expand the safety evidence is additional monitoring for new active substances and biologicals (including biosimilars), as well as other products if necessary. Eligible products are identified by a black symbol for 5 years after the initial authorization (which may be extended if necessary on the recommendation of PRAC).

Clear responsibilities for signal detection are laid down by the 2010 legislation. While marketing authorization holders are responsible for their products, the EMA leads on signal detection for centrally authorized products and member states, supported by the EMA, for nationally authorised products. Signal management, the key initial stage in the overall pharmacovigilance process, is now also recognised by EU legislation. Competent authorities in member states and the EMA collaborate closely for the monitoring of EudraVigilance, and there is a role for PRAC to perform the initial analysis and prioritization of signals based on potential public health impact. There is an obligation for authorities to inform each other and marketing authorization holders when signals are detected. Marketing authorization holders are obliged to evaluate all pharmacovigilance information scientifically, consider options for risk minimization and prevention, and take appropriate measures as necessary. EPITT supports the signal management process coordinated between member states by the EMA.

Although formal studies of safety are particularly used in the investigation of signals identified by methods such as spontaneous reporting (i.e., hypothesis testing), they may also provide the initial evidence producing a safety concern. Signals may also be detected from other sources, such as litera-

ture reports and from screening of the international spontaneous reporting database operated by the Uppsala Monitoring Centre in Sweden, a Collaborating Centre of the World Health Organization ([www.who-umc.org](http://www.who-umc.org)) to which EU data are contributed. Whatever the source of the signal, the aim is to identify it as rapidly as possible.

## EVALUATION OF SAFETY CONCERNs

When there is sufficient evidence of a hazard to warrant further investigation, detailed consideration is given to causality, possible mechanisms, frequency, and preventability. Assessment of these issues may require new epidemiological studies, but the hypothesis may be strengthened or weakened using immediately available sources of retrospective information such as worldwide spontaneous reporting, published literature, and epidemiological databases.

The broad principles relating to post-authorization studies have been set out in legislation and GVP (EMA, 2013c). When new data become available from purpose-designed studies, it is important that they are reviewed in the context of the existing data. An assessment is made of whether and how the new evidence changes the previous evaluation, focusing particularly on the strength of the evidence for a causal association and possible approaches to prevention. In the latter respect, detailed analysis of the data to identify possible risk factors for the hazard is important.

The output of an evaluation is an assessment report that brings together the key information on the hazards and facilitates discussion of the risks and benefits of the medicine and possible measures which may facilitate safe use. Experts in pharmacoepidemiology and relevant therapeutic areas are consulted and involved in such discussions, and at EU level the assessments are performed by PRAC.

## DECISION-MAKING

The objective of the EU competent authorities is to take regulatory actions which are justified by scientific evidence and allow users to make informed

decisions and to use medicines safely. Sometimes, the balance of risks and benefits will be sufficiently clear to allow firm recommendations (such as contraindications), whereas in other situations less directive advice will be warranted.

The types of action which may be taken vary according to potential means of preventing the adverse reaction. In particular, hazards may be minimised by targeting the medicine at patients least likely to be at risk of the reaction and by specifically contraindicating it in patients with identifiable risk factors. Dose and duration of treatment are often important issues as the risk of many hazards is related to one or both of these parameters. It is quite common for dosage regimens to change during the post-authorisation period in response to safety concerns, and many medicines have been initially recommended at doses higher than necessary. In re-evaluating dose in response to a safety concern, consideration is also given to the evidence of efficacy at lower doses.

The identification of a new adverse reaction or the accumulation of important new evidence about a recognized reaction leads to a need to make changes to the product information, and hence to vary the marketing authorization(s). Variations to marketing authorizations on safety grounds may be proposed by the competent authority or the pharmaceutical company. Regardless of who proposes the changes, there is exchange of information and discussion between the parties before a variation is submitted. When the competent authorities and companies are in agreement about the nature and impact of a safety issue, changes can be made on a voluntary basis by the marketing authorization holder. However, if companies do not agree about the actions required, then the competent authorities may exercise compulsory powers. In situations of particular urgency, the legislation provides for rapid processing of safety variations where either the marketing authorization holder or the competent authority can initiate an urgent safety restriction procedure that enables a change to the product information within 24h and is followed within 2 weeks by a formal variation (EC, 2008b; EU, 2012a). Exceptionally, when the issue has urgent public health implications, the authorities may immediately withdraw the product(s) from the

market. This can be effected either by suspension of the authorization(s) or by its revocation. The option to suspend is considered in situations whereby an urgent temporary measure is required as a precaution to protect public health whilst awaiting new data to emerge. Revocation is foreseen when data are already available demonstrating an unfavorable benefit–risk balance even in different subgroups of patients.

In the EU, a safety concern with an active substance or therapeutic class may relate to many originator and generic products authorized nationally in the different member states or the active substance may be subject to national as well as centralized marketing authorization procedures. For these situations, referral procedures have been established to facilitate harmonized decision-making at EU level.

## COMMUNICATION

Communicating information to users of medicinal products is a vital step in the process of handling a safety issue with a marketed medicine. An important consideration is how quickly information needs to be made available to users. A new life-threatening adverse reaction requires immediate communication, whereas the addition of information relating to a nonserious reaction could be added at the next routine revision of the product information. The distribution of safety information may be targeted at specialists or generalists, or both, and at other relevant health professionals and, of course, at patients. The 2004 revision of the legislation introduced new obligations for the member states' authorities and the EMA in relation to such communication to the public and imposed additional requirements on the companies. The 2010 revision of the legislation has further increased transparency of safety information and gave the EMA the responsibility for co-ordinating safety announcements by the competent authorities and the option to convene public hearings. A particularly important aim in safety communications is to ensure that essential information is clearly conveyed and not obscured by other, less important, information. Every effort is therefore

made to word the key facts and recommendations unambiguously.

The key principles with patient information are that it should, in substance, be the same as the information provided to health professionals and it should be presented in language that the patient can understand. Good patient information adds to and reinforces the main issues that should be discussed between health professionals and patients and does not make statements which could interfere with that relationship. To respond appropriately to the patients' demands, a working group with patient organizations has been in operation at EMA since 2003 and one of its aims is to provide overall recommendations and specific input to guidelines on communication and to new procedures; for example, for testing of product information (EMA PCWP, 2013). Patient and health professionals' representatives are also members of the new PRAC. Similar initiatives have been undertaken at national level in some member states.

Any change to the marketing authorization and product information that has significant safety implications is actively drawn to the attention of the relevant health professionals, usually by circulating the new product information under cover of a direct healthcare professional communication. With regard to information targeted at health professionals, the EMA has initiated dialogue with health professional organizations at EU level to support and complement national activities (EMA HCPWP, 2013). When the changes being made are vital for ensuring patient safety, they are implemented very quickly, and it is normal practice to make information available to the media and general public through press releases and/or the Internet.

The competent authorities recognize that successful communication about safety is a vital component of the pharmacovigilance process and needs EU-wide coordination. This is a particular challenge because of the need to translate messages into all the official languages of the EU (currently 24), and considerable attention is being paid to improving this aspect of the process. Intensive thought is currently given to the enforcement of existing procedures and the establishment of new procedures to optimize EU-wide coordination of safety com-

munication, as well as to the assessment of the public health impact of such communication. In terms of risk minimization, targeted information to health professionals and patients is seen as an important tool (EMA, 2012a).

## FUTURE CHALLENGES

The medicines legislation has been reviewed by the European Commission, with most of the resultant changes having come into force in July 2012. Many elements of the EU system have been re-enforced or newly introduced, with the aim to improve pharmacovigilance and to meet the higher expectations of EU citizens.

One important limitation of all current pharmacovigilance systems that the new legislation aims to tackle is the difficulty in measuring the effects of the actions taken. It will be particularly important for national competent authorities and the EMA to address this, using, for example, available electronic epidemiological databases. Expectations of consumers in respect of safety of medicines have increased considerably in recent years (EMEA 2005; EMA PCWP 2013) and are likely to continue to do so. To meet these expectations, processes will need to become even more transparent and demonstrably effective, and it will be important that both competent authorities and pharmaceutical companies ensure full compliance with their pharmacovigilance obligations.

## CONCLUSIONS

The system of pharmacovigilance established in the EU aims to promote the safe use of medicines in clinical use, thereby protecting public health. During the 1990s, existing pharmacovigilance systems in member states were brought together to form an EU-wide system that currently, after the EU enlargements of 2004, 2007, and 2013, covers a population of nearly 500 million people. The main challenges of the future include further EU enlargement and the increasing expectations of consumers. To meet these challenges, and to efficiently add further value in the protection of public

health, the system is continuing to evolve, particularly in response to scientific progress and technological developments. Optimal use of the best evidence and expertise for decisions will be essential to conduct proactive pharmacovigilance for medicines in any phase of their product life.

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## 13b

# Spontaneous Reporting: United Kingdom

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## INTRODUCTION

In the United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) is the executive arm of the Licensing Authority (Health Ministers) and is responsible for the control of the safety, quality and efficacy of medicines. The MHRA was formed on 1 April 2003 from a merger of the Medicines Control Agency (MCA), previously responsible for monitoring the safety, quality and efficacy of medicines, and the Medical Devices Agency (MDA). In 2013, the MHRA merged with the National Institute for Biological Standards and Control (NIBSC) and the Clinical Practice Research Datalink (CPRD). The Agency's primary objective is to safeguard public health by ensuring that medicines, healthcare products and medical equipment on the UK market meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

The Vigilance and Risk Management of Medicines Division of the MHRA is responsible for monitoring the safety of all medicines on the UK market, in order to identify and investigate possible hazards and take appropriate action to minimise the risks and maximise the benefits to users, thus protecting public health. Although data from a wide range of sources are used (Waller, Coulson and Wood, 1996), it is the UK's spontaneous reporting scheme (commonly known as the 'Yellow Card Scheme') that is the cornerstone of the monitoring process.

The aim of this chapter is to inform the reader about the past, present and future of the Yellow Card Scheme. First, the background to the evolution of the Yellow Card Scheme since its introduction in the 1960s is outlined, including examples of the safety hazards identified from spontaneous reporting, and some of the problems faced by the Scheme in past years. Secondly, we describe

some of the recent initiatives implemented in order to tackle these problems, focusing on areas such as widening the reporting base, facilitation of reporting and optimising the use of the data as a research tool. Finally, we outline some of the possible future directions for the Yellow Card Scheme that are intended to allow it to continue to fulfil its key role in pharmacovigilance in the years to come.

## BACKGROUND

While the quality and efficacy of a medicine are fairly well defined at the time of licensing, the clinical trials conducted in support of a licence application can only provide limited data on a medicine's safety profile; the safety profile of a medicine in normal clinical use can only be fully assessed after it has been marketed. The public health importance of controls on the safety of medicines was dramatically brought to the attention of the public in the early 1960s by the thalidomide tragedy. In the wake of this tragedy, many countries introduced systems for the systematic collection of reports of adverse drug reactions. In the United Kingdom, the Committee on Safety of Drugs (subsequently the Committee on Safety of Medicines (CSM) and now the Commission on Human Medicines (CHM) was set up. One of the main responsibilities of this new committee was to promote the collection and disseminate of information relating to suspected adverse effects of drugs (Griffin, 1992). To address this objective, the United Kingdom's spontaneous reporting scheme was introduced in 1964, when Sir Derrick Dunlop (the chairman of the Committee on Safety of Drugs) wrote to all doctors and dentists in the United Kingdom to announce the launch of the new Scheme (Griffin and Weber, 1992). In his landmark letter, Sir Derrick asked 'every member of the medical/dental profession in the United Kingdom' to report 'promptly details of any untoward condition in a patient which might be the result of drug treatment' and stated that 'All the reports or replies that the Committee receive from doctors/dentists will be treated with complete professional confidence by the Committee and their

staff.' This established four key principles of the Scheme, namely:

- 1 Suspected adverse reactions should be reported; reporters do not need to be certain or to prove that the drug caused the reaction.
- 2 It is the responsibility of all doctors and dentists to report.
- 3 Reporters should report without delay.
- 4 Reports could be made and would be treated in confidence.

Reports were to be made on specially provided yellow reporting forms, a supply of which was provided with Sir Derrick's letter. The significance of the yellow colour of the card is probably no more than that there was by coincidence a large supply of yellow paper unutilised at that time; however, as a result, the Scheme has come to be known as the Yellow Card Scheme. In the 50 plus years since the introduction of this Scheme, the design of the reporting form has changed progressively (Figure 13b.1), to include guidelines on reporting and to ask for additional specific pieces of information (e.g. Lawson, 1990; Griffin and Weber, 1992; Anon, 2000a). Reports are also received via the pharmaceutical industry, which has a statutory obligation to report suspected adverse reactions (Waller, Coulson and Wood, 1996). The CHM continues to be responsible for the Yellow Card Scheme, which is run on the Commission's behalf by the MHRA, using specialised databases to facilitate rapid processing and analysis of reports and detection of signals of drug safety hazards.

Developments in interpretation of data protection legislation resulted in the introduction of anonymised Yellow Card reporting in 2000. Importantly, in 2004 an independent review of the Yellow Card Scheme (2004) recommended greater access to data for research, and increased patient involvement. Following the introduction of patient reporting independent research conducted under the Health Technology Assessment programme reviewed the value of patient reporting of ADRs and made recommendations as to how patient Yellow Card reporting should be further strengthened (Avery *et al.* 2011). The findings of this research informed

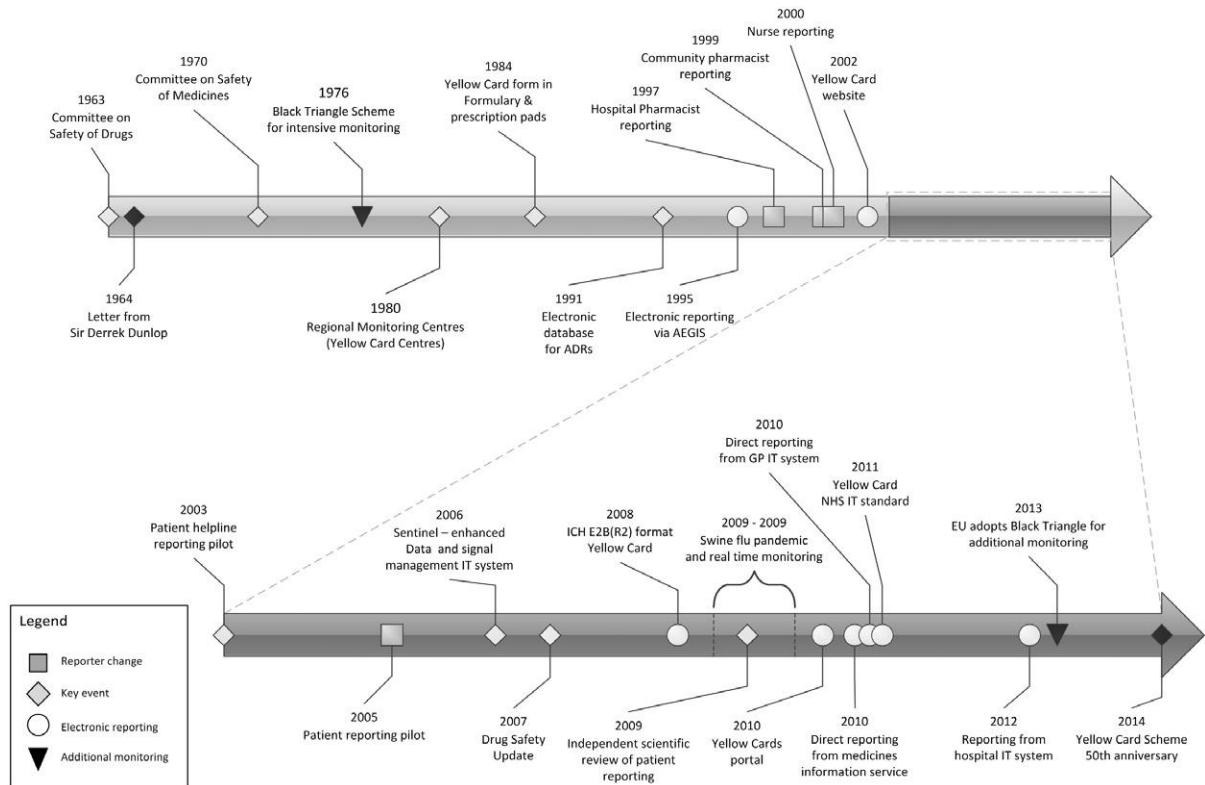


Figure 13b.1 Yellow Card timeline.

the introduction of patient reporting of ADRs throughout Europe in 2012.

#### STRENGTHS AND LIMITATIONS OF THE YELLOW CARD SCHEME

It is generally accepted (e.g. Amery, 1999) that it is not possible to detect all the adverse effects of a medicine during the pre-marketing clinical trials, because of a number of factors.

First, trials are generally small (on average 1500 patients for a new drug substance); although they will detect common side effects, particularly those that are predictable from the pharmacology of the drug, they are too small to detect side effects that occur rarely (incidence of 1 in 10 000 or less). Additionally, medicines are studied in clinical trials in a very controlled manner, that is they are given for a

limited duration, to carefully selected patients who are closely monitored. This is in complete contrast to the manner in which the medicine may be used once marketed, when it may be given in combination with other medicines to patients with co-morbidities or used in populations for which it was not intended, potentially for long periods of time. It is therefore vital to monitor the safety of medicines as used in routine clinical practice throughout their marketed life, in order to detect those side effects that are not identified through clinical trials.

The best established way to do this is to collect reports of suspected adverse drug reactions (ADRs) via a reporting scheme such as the Yellow Card Scheme. All spontaneous reporting schemes, including the Yellow Card Scheme, have a number of limitations, perhaps the most significant of which

is under-reporting (e.g. Griffin and Weber, 1992). Despite this, such schemes have a proven track record as an 'early warning' system for the identification of new drug safety hazards. Examples of drug safety hazards identified through spontaneous reporting have been described previously (e.g. Rawlins, 1988b; Griffin and Weber, 1992). Examples of ADRs identified via spontaneous reporting including Yellow Cards are shown in Table 13b.1.

A major strength of spontaneous reporting systems is the speed with which safety signals can be detected. For example, in 2004 following four Yellow Card reports suggesting adverse muscle effects of rosuvastatin in patients of Asian origin, advice was issued to restrict initial dosing to be agreed and communicated to prescribers.

The limitations of the Yellow Card Scheme are those of all spontaneous reporting schemes; these

Table 13b.1 ADRs identified via spontaneous reporting

Year	Medicine	Adverse Reaction	Action taken
2012	Dabigatran (Pradaxa)	Serious haemorrhages	Contraindications clarified and reminder to monitor renal function
2012	Tacrolimus oral products	Toxicity and graft rejection due to switching	Recommendations for routine brand prescribing and dispensing
2012	Proton pump inhibitors	Hypomagnesaemia	Long-term use warnings and measurement of magnesium levels
2012	levothyroxine 100 microgram tablets	Potential lack of efficacy	Suspension of marketing authorisation
2012	Blue dyes in lymph-node imaging	Serious allergic reactions	Warnings and monitoring recommendations post administration and surgery
2012	Statins	Hyperglycaemia and diabetes	Warnings and monitoring recommendations
2011	Citalopram and escitalopram	QT interval prolongation	New maximum daily dose restrictions (including in elderly patients)
2011	Lei Gong Teng ( <i>Tripterygium wilfordii</i> )	Risk of serious side effects	Healthcare professionals to advise stopping use
2011	Sitaxentan (Thelin)	Hepatotoxicity	Worldwide withdrawal from the market
2009	Finasteride (Proscar, Propecia)	Potential risk of male breast cancer	Product information for prescribers updated
2009	Antipsychotics	Venous thromboembolic events	Product information for prescribers updated
2009	Antiepileptics	Adverse effects on bone	Vitamin D supplementation should be considered for at risk patients
2008	Hedrin (dimeticone)	Hair fire accident	Warning
2008	Varenicline (Champix)	Depression, suicidal thoughts and behaviour	Warnings issued –monitoring patients with history of psychiatric illness
2007	St John's Wort, <i>Hypericum perforatum</i>	Interactions	Current warnings about interactions - include all antiepileptic medicines
2007	Aristolochia in Chinese herbal remedies	Renal failure, transitional-cell carcinoma	Reminder of warnings, and ban
2006	Linezolid (Zyvox)	Optic neuropathy	Improved warnings and monitoring recommendations
2006	Black cohosh ( <i>Cimicifuga racemosa</i> )	Hepatotoxicity	Improved warnings
2004	Rosuvastatin (Crestor)	Rhabdomyolysis	Revised dosing instructions and improved warnings
2001	Bupropion (Zyban)	Seizures	Improved warnings and revised dosing instructions

have been documented previously (e.g. Rawlins, Fracchia and Rodriguez-Farre, 1992; Meyboom *et al.*, 1997a, b). The limitation of greatest concern is under-reporting: it is clear from a number of studies that only a small proportion of ADRs are ever reported to the regulatory authorities, both in the United Kingdom (e.g. Smith *et al.*, 1996; Sweis and Wong, 2000) and in other countries (e.g. Chan and Critchley, 1994; Moride *et al.*, 1997; Alvarez-Requejo *et al.*, 1998).

Under-reporting of suspected ADRs may lead to delay in identifying a signal of a drug safety hazard or to under-estimation of the significance of a particular reaction. This is compounded by the fact that the magnitude of under-reporting is variable; studies have suggested that levels of reporting are influenced by factors such as the seriousness of the reaction, whether the reaction is labelled, the length of time a drug has been on the market, and promotion or publicity about the medicine or the reaction (Rawlins, 1988a; Griffin and Weber, 1992; Smith *et al.*, 1996; Haramburu, Begaud and Moride, 1997; Moride *et al.*, 1997; Alvarez-Requejo *et al.*, 1998).

Various studies have attempted to establish the reasons for under-reporting; surveys of attitudes to reporting of suspected ADRs suggest that lack of time and uncertainty as to whether the reaction was caused by a drug are among the commonest factors in deterring reporting (Belton *et al.*, 1995; Eland *et al.*, 1999; Sweis and Wong, 2000). An additional factor may be concerns over confidentiality. A survey in 1984 (Speirs *et al.*, 1984) found that only 16% of doctors who were eligible to report suspected ADRs to the Scheme had actually submitted a Yellow Card between 1972 and 1980. More recently in 2009 an analysis of GP reports received by MHRA suggested that only 6.6% of GPs had submitted a Yellow Card report during that year. It is clear that many doctors do not contribute to the Yellow Card Scheme but is very unlikely to be simply because these doctors do not see patients who have experienced an adverse reaction.

## VOLUMES AND SOURCES OF REPORTS

Since the launch of the Yellow Card Scheme in 1964, over 700,000 reports have been received by

the MHRA and the CHM from health professionals and in recent years from patients, either directly through the Scheme or indirectly via pharmaceutical companies (Figure 13b.2).

Reporting to the Scheme is voluntary by health professionals and patients; pharmaceutical companies have legal obligations to report to the MHRA ADRs that are brought to their attention (Waller, Coulson and Wood, 1996) in 2012 and 2013 they accounted for 46 and 48% of all ADR reports received respectively. For the past few years around 25 000 ADR reports received each year, although a significant increase in numbers has been seen in 2013. Over the past four years, about 7% of the total were Yellow Cards received directly from patients.

It can be seen from Figure 13b.2 that the annual number of reports has risen significantly since the introduction of the Scheme, with notable increases in reporting in the mid-1970s, and again in 1986. The reasons for peaks and troughs in reporting are typically associated with four factors. First, high profile drug or vaccine safety concerns, often attracting media coverage, stimulate reporting. The first of the increases in Figure 13b.2 coincided with the withdrawal of practolol following its association with oculomucocutaneous syndrome, and the introduction of the CSM drug safety bulletin Current Problems in Pharmacovigilance (Drug Safety Update from 2006). Secondly, national vaccination campaigns generate significant volumes of Yellow Card reports. In 2000, there was a dramatic rise in the number of Yellow Cards, with over 33,000 reports during this 12-month period. This can largely be accounted for by reporting of a large number of suspected adverse reactions in association with meningitis C vaccines, administered to children under the age of 18 in a nationwide immunisation campaign. An estimated 18.5 million doses of vaccine were distributed in just over a year and nurse reporting was permitted during the immunisation campaign. In 2010 the swine flu pandemic led to the administration of over 6 million doses of a vaccination and over 1 million doses of antivirals to UK patients, and resulted in 4581 ADR reports.

The third factor to which increased Yellow Card reporting volumes can be attributed is the introduction of new reporting groups. Fifty years ago the

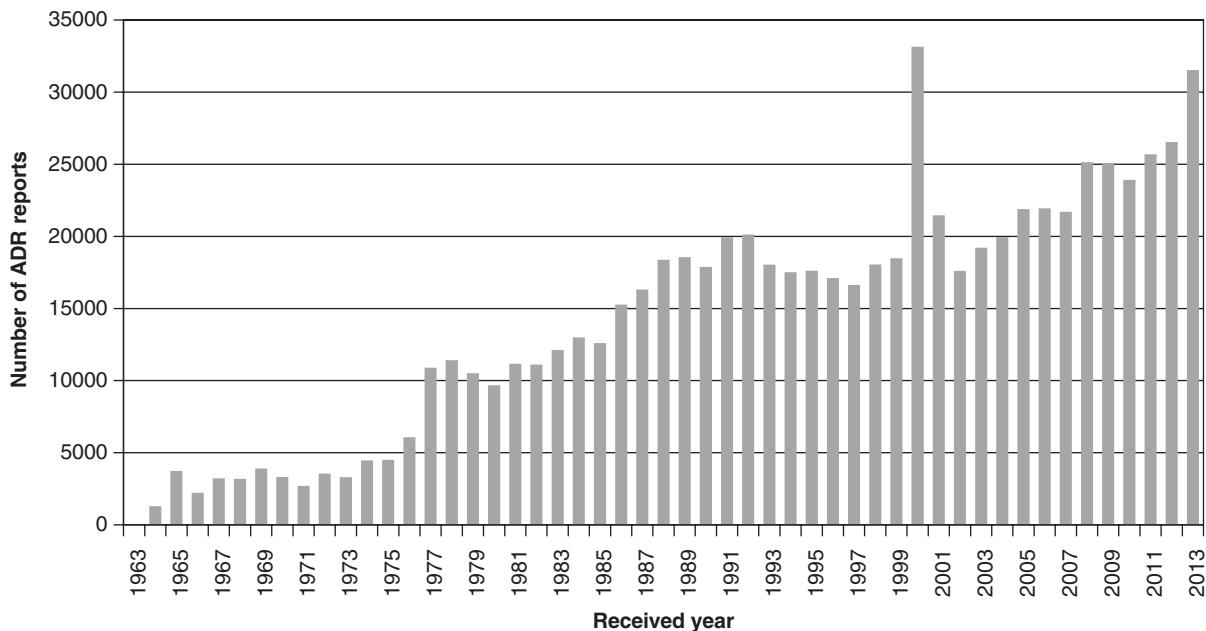


Figure 13b.2 Number of ADR reports received by year since 1964.

Yellow Card Scheme was set up for doctors and dentists only to report suspected ADRs, since then the Scheme has evolved a number of times, accepting reports from other health professionals and since 2005 from patients. The rise in reporting which can be seen in 2008 is due to the nationwide implementation of Yellow Card reporting for patients, parents and carers following a series of pilots starting 2005 (Ekins Daukes *et al.* 2006). This wider access to the Scheme is discussed in more detail later.

The final factor to consider, and possibly the most sustainable, is the development of new tools and mechanisms to facilitate reporting. Making reporting forms available at the point of patient care can serve as a reminder to doctors that they should report. This was first seen with the inclusion of a Yellow Card in the tear-off pads of paper prescription forms used by GPs, reminding them to report suspected ADRs. The second increase in Yellow Card reports is thought to have resulted from the increased availability of Yellow Cards to doctors, following their inclusion in the British National Formulary (BNF), which is supplied to all doctors (Rawlins, 1988a).

There was a significant change in the early 1990s when the annual number of Yellow Cards declined from a peak of just over 20 000 to an annual average of around 17 000. A number of factors may have been responsible for contributing to this decline; for instance, the number of Yellow Cards submitted on forms included in GPs' prescription pads fell dramatically over the 1990s (these so-called 'FP10' forms comprised 10% of all UK reports received in 1991, compared with 0.1% in 2001), reflecting the transition to use of electronic prescribing systems.

This move from paper to electronic systems signalled a need for the Yellow Card Scheme to follow from solely paper to new media. A number of projects to include an electronic Yellow Card in clinical systems introduced over the years and these are discussed in more detail later.

Two approaches which have been suggested as ways to enhance Yellow Card reporting, but which have not been taken forward, are firstly payment for reporting and secondly, introducing a legal requirement for health professionals to report suspected ADRs. Payment for the completion of Yellow Cards has been raised with the MHRA by doctors, both directly and through the GP focus groups

mentioned above; however, it is not considered that remuneration for the completion of a Yellow Card would result in an increase in high quality reports of serious reactions. Reporting of suspected ADRs is considered to be part of the professional responsibilities of health professionals. The second approach, a legal requirement to report, goes to the heart of the voluntary nature of the Yellow Card Scheme. France, Norway, Sweden and Spain have all introduced compulsory reporting of suspected serious ADRs to the regulatory authority (Moore *et al.*, 1985; Wiholm *et al.*, 1994) whereas in the majority of countries, including the United Kingdom, reports are submitted on a voluntary basis by health professionals. Although it would be expected that legislation to make reporting compulsory should increase the number of reports received, reporting rates are not clearly or consistently higher in countries where compulsory reporting has been introduced, compared with the United Kingdom (Griffin, 1986; Wiholm *et al.*, 1994). Furthermore, the introduction of a statutory obligation for health professionals to report would be almost impossible to enforce: there is no easy and systematic mechanism for identifying the ADRs that should have been reported, especially since the decision to report depends on the health professional's suspicion of a possible causal association. To date, the MHRA has not identified a case for the introduction of compulsory reporting in the United Kingdom.

Both of these approaches were considered within the Independent Review of Access to the Yellow Card Scheme. The Review recommended that the basic principles of the Scheme, as set out by Sir Derrick Dunlop, should not be changed, as incentive payments and compulsory reporting would change the Scheme's fundamental principles. The Scheme should remain as a voluntary Scheme and health professionals should consider it to be their professional duty to report ADRs.

## EVOLUTION OF THE SCHEME

### REPORTING BASE

As the importance of the Yellow Card Scheme in protecting public health by continuously monitor-

ing the safety of medicines in routine clinical practice is not in question, there is a constant need to tackle the issue of under-reporting by addressing some of the factors highlighted above. The environment in which the current-day Scheme operates has changed considerably compared with the 1960s when it was introduced.

There is ever-increasing public and media interest in the availability of medicines and their safety, new medicines are delivered more rapidly to the market place than ever before, and more medicines are available without a doctor's prescription. Additionally, it is clear that the roles of the wider healthcare team including pharmacists and nurses have evolved over recent years, as well as the increasing involvement of patients in their own care. For pharmacists, an increasing role in patient care is due at least in part to the increasing range of medicines being made available without prescription. Also, in the UK nurses are able to prescribe medicines, and have increasing involvement in the routine care of patients in the community, particularly in the management of chronic conditions. These changing roles now place pharmacists and nurses in a position in which they are increasingly likely to encounter suspected adverse reactions.

A number of initiatives have been undertaken in order to try to address some of the issues raised in the previous section. These initiatives fall into three main groups: initiatives aimed at increasing the general reporting base, those aimed at increasing reporting in particular areas where under-reporting is of particular concern such as in children, and those aimed at facilitation of reporting. Initiatives in each of these areas are described below.

The potential impact of any change to the Scheme has been assessed in relation to its effectiveness in detecting previously unrecognised drug safety hazards. Simply increasing the number of reports alone is not of particular value; the objective is to receive Yellow Card information of suitable quality to enable prompt signal detection and, where relevant, assessment of individual cases as part of the investigation of potential safety hazards. Furthermore, although numbers of reports are important for the identification of new hazards, it is paramount that reports of serious

suspected ADRs are collected, since these are more likely to impact on the balance of risks and benefits of the medicine than reports of minor side effects. An increase in the number of reports received also has resource implications. Yellow Cards are processed rapidly, according to tight timelines set out in the legislation, in order to ensure that data from the reports are available in analysable form on the database as quickly as possible for inclusion in the signal detection process. Any large increase in the volume of reports can slow down the time taken to make reports accessible for signal detection and may increase the signal-to-noise ratio.

#### PATIENT REPORTING

In January 2005, following an independent review of access to the Yellow Card Scheme direct patient reporting of suspected ADRs was introduced. Initially this was a limited pilot scheme but was expanded nationwide later that year. Patients were encouraged to report suspected ADRs experienced by themselves, or for someone they care for; a child, partner or family member.

In February 2008 as a result of a positive evaluation of the pilot (Ekins-Daukes S, 2006), patient Yellow Card reporting was formally established in the UK. The MHRA launched a six-week campaign targeting community pharmacists with the aim of encouraging them to mention the Yellow Card Scheme when talking to patients about their medicines. To raise awareness of the patient reporting scheme all pharmacies in the UK were sent an information pack containing patient Yellow Card reporting forms, information leaflets and a poster. Copies of patient Yellow Cards were also distributed to GP surgeries, pharmacies, hospitals, NHS Primary Care Trusts and various other patient organisations throughout the UK. The website for electronically reporting Yellow Cards was simultaneously launched.

The value of patient reporting of suspected adverse reactions was evaluated in 2010 by an independent research group, who identified that these reports provide valuable additional evidence to the drug safety monitoring system. The key findings

from the research were when compared with health-care professional reports, patients:

- reported a significantly higher number of suspected ADRs per report and were more likely to report more than one suspect drug showed different patterns of reporting of drugs and ADRs (this was also the case for reports on children)
- were equally likely to report ADRs that were classified as serious by the MHRA
- used more words, and richer accounts, to describe their ADRs and were more likely to describe the impact of ADRs on their lives
- Importantly, when assessed for causality, reports from patients and healthcare professionals were equally likely to show possible causal association and combining patient and healthcare professional reports resulted in some new signals being identified

#### PHARMACIST REPORTING

For many years, pharmacists have been recognised as reporters to national spontaneous reporting schemes in a number of countries (Griffin, 1986), and there is published evidence suggesting a valuable role for both hospital and community pharmacists in the monitoring and reporting of ADRs (e.g. Roberts, Wolfson and Booth, 1994; Smith *et al.*, 1996). The UK's Regional Monitoring Centres (RMC) now known as Yellow Card Centres (see below) played a key role in conducting pilot studies into the potential contribution of hospital and community pharmacists to the Yellow Card Scheme. A pilot Scheme for hospital pharmacist reporting, conducted by the Northern RMC, showed that, in comparison with hospital doctors, hospital pharmacists submitted a higher proportion of reports of serious ADRs, and reports from the two groups of reporters were of similar quality. Additionally, a survey of consultants whose patients had been the subject of a pharmacist report during the pilot study showed a high level of support for the continuation of the Scheme (Lee *et al.*, 1997). This study led, in April 1997, to the extension of the Yellow Card Scheme nationwide to include

reporting by hospital pharmacists (Anon, 1997a). A subsequent evaluation of hospital pharmacist reports made in the first year following this extension generally confirmed the findings of the pilot study, and indicated that reports received from hospital pharmacists expanded on those received from hospital doctors, rather than simply replacing them (Davis, Coulson and Wood, 1999). By the end of 2001, an excess of 4800 reports had been received directly from hospital pharmacists; in 2001, approximately 6.2% of Yellow Cards were submitted by this group.

A pilot study of community pharmacist reporting was conducted by four RMCs; an evaluation of reports received during the first 12 months of the pilot showed that community pharmacists submitted reports which were comparable to those received from GPs, with regard to both the quality of the reports and the seriousness of reactions reported. Furthermore, community pharmacists submitted a higher proportion of reports for herbal products compared with GPs (Davis and Coulson, 1999). An attitudinal survey carried out in Wales, one of the areas in which the pilot study was conducted, demonstrated a high degree of support among both GPs and community pharmacists for a role of the latter group in reporting suspected ADRs to the Yellow Card Scheme (Houghton *et al.*, 1999). In November 1999 in the light of the survey findings, nationwide reporting by community pharmacists was introduced (Anon, 1999). Community pharmacists are well placed to inform patients about, and be made aware of, any ADRs experienced in association with 'over the counter' products. In recent years, the role of pharmacists has changed with the introduction of supplementary prescribing for pharmacists in April 2003. This voluntary prescribing "partnership" between an independent prescriber and a supplementary prescriber allows pharmacists to implement an agreed patient-specific clinical management plan with the patient's agreement. In addition, pharmacists along with other health professionals can supply and administer medicines through patient group directions (PGDs) (Health Service Circular 2000/026). With their prescribing powers, both hospital and community pharmacists are important contributors to the

Yellow Card Scheme and in 2013, 3200 suspected ADR reports originated from pharmacists, representing 10% of all ADR reports received by the Agency.

## NURSE REPORTING

Over the past few years in UK the role and responsibilities of nurses have rapidly developed. Nurses have had a more active role in the provision of medicines to patients, illustrated by the introduction of independent nurse prescribing. Along with pharmacists, nurses are empowered to provide medicines under Patient Group Directions, and in April 2003 supplementary prescribing by nurses was introduced.

With their increased responsibilities it soon became apparent that nurses should be responsible for reporting their suspicions of ADRs experienced by patients in their care. There was some published evidence to support this (Hall *et al.*, 1995; Smith *et al.*, 1996; Van den Bemt *et al.*, 1999), although a lack of knowledge about adverse effects of medicines was identified in one study as a major constraint to their participation (Hall *et al.*, 1995).

During the UK campaign to vaccinate children against meningitis C, school nurses were the main body of health professionals administering the vaccine. When the campaign began, nurses began spontaneously to submit significant numbers of Yellow Card reports; the CSM subsequently recommended that nurses should be allowed to report suspected ADRs for meningitis C vaccine for the duration of this important public health campaign. Nurse reports received during the vaccination campaign were used by the MHRA to evaluate the potential contribution which this group might make to the Yellow Card Scheme. This evaluation also considered the findings of a pilot study of nurse reporting conducted by the RMC in Merseyside (Morrison-Griffiths, 2000).

An evaluation of nurse reporting by the MHRA suggested that nurses report similar levels of serious reactions to other health professionals, that their reports are of similar quality to those received from doctors and that, with appropriate formal training,

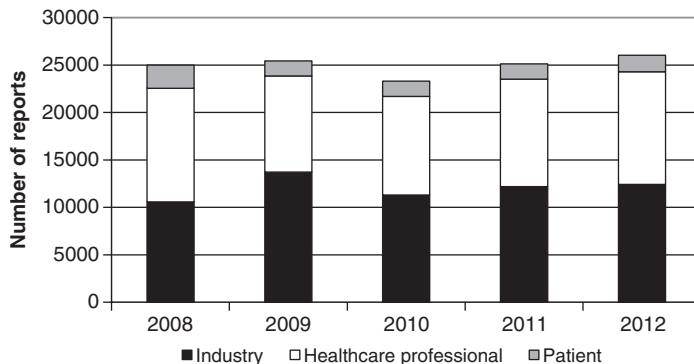


Figure 13b.3 Spontaneous ADR reporting by source 2008–2012.

they become important contributors to the Yellow Card Scheme. As a result, in October 2002 the Yellow Card Scheme was extended to all nurses, midwives and health visitors, an analysis of the role of community and hospital nurses in ADR reporting demonstrated that the proportion and quality of reports received from nurses were similar to those received from doctors (Morrison-Griffiths *et al.*, 2003). In 2013, 3,026 suspected ADR reports were received from nurses, comprising about 18% of Yellow Cards received directly from reporters that year. Nurses continue to make a significant contribution to Yellow Card reporting, notably in relation to reports of suspected ADRs in association with H1N1 influenza vaccine during the 2009/2010 pandemic and in association with the human papilloma virus (HPV) vaccination campaign starting in 2009.

Figure 13b.3 shows the number of Yellow Card reports received annually since 2008, with the proportions from industry, healthcare professionals and patients.

#### YELLOW CARD CENTRES

In the 1980s four Regional Monitoring Centres (RMCs), now known as Yellow Card Centres (YCCs) were introduced to provide valuable

support for the running of the Scheme. These Centres are in Merseyside (Liverpool), the Northern region (Newcastle), Wales (Cardiff) and the West Midlands (Birmingham) (e.g. Houghton *et al.*, 1996). In 2002 a fifth centre was opened in Scotland (Edinburgh) and the Northern RMC expanded its activities into Yorkshire. The main focus of the YCCs is to undertake regional education on pharmacovigilance and to raise awareness of the Scheme.

#### ELECTRONIC REPORTING

It seems self-evident that making reporting of suspected adverse reactions easier may increase levels of reporting; this is demonstrated by the rise in reporting in the mid-1980s following the move to make Yellow Cards readily available by including them in the BNF and in GP's prescription pads. This is supported by the fact that lack of time has been found to be one of the main factors in deterring ADR reporting in various studies (Bateman, Sanders and Rawlins, 1992; Belton *et al.*, 1995; Sweis and Wong, 2000), including the MHRA's work with GP focus groups.

It has been recognised for a number of years that for many healthcare professionals working where computerised systems are used the paper Yellow

Card is no longer the most convenient method of reporting. In the late 1990s, working with GP practice software companies, electronic reporting was made available to all users of these particular systems, by either the electronic submission of reports via a modem or semi-automated completion of an electronic Yellow Card which was subsequently printed out and posted to the MHRA.

In 1995, electronic reporting of suspected ADRs to the MHRA became routine for a small number of pharmaceutical companies who started submitting reports via the MHRA's Adverse Drug Reactions Online Information Tracking (ADROIT) Electronically Generated Information Service (AEGIS). From November 2005, under Directive 2004/27/EC, electronic reporting using the International Conference on Harmonisation (ICH) E2B standard (<http://www.ich.org/products/electronic-standards.html>) became mandatory for companies. Following on from the introduction of electronic reporting for companies, the MHRA piloted the use of electronic reporting for health professionals under the direction of the CSM's Electronic Reporting Working Group, resulting in the launch in 2002 of the electronic Yellow Card on the MHRA website.

In 2008 the Yellow Card website was redeveloped to make use of the ICH E2B standard, enabling Yellow Cards submitted via the website to be automatically loaded onto the MHRA's Sentinel database. In 2006 The Sentinel database succeeded ADROIT and was built to fully implement the E2B electronic reporting standard.

More recently a Yellow Card website portal was developed which enables external clinical systems to securely submit a Yellow Card to the MHRA using the E2B(R2) format. Based on the ICH E2B(R2) standard, the MHRA has developed an NHS Information Standard ([www.isb.nhs.uk/documents/isb-1582/amd-24-2011/index\\_html](http://www.isb.nhs.uk/documents/isb-1582/amd-24-2011/index_html)) which provides a formal system by which clinical systems used in the NHS can develop electronic Yellow Card reporting features. In late 2010 this format was introduced to one general practice software system which is used in approximately 20% of UK GP surgeries. Up to the end of 2013 over 6,500 Yellow Cards have been sent to the MHRA by users this one system. This has effectively reversed a wor-

rying decline in reporting from GPs, demonstrating the impact which facilitation of reporting and ease of access can have.

## YELLOW CARD SIGNAL DETECTION

Spontaneous reporting systems such as the Yellow Card Scheme are used for signal detection of new drug safety issues or the identification of increased frequencies of recognised ADRs. The science of signal detection is discussed in more detail elsewhere in this book. However for completeness it is also important to set out the relationship between Yellow Cards and signal detection methodologies here. The UK's drive to proactive pharmacovigilance has been enabled by the development and integration of robust methods for signal detection. This has been a strategic priority for MHRA given the high volumes of Yellow Card reports.

Initially proportional reporting ratios (PRRs) were piloted and introduced as an integrated statistical method for interpreting spontaneous ADR data (Evans, Waller and Davis, 2001). This statistical method compares the proportion of reactions to a drug which are for a particular adverse reaction of interest compared with all reactions to the drug, to the same proportion for all drugs in the database. In brief, a high PRR indicates that a potential signal of a drug safety issue has been identified and requires further evaluation. Importantly changing PRR scores can be tracked as reports are accrued for the medicine over time. In 2006 a more robust algorithm was added in addition to the PRR, the empirical Bayes geometric mean (EBGM) which is less unstable when only small numbers of reports have been received early in the medicine's life cycle.

Scenario-specific signal detection approaches have also been utilised, for example the maximised sequential probability ratio testing method for identifying signals associated with vaccines (Donegan K *et al.* 2013). A tool for prioritising signals arising from spontaneous ADR data known as Impact Analysis, was developed and piloted in 2004. This considers together the strength of evidence for causality and the public health implications of a safety signal (Waller and Evans, 2003).

With the use of such tools, for the early detection and prioritisation of drug safety signals, there is an improved capability to home in upon issues that are of importance to public health. A systematic approach to drug safety issue prioritisation has also been developed at the MHRA to help to reduce the subjectivity of reliance on individual judgement. (Seabroke *et al* 2013).

### CHILDREN'S MEDICINES

Over many years there has been significant public interest expressed in the safety of medicines used in children; particular concern surrounds the safety of medicines which are not specifically licensed for use or are used 'off label' (i.e. for unlicensed indications) in this patient group (Wells, 1996). Despite the lack of firm evidence of safety and efficacy in children, medicines licensed for use in adults are frequently used when treating children, especially where no licensed alternatives exist. Safety and efficacy in children cannot be assumed simply based on data from studies in adults; for instance, children differ from adults in terms of their pharmacokinetics (Leeder, 1996; Reed, 1996). It is possible that the adverse reaction profile of a medicine in children may differ from that in adults, and it is therefore particularly important to collect suspected ADR reports in this area. It is notable that under-18 year olds make up around 20% of the population, but the proportion of Yellow Card reports received for this age group is somewhat lower, usually less than 10% each year. However, this may be explained by lower morbidity experienced in these ages, so that there is lower use of medication and fewer ADRs experienced.

To investigate whether unlicensed or 'off label' use of medicines in children was leading to adverse reactions, and whether such reactions were being reported, a pilot Scheme to stimulate reporting of suspected ADRs in children was set up in the Trent NHS region in September 1998; this Scheme targeted paediatricians and hospital pharmacists.

An analysis by the MHRA of this pilot Scheme, two years following its introduction, showed that there was an increase in the absolute numbers of hospital reports of suspected ADRs in children received from the Trent region. Since the time

covered by this analysis overlapped significantly with the nationwide meningitis C vaccination campaign, it was perhaps not surprising that the majority of reports received were of suspected ADRs associated with this vaccine. However, when reports for meningitis C vaccine were excluded, it was notable that the underlying rate of paediatric reporting in the Trent region had remained relatively static between 1994 and 2000, and was comparable with national reporting rates for suspected ADRs in children; additionally a relatively low proportion (less than 30%) of reports related to serious reactions.

As a separate initiative, the MHRA collaborated with the British Paediatric Surveillance Unit (BPSU) (now the Royal College of Paediatrics and Child Health) on their 'Orange Card' reporting Scheme, where consultant paediatricians report particular disorders under surveillance in children (Verity and Preece, 2002), such as aspirin and Reye's syndrome. In order to improve the availability of medicines licensed for use in children and to seek ways of improving reporting of paediatric ADRs, the CSM established a Paediatric Medicines Working Group in July 2000. A move towards improving the safe use of medicines in children was also undertaken in Europe and in December of the same year a Council Resolution called on the European Commission to find solutions to the issue of inadequate medicines for children. In 2005, a regulation of the Council and the European Parliament on medicinal products for paediatric use came into force, with the overall objective of improving the health of children in Europe by increasing research, development and authorisation of medicines for paediatric use. As part of the proposal, a guideline on pharmacovigilance for paediatric medicines was published and a Paediatric Committee was established within the European Medicines Agency (EMA). The proportion of Yellow Cards received by the MHRA in under-18-year-olds has continued to be limited, contributing 4.4% all UK ADR reports received in 2011–2012.

### EUROPEAN LEGISLATION

In 2012 sweeping changes to European pharmacovigilance legislation were introduced Regulation

(EU) No 1235/2010 and Directive 2010/84/EU, with a significant impact on the way ADR data and subsequent signal detection activities are undertaken both in the pharmaceutical industry and at the National Competent Authorities in Europe. A particularly important change for the Yellow Card scheme was the wider definition of an Adverse Drug Reaction, which was changed to “A response to medicinal product which is noxious and unintended”. This definition therefore includes adverse reactions that are due to overdose, abuse, misuse and, most importantly, medication error. In the UK, patient safety incidents as a result of error have been reported to a different NHS-run system and not to the regulatory pharmacovigilance system. The MHRA therefore worked with the NHS to modify reporting systems so that medication error reports are now added to traditional Yellow Card data to enhance the UK pharmacovigilance system.

Since the late 1990s, EU Competent Authorities, the EMA and the European Commission have created a central pharmacovigilance database (EudraVigilance) supported by a system of mandatory electronic ADR reporting between the pharmaceutical industry and regulators. EudraVigilance has been developed as the European data-processing network and database management system for the exchange, processing and evaluation of Individual Case Safety Reports (ICSRs). From 2005, all pharmaceutical companies within the European Union have been obliged to electronically submit ICSRs for products authorised through national, mutual recognition or decentralised procedures under Directive 2001/83/EC as amended by Directive 2004/27/EC; likewise Regulation EC 726/2004 imposes the same electronic reporting requirements on centrally authorised products.

The International Conference on Harmonisation (ICH) E2B(M) standard defines the electronic reporting format that should be used with the Medical Dictionary for Regulatory Affairs (MedDRA) medical terminology for coding the reports. Under the revised European legislation, when the full functionality of EudraVigilance is developed, companies will report all ICSRs directly to EudraVigilance and not to the national competent authorities of the member states. The

EudraVigilance system will provide a copy of reports to the national authority of the member state where the ADR occurred thereby ensuring that national databases continue to include the totality of national ADR reports. National agencies remain responsible for the operation of the national spontaneous reporting schemes. The MHRA will therefore continue to develop and strengthen the Yellow Card Scheme.

### COMMON STANDARDS FOR EUROPEAN MEMBER STATES

The introduction of the 2012 EU legislation and the associated responsibilities in national competent authorities have placed a new focus on member states to operate their systems to the highest standards. In 2012 a European Commission funded project called SCOPE (Strengthening Collaborations to Operate Pharmacovigilance in Europe) was initiated. The strength of the EC commitment to ensuring member states operate pharmacovigilance to the highest standards is demonstrated by the fact the project was awarded “exceptional utility” status meaning the 3.3 million Euro investment represented 70% of the total funding. Such projects usually attract a maximum of 50% funding. Led by the MHRA the three year Joint Action project examines how member states operate their spontaneous ADR reporting systems so that best practice is established across Europe. Key elements of SCOPE include how to increase ADR reporting, raise awareness and develop new mechanisms to facilitate reporting.

### INTENSIVE MONITORING – THE BLACK TRIANGLE SCHEME

As previously mentioned new medicines are licensed on the basis of evidence collected through controlled clinical trials, and this evidence is inevitably limited. The Black Triangle Scheme has been in operation in the UK for more than 30 years to denote new drugs that are subject to intensive monitoring. The purpose of the inverted Black Triangle in formularies and on advertising was to highlight to prescribers the need to be extra vigilant and to report all suspected ADRs to these products, so

that the safety profile can be quickly established following the marketing of the product. Typically Black Triangle status has been applied to all new active substances and biological products, and remains in place until the risk benefit profile is known. At any one time, around 200 medicines are being monitored by MHRA under the Black Triangle.

The European pharmacovigilance legislation implemented in 2012 made equivalent provisions for the introduction of an intensive monitoring system across the European Union, known as Additional Monitoring. European system has gone further than the UK system in requiring that the black symbol must appear in the medicine's patient information leaflet, alongside a brief explanation and information on how to report adverse reactions. European patient groups were instrumental in selecting the inverted black triangle as the symbol for Europe.

#### PRESENT AND FUTURE INITIATIVES

The Yellow Card Scheme is operating in a changing environment, particularly with regard to advances in technology, extension of the reporting base, introduction of new regulatory requirements within specific areas and increased use of the data for research. The introduction of electronic Yellow Card reporting tools within clinical IT systems has already been proven to increase the number of ADRs reported to the MHRA. Extension of these initiatives in place with general practice to other secondary care and pharmacy systems is necessary to truly reap the rewards these technologies offer. With the introduction of patient reporting there is another focus on the use of IT that consumers use to discuss their health. Recent developments in the use of mobile technologies and social media have raised interest in the potential for exploiting these tools for the benefit of pharmacovigilance.

A number of prototype mobile Apps for ADR reporting have already been introduced, for example MedWatcher in the USA. Regarding social media it is recognized that there is increasing use of Twitter, Facebook, forums, blogs and

other such media for patients to share their experience with medicines, often citing suspected ADRs they have suffered. New technologies are available to rapidly review these media and may potentially support signal detection and validation. The European Innovative Medicines Initiative has initiated a call for research in this area and the MHRA has taken the lead role in investigations with a consortium of academic, IT, regulatory and industry partners.

New data management technologies allow not only rapid signal detection, but close to real-time safety monitoring of medicines, by accessing data on exposure and on background rates of events of interest in relevant populations, for example stratified by age. The MHRA has pioneered such approaches in the area of vaccines, and the challenge is to extend such methodologies to other therapeutic areas. This will be particularly important if adaptive or progressive licensing models are to be supported by robust safeguards in terms of active data collection.

The scientific basis of medicines has evolved and medicines have become more complex, with the increasing shift to biologicals and products of biotechnology, advanced therapies and drug-device combinations. This has been accompanied by a change in the pattern of signals, with long term effects such as cancer and signals related to quality changes and manufacturing alterations coming to the fore. There is also a shift to preventative therapies used in healthy people rather than agents for treatment of disease. Counterfeit medicines are an increasing risk at global level. The Yellow Card scheme will need to adapt to the changing healthcare environment while still maintaining its essential continuous monitoring and signal detection function.

#### CONCLUSIONS

The Yellow Card Scheme has been in existence for five decades. Despite its limitations, which are common to all spontaneous reporting schemes, it has a proven track record in the identification of previously unrecognised safety hazards. The

Scheme has undergone continual evaluation and development over the years, and this will continue in the foreseeable future. This will ensure that the Scheme will continue to fulfil its central role in UK pharmacovigilance in the changing climate in which it operates, whilst continuing to adhere to the key principles defined by Sir Derrick Dunlop at the inception of the Scheme: spontaneity and speed, confidentiality and above all the commitment of health professionals and patients to report their suspicions in the interest of protecting public health.

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# 13c

## Spontaneous Reporting: France

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### THE FRENCH PHARMACOVIGILANCE SYSTEM

The French pharmacovigilance system is based on a decentralized collection and validation of safety data through a network of 31 regional pharmacovigilance centers (RPVCs) and a centralized evaluation and decision-making process coordinated by the French National Agency for the Safety of Medicines and Health Products (ANSM).

### ORGANIZATION

The 31 RPVCs have a duty to collect, record, and evaluate adverse drug reactions (ADRs) reports, and input them into a common national database, after causality assessment. The heads of the RPVCs meet monthly at the ANSM in the Technical Committee (Advisory Board). The Technical Committee is responsible for coordinating the collection and

evaluation of information on ADRs, conducting surveys and providing recommendations that are forwarded to the General Director of the ANSM, to prevent, reduce, or eliminate drug-related accidents.

The ANSM is responsible for implementing the national pharmacovigilance system. It defines the general politics of pharmacovigilance and coordinates the actions of the various partners involved. The Security Department of ANSM centralizes via the national database all the data collected on France by the RPVCs and data collected by the pharmaceutical companies (who report ADRs directly to the Pharmacovigilance Department). This department coordinates the CRPVs' activities, the organization of meetings held by the Technical Committee, and the exchange of information with other competent authorities: the European Medicines Agency (EMA), other member states, the World Health Organization, competent authorities in third countries (Food and Drug Administration

(FDA), etc.). It also monitors compliance with pharmacovigilance regulatory obligations of each partner involved.

This organization enables the ANSM to ensure the safe use of medicinal products after marketing with the objective to protect public health in France.

## REGIONAL PHARMACOVIGILANCE CENTERS

The 31 RPVCs have a defined geographical area of intervention and form a network covering the whole country, thereby representing a large monitoring area. These decentralized structures for collecting ADRs encourage exchange of information with healthcare professionals and constitute a particularity of the French system. RPVCs are located in departments of clinical pharmacology or clinical toxicology in the university hospitals and have a scientific association included within the French Pharmacological Society.

They have several missions (Moore *et al.*, 1985):

- collecting, recording and evaluating reports of ADRs;
- providing information on ADRs and good use of drugs to healthcare professionals;
- conducting pharmacovigilance investigations at the ANSM's request;
- contributing to scientific progress by conducting research on drug-related risks;
- teaching pharmacovigilance and good use of drugs to students and health professionals.

## SOURCE AND MANAGEMENT OF REPORTS

Reports to RPVCs come from several sources:

- Spontaneous reports sent by healthcare professionals, patients, or patients' associations.
- Reports gathered in clinical departments, regularly visited for hospitalized ADR-related cases, directly from the university hospital where the RPVC is located or indirectly from local correspondents in regional hospitals.

- A large number of reports come from the requests for information by health professionals. In this interaction, the clinician receives help from the RPVC for a specific problem and, in return, the RPVC receives a case with better information (Moore, 2001). This activity is viewed as a service rendered to local healthcare professionals, making them more willing to call and report. This will also have an influence on the types of reports retrieved, since physicians are more likely to call in for unusual, severe, or unexpected events than for well-known ones, which after all is the main objective of spontaneous reporting systems.

The 31 RPVCs are directly connected to the common national database located in the Security Department of the ANSM. After assessment of causality using the French imputation method (Begaud *et al.*, 1985), reports are input to the national pharmacovigilance database at the RPVC. Centers are required to report all serious reactions to the ANSM within 15 days. At any time, every RPVC can access the complete database. There are no automated alerting processes functioning routinely on the database at this time. Serious reports are automatically retrieved from the database at the ANSM on a daily basis and forwarded to the relevant marketing authorization holder (MAH), and in the case of centrally authorized products to the EMA (Eudravigilance) as required by the European pharmaceutical legislation.

Pharmaceutical companies also have to comply with the European legislation, including 15-day transmission of serious ADRs occurring on French territory to the ANSM, and the submission of periodic safety update reports according to defined periodicity.

## ALERT MANAGEMENT

Alerts can arise from individual case reports at the regional level or from other European competent authorities through the rapid alert system or from FDA alerts, from literature data, or any other source.

During each monthly Technical Committee meeting, current problems are reviewed, results of ongoing investigations are presented, methodological matters broached, and new investigations decided upon and attributed. Whenever it is decided that a problem should be investigated, a RPVC is designated to take responsibility for the investigation as RPVC "Rapporteur." The rules for these investigations are outlined in the Good Pharmacovigilance Practices (ANSM, 2010).

When an investigation is decided upon, the cases reported to the RPVCs and to the MAH are pooled. All cases are reviewed together by the MAH and the RPVC Rapporteur. The population exposure to medication is estimated, resulting in reporting rates. Additionally, indications of risk factors such as age, concomitant diseases, or medication are looked for.

The assessment report written by the RPVC Rapporteur is sent to the MAH for comments and presented to the Technical Committee. The latter ensures that the investigation has been carried out properly, validates it (or not), usually after a consultation meeting with the MAH, and provides advice to the General Director of the ANSM on the measures to be taken. In case of required evaluation of the benefit/risk ratio, The Technical Committee or the General Director can ask for the advice of a specific commission, dedicated for the re-evaluation of the benefit/risk ratio. In the case of centrally authorized products, the commission's recommendation is forwarded to the Committee for Medicinal Products of Human Use (CHMP) of the EMA and other member states for possible further action.

The French pharmacovigilance system provides an active participation at the European level, which relies on a close cooperation between member states ensuring a common evaluation and management of safety concerns.

## FUTURE PERSPECTIVES

Over the past years, risk management activities and safe use of the medicinal products have been improved in order to detect signals earlier, and additional tools have been introduced by the European legislation: reinforcement of the evalua-

tion of safety data before granting a marketing authorization, risk management plans, more effective communication on pharmacovigilance issues to healthcare professionals and the public, etc.).

In France, the benfluorex (Mediator) scandal prompted calls for wide reform of the French drug regulatory system. Several changes are implemented in the new law voted in December 2011 (LOI, 2011), leading to:

- reinforcing the policy on conflicts of interests between pharmaceutical companies and all actors in position to influence the regulatory process;
- specifying rules concerning off-label prescription;
- authorizing the withdrawal of a marketed drug for lack of therapeutic effects;
- restricting drug promotion;
- adding the requirement of comparing new drugs in clinical trials to existing medications of the same type and not just to placebo;
- formalizing the use of the health insurance system databases to study postmarketing drug utilization and risks.

In conclusion, the French pharmacovigilance system is still organized on the basis of decentralized regional units (RPVCs) but has been centrally reinforced by a newly restructured national agency.

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# 13d

## How Pharmacovigilance is Organized in Germany

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### INTRODUCTION

Pharmacovigilance has now been established as a science that has some specific aspects. It is a combination of research in basic life sciences, diagnostic procedures or biotechnological tools, clinical pharmacology and medical practice, biostatistics, epidemiology, and communication. And it includes development as well as implementation and use of specific procedures.

### DEMOGRAPHIC AND ECONOMIC DATA

After the reunification in 1990, Germany has now around 82 million inhabitants. There are major differences in the population density, with larger rural areas in the eastern federal states and more industrialized regions in the west. The average income

and the economic potential differ accordingly, which in turn influences the regional structure and capacity of the health system. Approximately 220 000 physicians are presently working as general practitioners or in hospitals. There are around 21 000 public pharmacies in Germany, which are run completely on a private basis. About 88–92% of the population are insured in the 160 public, non-private health insurance companies. Overall, €296 billion were spent in 2011 in the national health system, and around €46 billion are paid in total (prescriptions and self-medication) for medicinal products (2012; corresponding to about 16% of total expenses). About 75 800 medicinal products, including generics, herbal medicines, and complementary medicinal products, are licensed for being marketed in Germany, including 662 brand names of centrally authorized products at the EU level (July 2012).

## THE GERMAN PHARMACOVIGILANCE SYSTEM AT A GLANCE

### NATIONAL AGENCIES

In Germany, two national agencies are responsible for licensing and pharmacovigilance activities for human medicinal products: the Federal Institute for Drugs and Medical Devices (BfArM), dealing with all chemically defined medicinal products, herbal drugs, and drugs used in complementary medicine, and the Paul Ehrlich Institute (PEI), dealing with medicinal products containing active ingredients derived from blood, vaccines, drugs containing antibodies, devitalized tissue implants, and innovative gene therapy products. In pharmacovigilance issues they act on a nearly identical legal basis and have similar instruments for pharmacovigilance measures at their disposal.

Both agencies, BfArM and PEI, are independent from one another and act as centralized agencies in the frame of their responsibility. The Ministry of Health, on the higher level, has a supervising role on both agencies; for example, in regard to budget, basic characteristics, and performance of the pharmacovigilance system, or reporting to politicians or the parliament, respectively. However, the Ministry of Health is not involved in the decision-making process within specific and formal risk-assessment procedures, except in exceptional cases; for example, licensing of thalidomide for the treatment of multiple myeloma.

### GERMAN FEDERAL STATES AND THEIR ROLES

Germany consists of 16 federal states who have their own and widely independent governments. Responsibilities at state level and the scope of “worksharing” between federal states and the Federal Government, is basically specified in the German constitution. In regard to pharmaceutical legislation, and particularly to pharmacovigilance, the competent health authorities of the federal states are responsible, roughly, for monitoring manufacturing of medicinal products (GMP) at companies in their territory, the distribution system for drugs, and the promotion of pharmaceutical companies and institutions. Close cooperation and

tight communication between the country's health ministries and BfArM or PEI are essential, with the latter acting as central competent authorities for licensing medicinal products.

### ROUTINE BUSINESS AND ACTIVITIES

#### SPONTANEOUS REPORTING SYSTEM, REPORTING ROUTES, AND ELECTRONIC SUBMISSION

A spontaneous reporting system has been established in Germany since 1979, having undergone various modifications and modernization since then. A three-way reporting system is in place. Healthcare professionals can report suspected cases of adverse drug reactions (ADRs) (i) directly to one of the two national agencies for human medicinal products, (ii) to the Drug Commission of the German Medical Association, or (iii) to the MAH of the medicinal product suspected to have caused the ADR. However, both national drug agencies are the final and only institutions where the ADR reports are collected in unique databases. Legal reporting requirements for the MAH and contractual rules between the national agencies and the Drug Commission of the Medical Association assure that all single case reports are stored in the central databases, whichever reporting route is chosen by the individual reporter. Consumer reports are accepted by both, BfArM and PEI, by which way ever. Both agencies offer on their websites tools for electronic reporting of ADRs, providing different versions for healthcare professionals or consumers/patients. ADR reports received by BfArM or PEI are forwarded electronically and automatically to the EudraVigilance database at the EMA since its start in 2001 and, on a regular basis, to the WHO Uppsala Monitoring Centre (UMC).

The system in place to receive and send ADR reports electronically enables BfArM to fulfill legal reporting obligations towards the EMA. The system is fully compatible with international standards defined in the ICH-E2B/M2 guidelines and supports manual data entry as well as electronic reporting according to these standards. Controlled

vocabulary and classification systems have been implemented in accordance with EU requirements (e.g., MedDRA in its latest version for coding medical information, ISO catalogue of country codes, WHO Drug Dictionary, and anatomical therapeutic chemical (ATC) classification).

Marketing authorization holders (MAHs) are obliged to send reports electronically to BfArM or PEI and the EMA. More than 98% of individual case reports are now received electronically. Companies with a very low number of reports per year may apply for a waiver that allows paper-based reporting. On a daily basis, BfArM and PEI forward all new reports in their databases electronically to the EudraVigilance database run by the EMA.

#### DRUG COMMISSION OF THE GERMAN MEDICAL ASSOCIATION (BUNDESÄRZTEKAMMER)

The Drug Commission of the German Medical Association is an expert panel of experienced clinicians with a smaller core group handling incoming reports which they receive directly. The core group is doing preliminary case assessments with regard to seriousness, causality, and reporting quality. The Drug Commission of the German Medical

Association is a close and regular partner of BfArM and PEI. Both national agencies consult the Drug Commission of the German Medical Association with regard to new or ongoing safety issues and ask for scientific advice. There are contractual and legal rules in place that regulate cooperation between the competent authorities and the Drug Commission of the German Medical Association; however, this expert panel is not involved mandatorily in pharmacovigilance decision making processes; that is, it is not an official national committee for drug safety.

#### REPORT NUMBERS AND REPORTERS

With regard to actual figures, BfArM receives about 26 000 case reports originating from Germany per year, not counting duplicate reporting and follow-up reports (Figure 13d.1). Report numbers from foreign countries, EU as well as non-EU, amount to about 231 000 annually (2011). In total, the BfArM ADR database contains around 390 000 case reports from Germany and 880 000 from foreign countries (by end of 2011). Since May 2013, BfArM has opened an access to its entire ADR database to the public, offering search tools under various aspects (<http://www.bfarm.de>).

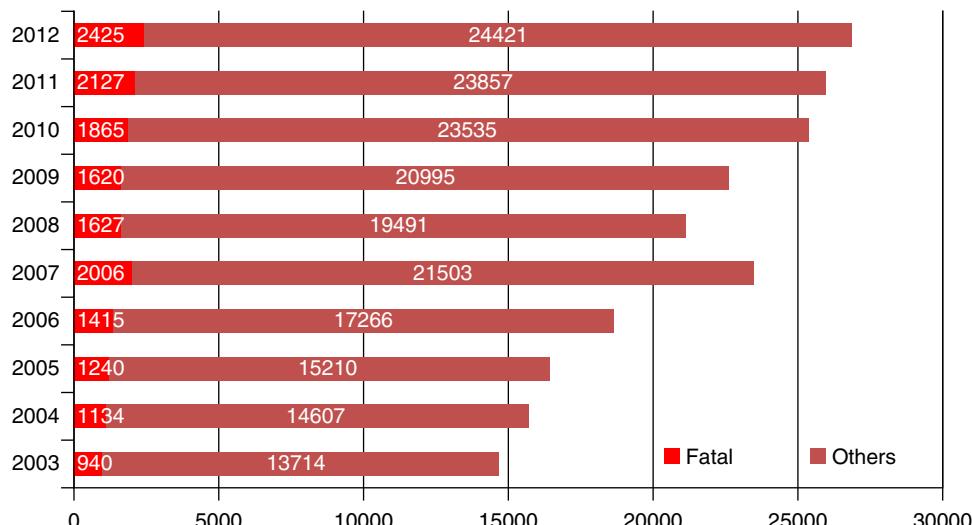


Figure 13d.1 Number of domestic reports to BfArM in the period 2003 to 2012. Total numbers and number of reports documenting a fatal outcome of a suspected ADR.

Unlike in other countries, BfArM receives the majority of domestic cases via pharmaceutical companies (in fact, these reports originate from physicians who reported first to a MAH). As far as national reports are concerned, 86% of the incoming information in 2011 is derived from this source. The remaining portion of reports (14%) is received from other sources (directly from healthcare professionals, consumers). Consumer reports (i.e., reports from patients or their relatives or care givers) amount to only a very low number (about 100 per year). Direct consumer reporting has not been encouraged actively and publicly by BfArM. The BfArM tends more to follow the international recommendations that patients should see their doctors first to seek medical advice and to transmit more informative case reports that are the result of collaboration between patient and physician.

#### **REGIONAL PHARMACOVIGILANCE CENTRES**

Regional pharmacovigilance centers at four university hospitals in eastern Germany have been financed by BfArM for more than a decade. Funding of these regional pharmacovigilance centers was terminated in 2011. The program of running regional pharmacovigilance centers has been replaced by a program of funding specific pharmacovigilance research projects. Apart from these, a register of nonsystematically reported drug exposure during pregnancy with follow-up and pregnancy outcome surveillance is established at a hospital in Berlin (<http://www.embryotox.de>).

#### **IDENTIFYING SAFETY ISSUES FROM THE SPONTANEOUS REPORTING SYSTEM AND OTHER SOURCES**

##### **SIGNAL DETECTION FROM ADVERSE DRUG REACTION DATABASES**

Signal detection should function as a measure of security – a second safety net. It must be emphasized that output of such electronic tools needs careful review and assessment by medically qualified staff, since these systems also bear the risk to detect false positive “signals” (CIOMS, 2010).

In BfArM's system, three strategies have been implemented:

- 1 Identification of new substance–ADR combinations reported within a specified period of time; that is, those that have not yet been reported at all or very seldom. The time periods covered and the number of reports necessary to trigger an output are flexible; that is, can be adapted as needed and to exclude “noise.”
- 2 Identification of trends comparing substance–ADR associations of equal sequential time periods.
- 3 The proportional reporting ratio approach, which enables the comparison of a specified substance–ADR association compared with the whole database or with substance–ADR associations concerning drugs of the same ATC group.

The current signal detection tools not only focus on specific ADR terms, but also on term groupings developed in the CIOMS/ICH Working Group on Standardised MedDRA Queries (SMQ). The SMQs are groupings of terms from one or more MedDRA system organ classes that relate to a defined medical condition or area of interest (CIOMS, 2004).

#### **SINGLE CASE ASSESSMENT**

Medical assessors are responsible for, and have special expertise in, assessing ADRs caused by drugs which belong to one (main) ATC group plus, in some cases, to one or more ATC subgroups. The guiding concept behind this is that assessors are generally medical specialists (e.g., in cardiology, neurology, infectiology) and have the best and complete insight in the related diseases and therapeutic options in that field. This is relevant in a comparative risk-to-benefit assessment and in the decision-making process.

Since full implementation of electronic reporting and considering the high numbers of reports, BfArM and PEI have switched, as a general rule, from assessing each incoming single case report towards using widely electronic statistical tools for signal detection in their databases.

## PERIODIC SAFETY UPDATE REPORTS

Periodic safety update reports (PSURs) are submitted by MAHs to BfArM or PEI according to the existing legislative rules in the EU or Germany. BfArM receives a huge number of PSURs despite being strongly involved in the EU PSUR work-sharing project (for more information, see [www.hma.eu/80.html](http://www.hma.eu/80.html)). The concept of writing PSURs on the company's side and assessing the compiled data at the national agencies' side will fundamentally change by implementation of the new EU pharmaceutical legislation. Amongst other changes, the EMA and national agencies will have the possibility and right to give far-ranging waivers to MAHs to submit PSURs, particularly for generic products. Currently, it remains open whether the new rule will lead to a substantial loss of risk information relating to widely used medicinal products (i.e., generics). This is of relevance, as in a previous revision of the EU pharmaceutical legislation repeated renewal procedures for marketing authorizations beyond a 5-year period after first licensing have been deleted from the law.

## RISK ASSESSMENT AND DECISION-MAKING PROCESSES

### INTERNAL PHARMACOVIGILANCE MEETINGS

The scientific staff of the pharmacovigilance department meets regularly once a month with representatives from BfArM's licensing units to exchange information on new safety issues, ongoing risk-to-benefit assessments, and internal and external decisions (e.g., at Committee for Medicinal Products for Human Use or Pharmacovigilance Risk Assessment Committee (PRAC) level). These meetings allow coordination of actions and procedures within the agency. This is important because, for instance, there may be licensing applications under discussion with substances that are under review because of new safety information. Such meetings also are held together with representatives from the herbal products department, the narcotics department, and the legal or pharmaceutical administrative departments. However, the pharma-

covigilance departments basically are independent from the licensing departments in decision making, but under one roof within the agency, and they refer to the agency's director.

## DECISION-MAKING PROCESS

In general, BfArM and PEI take regulatory decisions most frequently within the formal referrals according to Article 31 or Article 107i-m of Directive 2001/83/EC as amended or Article 20 of Regulation 726/2004/EC as amended, irrespective of whether rapporteurship has been given to one of the two agencies or not. This includes so-called class reviews resulting in changes of the summary of product characteristics or patient information leaflet, or establishing risk management plans. There are few purely national risk assessment procedures that are not extended to other EU member states because of lacking community interest. Whichever procedure is chosen or started, BfArM or PEI initiate a formal national and administrative risk assessment procedure, intended to exchange information with the national stakeholders, to implement, once agreed, regulatory actions, and to communicate.

Once a safety issue has been identified and action for minimizing the risk is considered necessary, a team that includes in-house experts in the field drafts a list of questions to the MAHs (all who hold a license with the substance under review). This normally relates to active substances, but might even concern an excipient or group of excipients, or application forms or modes of application. The request to the MAHs explains why the agency has concerns on whether the risk-to-benefit balance is still acceptable. The MAHs have to submit all relevant data requested, but also have the opportunity to comment on the concerns and the proposed regulatory action. The time frame for responses depends on the severity and urgency of the issue. The agreed regulatory actions, on the EU-level or on purely national level, are ordered formally by BfArM or PEI (i.e., centralized and valid for Germany as a whole) to the MAHs, and detailed reasons are given. In principle, the MAHs have the right to appeal against the decision; however, an appeal cannot lift the decision unless there are exceptional circumstances.

## RISK COMMUNICATION

BfArM has the policy of sharing information from the ADR database with people who ask for it. They must not have any specific reasons for their request (e.g., having experienced an ADR themselves). Information is given strictly in line with the existing confidentiality rules. BfArM regularly explains the origin of the reports, their validity with regard to causality, and that any frequency calculations cannot be made using report numbers from spontaneous reporting systems. A respective caveat paper, very similar to that used by the UMC, is sent out.

Since 2005, BfArM publishes on its website agendas and minutes of meetings of official expert panels (e.g., the twice-yearly routine meetings of representatives of the German federal states), or of the expert panels for switching prescription-only to over-the-counter medicines or vice versa. Information on all newly initiated risk assessment procedures, irrespective of being EU wide or purely national, are available from the website, as well as all direct to healthcare professional communications and other relevant risk-related information.

## RESEARCH

Currently, specific projects in psychiatric hospital units are under development and will be funded through BfArM. They will be concerned with the collection of ADR reports and data related to real-life treatment practice in hospitalized psychiatric patients.

Moreover, BfArM has defined some main areas of research and established some research groups. The focus is on specific questions (e.g., in toxicology, microbiology, immunology, methods in epidemiology, and pharmaceutical quality). Research projects are financed through BfArM with contributions from partners (industry, academia, etc.). Tentative research projects are published on the BfArM website, and interested parties may apply for cooperation and financial support.

The PEI has, historically, a major focus on research. The main areas are quality, safety and efficacy of biomedicines, experimental vaccines, therapies and diagnostics, immune activation and evasion, and host interactions with pathogens and retroelements. Research is financed by PEI itself and by third parties.

## IMPLEMENTATION OF THE NEW EUROPEAN UNION PHARMACOVIGILANCE LEGISLATION

In Germany, BfArM and PEI have implemented the new requirements of the new EU pharmacovigilance legislation as well adapted already existing practice and rules of operation. New requirements – that is, in regard to the conduct of risk assessment procedures (“referrals”) according to Directive 2001/83/EC or Regulation 726/2004/ EC as amended, membership at the PRAC, PSUR work-sharing, or handling the huge number of single case reports as a consequence of extension of reporting requirements – came, or will come into effect, in line with the schedule of the transitional period.

## ACKNOWLEDGMENTS

We would like to thank Brigitte Keller-Stanislawska for providing data and information from the Paul Ehrlich Institute as well as for comments on this text.

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## 13e

# Organization of Pharmacovigilance in the Netherlands

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## COUNTRY GENERAL SYSTEM

In the Netherlands, the Ministry of Health is ultimately responsible for the safety of drugs. In ensuring that a patient receives safe drugs, several players are involved. The Inspectorate of Health is responsible for the product quality as well as the use of the drug (off-label use, medication errors). The Central Committee on Research Involving Human Subjects is responsible for the safety of drugs (both registered and not registered drugs) used in clinical trials. However, the two main players in pharmacovigilance in the Netherlands are the Medicines Evaluation Board (MEB) and the Netherlands Pharmacovigilance Centre Lareb.

The MEB is responsible for the registration of a drug in the Netherlands and coordinates all pharmacovigilance activities that have regulatory implications. The MEB assesses the periodic safety update reports submitted by the marketing authorization holders (MAHs) and is responsible for a

continuous benefit/harm evaluation of the drug, in cooperation within the European Medicines Agency (EMA). If necessary, the MEB has the power to change to conditions for marketing authorization (for example, restriction of indication and adding new adverse drug reactions (ADRs) to the summary of product characteristics) and may, in exceptional circumstances, withdraw a drug from the market.

The spontaneous reporting system in the Netherlands is, in contrast to many European countries, not a part of the regulatory authorities but an independent foundation. This model has been chosen since conflicts of interest might arise if one organization is responsible for both the registration and the safety monitoring of the approved drug. However, a close collaboration exists between the two organizations.

The Netherlands Pharmacovigilance Centre Lareb is responsible for maintaining the spontaneous reporting system for the collection of ADR

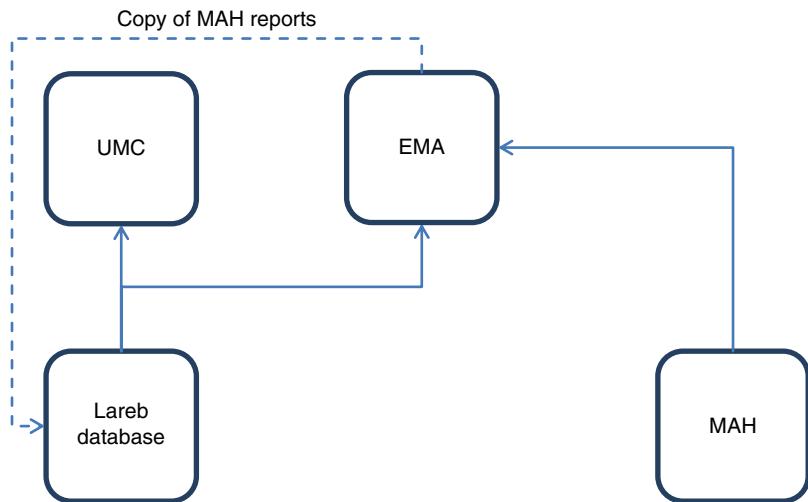


Figure 13e.1 Routing of reports in the Netherlands. Reports are forwarded from the Lareb database to both the EMA and UMC. The MAHs forward their reports to the EMA. Copies of these MAH reports are filed in the Lareb database. The MEB has online access to the Lareb and EudraVigilance database.

reports, including reports of vaccines. Lareb started in the 1980s as a regional cooperation between pharmacists and general practitioners with the aims to detect ADRs and improve pharmacotherapy. In 1996 it became the national center for ADR reporting, but it has always kept close ties to its roots, the practicing physician and pharmacist.

At the beginning of the 21st century Lareb felt the need to expand the group of reporters from including only healthcare professionals to also include reports from the general public. Since 2003, patients have been able to report ADRs directly to Lareb. The Lareb board consists of representatives from the large Dutch medical and pharmacists' associations as well as patient organizations.

In addition to the spontaneous reporting system, Lareb is the knowledge center for drug use during pregnancy and lactation. Health professionals and members of the public can get advice about possible teratogenic effects of drugs.

In the next sections the workflow with regard to the spontaneous reporting system will be described.

#### ADVERSE DRUG REACTION REPORTING

Suspicions of ADRs of medicines and vaccines can be reported by healthcare professionals and patients

on a paper form or via the reporting forms on the Lareb website. All reports submitted to Lareb are individually coded using the MedDRA terminology and assessed. Feedback is provided to the reporters. After a report is filed into the Lareb database, an anonymous copy is forwarded to the EudraVigilance database of the EMA and the database of the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre in Sweden. The MAHs of the products involved will receive a copy of the reports on their products within 15 days of receipt by Lareb. A copy of the reports submitted to the EudraVigilance database by the MAH is also filed in the Lareb database, making the database complete with all spontaneous reports reported in the Netherlands.

An overview of the flow of reports is shown in Figure 13e.1.

#### NUMBER AND TYPES OF REPORTS

The majority of the reports received are submitted by healthcare professionals. Over the past years, the number of reports submitted by patients and medical specialists has gradually increased; see Figure 13e.2. In 2011, Lareb received 11 420 reports, of which 4968 were reported by healthcare professionals and

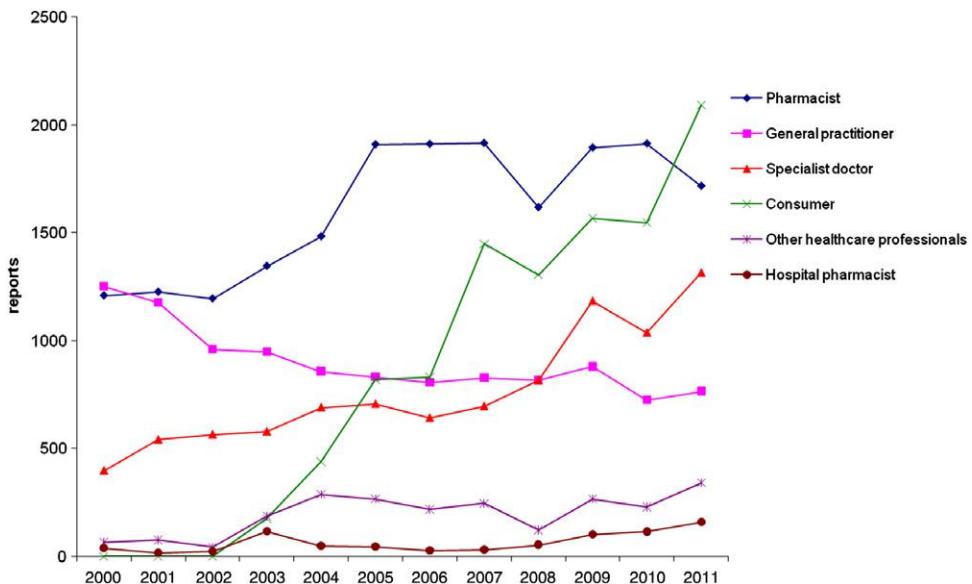


Figure 13e.2 Number of reports stratified by source since 2000.

2089 by patients. A total number of 1421 reports were associated with the use of a vaccine.

### SIGNAL DETECTION AND MANAGEMENT

Evaluation of the reports on a case-by-case basis is carried out in a weekly assessment meeting. In addition, disproportionality analysis is used to support the signal detection process where reporting odds ratios are used as a measure of disproportionality (Van Puijenbroek, 2001). If new signals are identified, Lareb informs the MEB of its findings in a quarterly report, in which the most important observations and signals are presented. This report may also include overviews of reported ADRs of new drugs, especially those products for which the Netherlands is reference member state. The scientific advisory board monitors the quality of the signals being issued.

As mentioned above, the MEB is responsible for making the final decision regarding marketing authorization for products marketed in the Netherlands. Possible signals detected by Lareb on the spontaneous reporting data are being forwarded to the MEB in the form of a quarterly report, where they will be evaluated and discussed together with

a representative of Lareb. If needed, regulatory actions will be taken and signals will be forwarded to other member states and discussed at EMA level. If signals warrant further evaluation, additional studies will be carried out by the MAH and other research institutions.

### DISSEMINATION OF INFORMATION

Besides the regulatory route, it is also important to inform healthcare professionals as well as the general public about ADRs. On the website of the Netherlands Pharmacovigilance Centre, the database is made available for the general public. In addition, all signals as published in the quarterly reports that have been sent to the MEB are available in an unabridged version. Healthcare professionals are informed by means of publications, presentations, and an electronic newsletter. In 2011, Lareb published 23 articles and abstracts in both national and international journals.

### INTENSIVE MONITORING

Next to the spontaneous reporting system, Lareb also maintains an intensive monitoring program

called Lareb Intensive Monitoring (LIM). With LIM, prospective cohorts of patients who are using selected drugs for the first time are followed over time. By means of web-based questionnaires, information is collected about possible ADRs associated with the drug under study (Harmark *et al.*, 2011). At the moment, community pharmacy is used as the inclusion point, but the system has been further developed in order to be used also in the intramural setting. In 2011, 19 drugs and 1655 patients were followed with LIM.

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# 13f

## Pharmacovigilance in Spain

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### INTRODUCTION

According to current national legislation, pharmacovigilance is understood as the discipline that covers all the activities aimed at the identification, quantification, and evaluation of risks associated with the use of medicines, as well as the establishment of the necessary measures for maintaining a favorable benefit–risk, and the evaluation of their impact.

The Division of Pharmacoepidemiology and Pharmacovigilance of the *Agencia Española de Medicamentos y Productos Sanitarios* (from now on Spanish Medicines Agency), is responsible for the evaluation of the risks that emerge after the authorization of the medicinal products for human use, with the aim of taking measures when appropriate for ensuring that marketed medicinal products have a positive benefit–risk balance. For the identification of new risks, the Division of Pharmacoepide-

miology and Pharmacovigilance is supported by the Spanish Pharmacovigilance System, which includes 17 regional centers responsible for a spontaneous reporting scheme of suspected adverse reactions.

Obligations on pharmacovigilance are included in Royal Decree 577/2013 (available on the Spanish Agency website, [www.aemps.gob.es](http://www.aemps.gob.es)). This Royal Decree transposes the new obligations of Directive 2010/84/EU.

### RISK IDENTIFICATION

The spontaneous reporting system, called the Spanish Pharmacovigilance System, is based on a decentralized scheme, coordinated by the Spanish Medicines Agency, where regional centers in the 17 autonomous regions are responsible for the

collection, evaluation, and registration of the spontaneous reports coming from healthcare professionals. These data are registered in a common database, FEDRA, managed by the Spanish Medicines Agency and contains all spontaneous cases reported by Spanish healthcare professionals, either directly or through marketing authorization holders. Quality data checks, causality assessment, and duplicate detection are performed by the regional centers before data are available in FEDRA. The number of reports received yearly is in the range of 10 000–15 000, with medical doctors from primary healthcare being the ones that contribute most, although reports coming from hospitals have been progressively increasing over recent years. Around 80% of the reports are sent directly to the regional centers of the Spanish Pharmacovigilance System, and 20% are received by the system through marketing authorization holders.

All regional pharmacovigilance centers have permanent access in real time to FEDRA, in order to identify new signals. Besides this, they have specific programs for promoting spontaneous reporting among healthcare professionals and research activities in the field of pharmacovigilance. Some of them are also drug information centers.

Coordination by the Spanish Medicines Agency is performed through a Technical Committee, where all regional centres are represented. This committee meets regularly and its aim is to analyze the signals identified by the centers, as well as to harmonize working procedures and programs on pharmacovigilance, among others.

Procedures for enabling patient reporting are implemented, including web-based reporting.

FEDRA enables the electronic exchange of spontaneous reports with marketing authorization holders and the European Medicines Agency (EudraVigilance database) according to agreed international standards. These tasks are managed by the Spanish Medicines Agency. With the new legislations, reports from healthcare professionals to marketing authorization holders will be sent directly to EudraVigilance and automatically rerouted to FEDRA. Reports coming directly from healthcare professionals and patients to the Spanish Pharmacovigilance System will be elec-

tronically sent to EudraVigilance according to the legally established deadlines.

## SPECIFIC PROGRAMS FOR RISK IDENTIFICATION AND QUANTIFICATION

The Spanish Medicines Agency is well aware of the importance of performing studies to further characterize and quantify risks. Therefore, it contributes to the financial support of independent data sources for pharmacoepidemiology research.

These registries are run by researchers from the public healthcare system or scientific societies. The Division of Pharmacoepidemiology and Pharmacovigilance of the Spanish Medicines Agency receives periodic reports that analyze the safety data gathered and replies to ad-hoc queries regarding newly identified safety issues.

The registries that are currently financially supported by the Spanish Medicines Agency are registries of diagnosis that not infrequently are involved as adverse drug reactions, such as serious liver disease or severe blood dyscrasias, or registries where a cohort of patients exposed to new drugs is followed over time, such as patients with rheumatoid arthritis or psoriasis treated with biological medicines.

Financial support basically depends on the relevance of the topic from a regulatory perspective and on the scientific quality of the project. Therefore, supported projects may change over time.

Over the years, these registries have helped in the identification of new risks, quantification of already identified signals, and also on the evaluation of the impact of risk minimization measures (Andrade *et al.*, 1999; Gómez-Reino *et al.*, 2003; Ibañez *et al.*, 2005).

## PRIMARY HEALTHCARE RECORDS DATABASE (BIFAP)

The BIFAP database is a computerized, population-based database of anonymized longitudinal medical records of general practitioners in Spain

(Salvador-Rosa *et al.*, 2002). Its main objective is the performance of independent research on pharmacoepidemiology. BIFAP is kept by the Spanish Medicines Agency and collates, from 2001 onwards, the computerized medical records of 1883 general practitioners (GPs) throughout Spain. Of these GPs, 1150 are currently active. GPs play a key role in the Spanish healthcare system as they act as the gatekeepers of healthcare and are responsible for primary healthcare and specialist referral.

The research BIFAP database includes anonymized information on 3 180 161 patients, representing 11 526 376 person-years of follow-up. The dataset is comparable to the Spanish population with respect to its age and sex distribution. Data recorded in BIFAP include demographic information, prescription details, clinical events, specialist referrals, and laboratory test results.

## RISK EVALUATION

The evaluation of newly identified risk associated with the use of medicines once authorized is performed by the Division of Pharmacoepidemiology and Pharmacovigilance of the Spanish Medicines Agency. Available safety data for authorized medicines is periodically reviewed, in collaboration with the network of regulatory agencies of member states and with the EMA. There are also specific arrangements with some clinical pharmacologists belonging to university departments, so that they act as experts collaborating with the Division of Pharmacoepidemiology and Pharmacovigilance in some of the assessments. A network of clinical experts is also available for ad-hoc support from specialists in different areas.

A Committee on Safety of Medicines gives advice on safety-related issues identified after drug authorization that may lead to relevant restrictions in the conditions of authorization of a product or group of products or to drug withdrawal or suspension of commercialisation. Therefore, members appointed by the Spanish Medicines Agency at the Pharmacovigilance Risk Assessment Committee of the EMA are supported by the scientific advice

of clinical experts. New signals identified by the Spanish Pharmacovigilance System that are considered robust enough to proceed with further evaluation are also discussed in the Committee on Safety of Medicines and shared with the European network.

The Committee on Safety of Medicines includes independent multidisciplinary experts, mainly clinical pharmacologists, pharmacists, and medical doctors from several disciplines, such as internists, geriatricians, pediatricians, and primary healthcare physicians. Depending on the subjects to be discussed, ad-hoc experts may be invited. All of them have to sign a declaration of interests periodically and have to declare their potential conflict of interests before every meeting, in view of the topics included in the agenda.

This committee works independently from the advisory Committee on Evaluation of Medicines, another committee of the Spanish Medicines Agency that advises on the authorization of medicinal products.

## RISK MANAGEMENT

The Division of Pharmacoepidemiology and Pharmacovigilance implements the necessary measures for mitigating risks. These measures range from a change in the product information, to the withdrawal of the medicinal product from the market, when it has been authorized by the Spanish Medicines Agency.

Changes in product information in the sections of indications (in case of restrictions), warnings, contraindications, and adverse reactions are managed by the Division of Pharmacoepidemiology and Pharmacovigilance. More than 1000 modifications are handled yearly. Information material produced by marketing authorization holders with the aim of minimizing serious risks is also evaluated before being delivered to healthcare professionals or patients, and specific programs aimed at managing risks are also supervised, seeking the advice of the Committee on Safety of Medicines if deemed necessary.

## RISK COMMUNICATION

The Division of Pharmacoepidemiology and Pharmacovigilance elaborates specific communications, including safety announcements to healthcare professionals and to citizens for relevant safety-related issues that need to be known without delay. These communications are available on the website of the Spanish Medicines Agency, but are also sent electronically to autonomous communities, scientific societies, and other strategic organizations, so that the message is amplified through different channels, increasing the chances to reach its target.

Autonomous communities have also in place several strategies for disseminating these safety communications, and in some regions the message pops up when the medicinal product involved is registered in the electronic patient health record, making use of the electronic prescription.

The content of “dear healthcare professional communications” delivered by marketing authorization holders is previously reviewed and the non-promotional safety content of the letter is identified in the envelope with a specific legend. Educational materials aimed at minimizing risks and part of risk management plans are also reviewed.

## EVALUATION OF THE EFFECTIVENESS OF THE MEASURES TAKEN

Although not systematically performed, there have been some instances where drug utilization data from the National Health Service, data from BIFAP, and data from the registries supported by the Spanish Medicines Agency have been analyzed to evaluate the effectiveness of the risk minimization strategies put in place. Further developments in this area are envisioned.

## NONINTERVENTIONAL POST-AUTHORIZATION STUDIES

The Division of Pharmacoepidemiology and Pharmacovigilance has tried over the years to both

promote and collaborate on the performance of noninterventional post-authorization studies.

Besides this, and together with the autonomous communities, a specific regulation was set up in 2002 with the aim of promoting good quality research, protecting participants, and avoiding promotional studies. Specifically, protocols of studies classified by the Division of Pharmacoepidemiology and Pharmacovigilance as prospective observational studies have to be reviewed and authorized by the authorities of the region in which the study is to be performed. The procedure is simplified for studies performed at the request of the European network of regulatory authorities and for independent studies supported by public funding or sponsored by health administrations.

From methodological and ethical points of view, these measures have contributed to the improvement of the quality of noninterventional post-authorization studies in Spain (De la Fuente Honrubia *et al.*, 2010).

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# 13g

## Italian Pharmacovigilance System

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The Italian pharmacovigilance system is centered on the *Rete Nazionale di Farmacovigilanza* (hereafter the National Pharmacovigilance Network, NPN), which collects, analyzes, elaborates and shares Italian data on adverse drug and vaccine reports. This system networks regions, regional centers for pharmacovigilance, more than 350 peripheral structures (in teaching hospitals and local health service units) and marketing authorization holders (MAHs) to the Pharmacovigilance Office of the Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA). The NPN was created by the AIFA in November 2001.

Healthcare professionals and citizens can report observed suspected adverse reactions by filling in two different paper forms, one for health professionals and another for citizens, both available on the AIFA website; the compiled forms have to be sent to the local person responsible for pharmacovigilance (LRP) of the health peripheral structure to which the reporter belongs. This person is

the user responsible for the data entry process in the NPN and for providing a feedback to the reporter.

The LRP has to load the report into the NPN within 7 days after having checked the completeness and the congruity of the reported data and after having codified the data according to the MedDRA dictionary (Italian version). Furthermore, regional pharmacovigilance centers perform quality control and regularly check the causality assessment of the reports loaded into the NPN by using the Naranjo algorithm. This assessment is made when the necessary data are complete.

The NPN includes automatic tools for the data matching to identify duplicates.

After 10 days the serious reports loaded in the NPN are electronically transferred in EudraVigilance database according to the ICH E2B standard.

The NPN includes a dedicated, closed, electronic e-mail system (accessible by authorized users only)

that generates an automatic message for every input or update of reports, thus updating MAHs and regions on the latest information. This mailing system is also used to send urgent information to all local health units or to hospitals and to share important information concerning drugs and vaccines safety.

The persons responsible for pharmacovigilance inside MAHs are authorized, by proving themselves with a user-ID and a password, to access the network in order to check messages and adverse drug reaction (ADR) reports. If needed, additional information can be requested by the MAHs only by the pharmacovigilance-responsible person of local health units, hospitals or directly to the AIFA.

The NPN offers the possibility to perform queries; through this functionality it is possible to elaborate reports by year/region, system organ class (SOC)/adverse reaction terminology (ART) (according to the MedDRA dictionary), gender/age patient, anatomical therapeutic chemical classification, drug, substances, year/age, and so on. In the NPN, every user has a different access related to their specific role:

- the Pharmacovigilance Office of AIFA has access to all applications and functionalities;
- healthcare structures have access to the management of reports (input, update, deletion) and have visibility of the national data summary;
- regions have the visibility of the national data summary;
- pharmacovigilance regional centers have access to the management of reports in order to perform quality control and to support the local health units providing feedback to the reporters;
- companies have access to the reports related to their own medicinal products, and have visibility of the summary data on line and of the report list related to the active substances for which they are MAHs.

The aims of the LRP are to collect the spontaneous reports and to put them into the RNF, to give answers and information to reporters, and to disseminate pharmacovigilance information ("Dear Doctor" letters and other safety information). For

this reason, the regional centres aim to control coding quality, perform the causality assessment for serious reactions, plan continuous medical education in pharmacovigilance, and, together with the national centre, to perform data-mining.

The presence of many LRPs allows one to reach the healthcare professionals and to train them easily.

Statistical analyses of data registered in the NPN are coordinated by AIFA with the support of a regional pharmacovigilance center.

Signal detection and evaluation are carried out both with a case-by-case analysis and a statistical approach (disproportionate reporting). A signal detection procedure is carried out twice a year and starts with the evaluation of the reaction monitoring report (RMR). Even if the signal detection procedure is carried out every 6 months, the RMR is prepared quarterly.

To improve the efficacy of signal identification and to avoid excessive splitting of ADRs in many preferred terms, MedDRA codes are converted to WHO-ART terminology. The bridge MedDRA–WHO-ART has been created and maintained by one regional center. The RMR groups the adverse reactions at WHO-ART preferred term level. However, the available software allows analysis to be done with MedDRA both at preferred term and SOC levels.

Every 3 months the RMR is distributed to each regional pharmacovigilance center. The report includes all the drug–adverse reaction pairs (grouped at WHO-ART preferred term level) reported in the last 3/6 month period. For each pair, the following data are listed: number of cases reported in the period, total number of cases associated with the drug in the period, total number of cases in the database, total number of reports associated with the drug in the database, total number of reports with the same reactions associated with all the other drugs, total number of reports associated with all the other drugs in the database, and proportional reporting ratio (PRR) with the 95% confidence interval. For each pair, the following data are also reported: the related SOC, the seriousness, and if the reaction is labeled (present in the SPC) for that drug. A red flag is present in each row if three conditions are present: total number of

cases  $\geq 2$ , PRR  $\geq 3$ , and lower limit of 95% confidence interval  $\geq 1.5$ .

Every 6 months, after the distribution of the RMR, each regional center sends a list of identified proposed signals (with a brief introduction) to the national center.

Criteria evaluated for signal identification include the number of reported cases, seriousness/labeling of the reaction, PRR value, causality assessment evaluation, and use of the drug in the population. Within this evaluation, a case-by-case analysis is made on the most interesting drug–ADRs pairs to analyze the information present in each report.

The list of the proposed signals is discussed and analyzed by a commission that includes doctors, pharmacists, clinical pharmacologists, and epidemiologists working in the regional centers. The commission selects a final list among the proposed signals for a detailed comment that may be evaluated for regulatory purposes and/or publication on the AIFA website.

The software used to prepare the RMR is developed by a regional center in collaboration with AIFA. The application is based on open-source software. The tool, available to all the regional centers, lets the user calculate PRR values by grouping drugs and adverse reactions.

Drug utilization data can be available on demand. Periodic reports on the drug utilization are also available. Both static and dynamic PRR values are calculated according to different groupings of both drugs and reactions.



# 13h

## Pharmacovigilance in Turkey

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### GENERAL DESCRIPTION

In Turkey, the Drug Safety Monitoring and Evaluation Department – Turkish Pharmacovigilance Center (TÜFAM) of the General Directorate of Pharmaceuticals and Pharmacy of the Ministry of Health is responsible for the safety of drugs.

Pharmacovigilance activities started in 1985, by the establishment of Turkish Adverse Drug Reaction Monitoring and Evaluation Center (TADMER). Two years later, in 1987, Turkey joined the Uppsala Monitoring Centre (UMC) of the World Health Organization, and has since been reporting adverse drug reactions (ADRs) to the UMC database.

In 2004, the Drug Safety Monitoring and Evaluation Department was established. One year later, Turkey introduced new national regulations for pharmacovigilance activities to harmonize the system with that of the European Union (EU): on January 14, 2005, the Advisory Committee for

Monitoring and Assessment of Safety of Medicinal Products for Human Use (BTUGIDDK) was established. Shortly after, this committee published new regulations on March 22, 2005, in the *Official Gazette* (Regulation on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use) (Resmi Gazete, 2005). On June 30, 2005, the resulting Pharmacovigilance Guidelines for Registration Holders of Medicinal Products for Human Use came into force. As one of the implementations of these new guidelines, TADMER became TÜFAM (Turkish Pharmacovigilance Center) with increased responsibility for national pharmacovigilance activities (TÜFAM, 2005).

### PHARMACOVIGILANCE CONTACT POINTS

Following the publication of the regulations in 2005, pharmacovigilance contact points (PCPs)

were established within the national pharmacovigilance system. University hospitals, research & training hospitals, and private hospitals with  $\geq 50$  beds in Turkey are obliged to have a PCP. The PCP may be a physician or a pharmacist (or a dentist in specialized dental center), and these are responsible for providing all hospital departments with ADR reporting forms, encourage ADR reporting, collecting pharmacovigilance data and transmitting this to TÜFAM, organizing training activities for the healthcare professionals (HCPs), and attending training activities organized by TÜFAM.

There are a total of 951 PCPs according to TÜFAM (Sagis *et al.*, 2010; [www.iegm.gov.tr/Default.aspx?sayfa=irtibat&lang=tr-TR](http://www.iegm.gov.tr/Default.aspx?sayfa=irtibat&lang=tr-TR)). Most of them are located within the first three metropolitan areas of Turkey: Istanbul (18%), Ankara (7%), and Izmir (5%). Thirty-four percent of the PCPs are in private hospitals, 7% in research & training hospitals, and 5% in university hospitals. In 2008, 84% of ADR reporting was done by authorization holders, 2% by PCPs, and 14% were direct reports. Reporting by the PCPs increased to 6% in 2010. Through 2008–2010, the most ADR reporting HCPs were physicians (Aykac *et al.*, 2011).

## ADVERSE DRUG REACTION REPORTING

ADR reporting is done by HCPs (physicians, pharmacists, dentists, and nurses). They are required to report to the TÜFAM within 15 days all serious and unexpected ADRs of the products that have well-known safety profiles, as well as all suspected adverse reactions (ARs) of the new products authorized for marketing in Turkey. HCPs can report ADRs (i) directly to TÜFAM, (ii) to the PCP to which their hospital is affiliated, and this PCP then transmits the reported ADRs to TÜFAM, and (iii) to the marketing authorization holder (MAH) of the medicinal product that caused the ADR. ADR reporting can be done either by filling in an ADR reporting form (TÜFAM, 2005) or by written declaration if the form is not available. According to the new regulations, pharmaceutical companies are also required to submit reports of suspected serious ADRs to TÜFAM within 15 days. They also have to submit periodic safety

update reports to the Turkish Ministry of Health in line with EU regulations. TÜFAM uses a web-based system (Vigiflow database) to report ADRs to the UMC database. Spontaneous reports are classified according to WHO-ART, anatomical therapeutic chemical codes are used for drug classification, and system organ class is used for ADR classification. The source (MAH, PCP, direct reporting) of ADR reporting, the type of HCP, and the reporting organization are also recorded in this database.

## RISK MANAGEMENT PLANS

In Turkey, it is mandatory to submit a risk management plan (RMP) according to the relevant guidelines during the marketing authorization application process of biosimilar products (Ministry of Health, General Directorate of Pharmaceuticals and Pharmacy, 2011). However, an RMP for drugs with suspected safety issues may be submitted by the MAH themselves or upon the request of the ministry during or after the authorization application process. Guidelines on risk management systems were published on 10 May 2011 (Ministry of Health, General Directorate of Pharmaceuticals and Pharmacy, n.d.).

In line with the Regulation on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use, TÜFAM is also responsible for the follow-up of safety-related matters and performing the necessary actions. During the conduct of its activities, TÜFAM benefits from comments of the BTUGIDDK when required.

## TRAINING AND EDUCATION ACTIVITIES OF TÜFAM

TÜFAM started its training activities after the Regulation on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use came into force. The training activities are performed for PCPs and product safety officers of pharmaceutical companies (TÜFAM, n.d.) in order to inform on the new pharmacovigilance regulations to increase compliance with these.

## TÜFAM CONTACT INFORMATION

Address: Söğütözü Mahallesi 2176. Sokak, No: 5, 06520 Çankaya, Ankara, Turkey. Phone: +90 312 218 33 00. Fax: +90 312 218 32 96. E-mail: [TUFAM@iegm.gov.tr](mailto:TUFAM@iegm.gov.tr); website (in English): [www.iegm.gov.tr/Default.aspx?sayfa=drug\\_safety&lang=en](http://www.iegm.gov.tr/Default.aspx?sayfa=drug_safety&lang=en).

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## **Part II: PHARMACOVIGILANCE SYSTEMS**

### **Pharmacovigilance in the Americas**

# **14a**

## **Spontaneous Reporting and Pharmacovigilance Practice: USA**

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### **INTRODUCTION**

The US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) approves therapeutic drug and biologic products for marketing based on a comprehensive review of chemistry, pharmacology, toxicology, preclinical, and human clinical safety and efficacy data submitted by applicants. The safety data derived from a review of the pre-market information serves as the basis for characterizing the safety profile of the product at the time of approval. The safety experience associated with other drugs in the same pharmacologic class that are marketed in the USA or other countries, and various aspects of the product's clinical pharmacology, including its pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics, may provide additional information related to organ-specific toxicity or drug-drug interactions.

The FDA-approved product labeling (also known as the "package insert") is a compilation of information necessary for safe and effective use of the product. Safety information is included in one or more sections (such as contraindications, warnings and precautions, adverse reactions, and overdose) of the package insert.

At the time of approval, the package insert is not expected to contain all possible safety risks that may occur with the product because information obtained from premarket clinical trials is often inadequate to identify rare serious safety concerns. Premarket clinical trials frequently enroll patient populations that are too small and involve durations of observation that are too short to detect any rare safety issues. In addition, patient selection criteria often exclude specific subgroups (such as pediatric and elderly patients) and patients with co-morbid conditions (such as hepatic or renal impairment) who may be at higher risk to develop

adverse reactions to drugs and other medical products.

For some drugs and biologic products, additional potential safety signals only become evident after they have been prescribed to a broader population of patients over longer time periods under “real-world” conditions, including patients receiving multiple concomitant medications or who have serious concurrent medical conditions that would have been excluded from premarket studies. Accordingly, it is critical to continue vigilant surveillance throughout product’s life cycle to further assess new safety issues and characterize the product’s risk–benefit profile to inform patients and prescribers about safe use of the products.

In the USA, adverse event reporting is generally voluntary for healthcare professionals, patients, and consumers. These voluntary (spontaneous) case reports of adverse events submitted to the FDA constitute a critical source of postmarketing safety data and are a major focus of pharmacovigilance efforts. The FDA uses information from these spontaneous reports along with other sources of safety data, such as case reports published in the scientific literature, observational studies, postmarketing clinical trials, and foreign regulatory agencies, to generate new “safety signals” of potential risks associated with medical products.

Pharmacovigilance, which refers to all scientific and data-gathering activities relating to the detection, assessment, and understanding of adverse events, including their nature, frequency, and potential risk factors, involves continued monitoring for possible adverse effects and potential safety risk associated with medical products (The Uppsala Monitoring Centre, 2011). Pharmacoepidemiology involves population-based studies of the use and safety of drugs. Pharmacoepidemiologic analysis of actual product use, physician’s prescribing patterns, and study designs that range from purely descriptive to hypothesis testing provide important data relevant to risk–benefit analysis.

This chapter will describe the FDA/CDER’s current pharmacovigilance practices using spontaneous reports and other postmarket data sources to monitor, detect, investigate, and assess safety signals. Such efforts enable the FDA to make appropriate and timely regulatory actions to assure

the safe use of the medical products (FDA, 2005a). The chapter also summarizes the pharmacoepidemiologic methodology used to estimate the risk of adverse effects of a product on exposed populations. Additionally, multiple pharmacovigilance and product safety-related initiatives pursued by the FDA will be summarized.

## THE ADVERSE EVENT REPORTING SYSTEM IN THE USA

### ADVERSE EVENT REPORTING SYSTEM

Spontaneous adverse event and medication error reports are submitted either directly to FDA or by the product’s manufacturer. Laws and regulations require that manufacturers submit specified adverse event reports they receive to the FDA. The reported events and indications for use are coded using the Medical Dictionary for Regulatory Activities (MedDRA®), which was developed by the International Conference on Harmonisation (ICH) (<http://www.meddra.org/about-meddra/organisation/mss0>).

The adverse event reporting system (AERS) is a database that contained approximately 6 million records of adverse event reports reflecting data received by FDA since 1969, including US and foreign source reports, covering prescription drugs, therapeutic biological products, and over-the-counter (OTC) products marketed in the USA. AERS serves as a single centralized repository for spontaneous adverse event reports, and is particularly useful in identifying previously unrecognized serious adverse events and medication errors that were not identified during clinical trials. AERS data are also helpful in identifying potential demographic groups and other factors that may contribute to product risks.

The assessment of spontaneous adverse event reports retrieved from AERS is subject to several limitations, including reporting bias, underreporting, missing and incomplete data, stimulated reporting (by publicity or litigation), and duplicate reporting. Additionally, since AERS does not provide information related to the total number of persons treated with a particular drug or biologic

product, it is not possible to directly estimate the incidence of a specific adverse reaction.

#### ADVERSE EVENT REPORTING DIRECTLY TO THE US FOOD AND DRUG ADMINISTRATION

Direct-to-FDA reports are received through MedWatch, the FDA's safety information and adverse event reporting program (FDA, 2011b). MedWatch provides several reporting mechanisms for consumers, patients, and healthcare professionals (FDA, 2011a). The MedWatch website is also a useful source of new safety information that has been communicated by the FDA on all of its regulated medical products.

#### ADVERSE EVENT REPORTING REQUIREMENTS FOR INDUSTRY

Drug and therapeutic biologic product manufacturers are required by law and regulations to review adverse event information they receive and determine if the information is reportable to the FDA.

For example, under the provisions of 21 CFR 314.80 (FDA, 2011c), those with an approved new drug application or abbreviated new drug application are required to report each adverse drug experience as shown in Table 14a.1.

For regulatory purposes, “expected” means that the event (experience) is listed in the current approved labeling. A serious adverse drug experience is defined as any adverse experience occurring at any dose that results in any of the following outcomes:

**Table 14a.1 Reporting for each adverse drug experience for an approved new drug application or abbreviated new drug application.**

Type of report	Serious	Expected	Timeline
15-day alert report	Yes	No	15 days
Non-15-day report	Yes	No	Periodically*
Non-15-day Report	No	Yes	Periodically*

\*Quarterly for the first 3 years after approval, annually thereafter.

- death;
- life-threatening;
- inpatient hospitalization, or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity; or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered as a serious adverse drug experience when, upon medical judgment, the event may jeopardize the patient's health or may require medical or surgical intervention to prevent one of the outcomes listed above.

In addition to the “spontaneous” reports that manufacturers are made aware of through telephone calls and other interactions with healthcare professionals and patients, manufacturers must submit 15-day Alert reports (for serious, unexpected events) based on information from literature articles and postmarketing studies. Further, adverse event reports arising from postmarketing studies must be submitted to the FDA only if they are serious and unexpected, and if there is a reasonable possibility that the drug caused the adverse event; in these cases, the reports must be submitted as 15-day Alert reports.

#### THE PHARMACOVIGILANCE PRACTICES AT THE US FOOD AND DRUG ADMINISTRATION

##### REVIEW AND ANALYSIS OF SPONTANEOUS ADVERSE EVENT REPORTS FOR POTENTIAL SAFETY SIGNALS

Review and analysis of postmarket spontaneous adverse event reports in AERS, data from published scientific literature, and other sources is a crucial component of the FDA's pharmacovigilance activities. At the US FDA, the Office of Surveillance and Epidemiology (OSE) in CDER has clinical reviewers to systematically monitor the safety of all marketed drugs and therapeutic biologic products to prompt early signal detection and investigation of new and serious adverse events and

medication errors that can impact safe use of the products.

Safety signals that may warrant further investigation may include, but are not limited to, the following:

- new unlabeled adverse events, especially if serious;
- an apparent increase in the severity of a labeled adverse event;
- occurrence of serious adverse events thought to be extremely rare in the general population;
- new product–product, product–device, product–food, or product–dietary supplement interactions;
- identification of a previously unrecognized at-risk population;
- confusion about a product's name, labeling, packaging, or use;
- concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);
- concerns arising from potential inadequacies of a currently implemented risk evaluation and mitigation strategy; and
- other concerns identified by the manufacturer or FDA.

The FDA clinical reviewers search AERS and other data sources for clinically relevant cases frequently employing a case definition to identify clinically relevant cases. Each clinically relevant case report will be evaluated for clinical content and completeness; therefore, the quality of the reports is critical for the appropriate characterization of a potential relationship between the product and the observed adverse event(s). Complete information obtained during initial contacts with the reporting individual and subsequent follow-up is very helpful for case assessment. When an adverse event report is submitted by a consumer, it may be necessary to obtain permission to contact the healthcare practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

In general, the most informative adverse event reports include the following elements with minimal or no missing data: date of initiation of the suspect

drug or biologic product; description of the adverse event(s) or disease experience, including time to onset of signs or symptoms; suspected and concomitant product therapy details; patient demographic characteristics; baseline medical condition prior to product therapy; co-morbid conditions; concomitant medications; results of relevant laboratory and diagnostic medical imaging tests; presence of other potential risk factors for the event; and action taken with respect to the suspect product, including medical interventions implemented in order to manage the adverse event (e.g., systemic corticosteroids, organ transplant). Additionally, documentation of the diagnosis of the event and its clinical course are important to the overall assessment of the potential association between the product and reported adverse event.

Interpretation of pharmacovigilance data derived from the review of individual postmarket adverse event reports can be complicated by confounding factors, such as concurrent medical conditions and concomitant medications, which may actually be responsible for the reported adverse event rather than exposure to the suspect drug. The clinical course and laboratory features of an adverse drug reaction may provide information that distinguishes it from underlying disease processes (Meyboom *et al.*, 1997). For example, a profound hypotensive episode shortly before the development of acute liver failure may be the causative factor rather than the drug the patient was taking. Alternatively, the natural course of the patient's medical condition(s) may be associated with the event of interest. Additionally, other medications, including herbal or dietary supplements, taken by the patient may be linked to the adverse drug reaction. However, despite the limitations, confounded cases could still provide suggestive evidence of the adverse effects of a product under review.

In reviewing postmarketing adverse event reports, several aspects to consider in the overall analysis include assessment for a temporal relationship between exposure to the product and the onset of the adverse event, potential confounding by underlying medical disorders or concurrent medications that could represent a more likely cause for the event, and pathophysiologic plausibility of a medical product-induced adverse event.

An assessment of suggestive evidence of a temporal association between exposure to the product and the subsequent development of an adverse reaction should consider: the onset of the adverse event following exposure to the suspect drug or biologic product; the duration of exposure, the onset of the adverse event is consistent with the proposed underlying pathophysiologic mechanism for the adverse reaction; and any positive challenge results, including positive dechallenge or positive rechallenge.

Overall assessment should consider whether there is consistency of the clinical and pathophysiological aspects of the adverse event with the established pharmacological and toxicological profile of the product, consistency with established infectious or immunologic mechanisms of injury, consistency of the event with the known adverse effects of other products in the same pharmacologic class in which the event is known to be causally associated, and if there has been existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies.

In assessing spontaneous reports, it is rarely possible to know with a high level of certainty whether the adverse event was caused by the product. To date, there are no uniform standardized criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g., stroke, pulmonary embolism). However, in general, causality assessments of potential safety risk posed by the drug–adverse event safety signal in question involve consideration of the following factors:

- information from dechallenge/rechallenge;
- temporal relationship of product use and the adverse event;
- consistency of findings across multiple data sources;
- evidence of a dose-response for the adverse effect;
- biologic plausibility; and
- seriousness of the adverse event relative to the disease being treated;
- absence of a plausible alternative cause for the adverse event.

Additionally, the intent of the case report review is to characterize the potential safety risk and, if possible, to identify risk factors.

In general, a signal results if there are high-quality, unconfounded cases plus supporting cases with fewer confounding factors present.

For safety signals or risks that warrant further investigation and analysis beyond case report review, it is important to put the risks into context by quantifying the identified risk in the exposed population compared with a background incidence rate in the general population, by comparing the identified risks with other available products, by using available epidemiological data to study and further define the risks, or by considering the degree of benefit that the product provides in the intended exposed population.

## DATA MINING AND SAFETY SIGNAL DETECTION

“Data mining” involves the use of computerized algorithms to extract information from large complex safety databases about observed reporting relationships between specific drugs or biologic products and adverse events; it has been used for quantitative signal detection within spontaneous databases, such as AERS (Almenoff *et al.*, 2005; Bousquet *et al.*, 2005).

Beginning in 1998, the FDA has explored new automated and rapid Bayesian data mining techniques to enhance its ability to monitor the safety of drugs, biologics, and vaccines (Szarfman *et al.*, 2002, 2004).

Currently, the FDA uses empirical Bayes and the MGPS data mining algorithm (FDA, 2005a; Szarfman *et al.*, 2002) for the analysis of safety data from the entire AERS. MGPS generates adjusted relative reporting ratios, also known as empirical Bayes geometric mean (EBGM) values that provide an estimate of the relative reporting ratio of any adverse event for a particular drug relative to all other drugs and adverse events in AERS. MGPS also calculates lower and upper 90% confidence limits for the EBGM scores, denoted as EB05 and EB95, respectively. Higher EBGM values for a particular drug–adverse event pair suggest greater disproportionality in the reporting rate between that drug and the adverse event in AERS compared with all other drugs and adverse events in the database. In general, drug–adverse event pairs with

$EB05 \geq 2$  are more frequently evaluated as potential safety signals, as these are adverse events that occur at least twice the expected rate for a particular drug or biologic product.

Data mining is primarily exploratory and hypothesis generating. Data mining results *cannot* establish or refute causal associations between drugs and adverse events. Additionally, the absence of a signal based on data mining algorithms does not rule out a safety problem. Review of individual adverse event reports is critical to the evaluation of potential safety signals identified through data mining. Data mining does not quantify the magnitude of risk, and caution should be exercised when comparing drugs.

The potential limitations of data mining are related to the constraints inherent in spontaneous reporting databases, such as AERS. Results obtained from data mining should be interpreted with caution and with the knowledge of the weaknesses of the spontaneous reporting system (FDA, 2005b).

## PHARMAEOPIDEIOLOGY ASSESSMENT OF SAFETY SIGNALS

Safety signals from AERS and other data sources may warrant further investigation and analysis in order to put them in the context of the population at risk. The epidemiologists quantify the reporting rate for the adverse event of concern relative to the number of the exposed population at risk estimated from available product usage data. Beyond AERS analysis, formal pharmacoepidemiologic studies (e.g., case-control studies, cohort studies) or randomized clinical studies may be performed to confirm and quantify the safety risk of concern suspected to be associated with a drug product, but they are beyond the scope of this chapter.

## REPORTING RATES

Calculated reporting rates or ratios are often used as a crude method to quantify the relationship between the specified adverse event and the population at risk for the adverse event of interest. A reporting rate is the number of reported cases of a

particular adverse event (numerator) divided by some measure of the suspect drug's utilization or patient exposure (denominator), in a specified time period. As such, reporting rates are not true rates and cannot be viewed as incidence rates of the adverse event. Both the numerator and the denominator measures have important shortcomings. The numerator underestimates the actual number of events due to incomplete ascertainment and under-reporting, the extent of which remains unknown and may be variable. The denominator is based on estimated data (such as numbers of patients, numbers of prescriptions, and sales data) derived from proprietary drug utilization databases.

There are two purposes to further quantify the magnitude of the reporting rates. One is to compare the reporting rate for an adverse event of interest for a suspect drug or class of drugs with a known background rate (incidence or prevalence rate). This is done to assess if the adverse event is occurring above the expected based in comparison with a known background rate, the so-called observed-to-expected comparison. The other purpose is to answer the question of whether there are differences between members of a drug class with respect to their relationship to a reported adverse event. This is generally done by comparing the rate for each product within the same drug class, indication, and marketing calendar.

## Proportion-Based Reporting Rate Methods

The various approaches below primarily vary by the type of denominator used to calculate the rate.

A *patient-based approach* divides the number of adverse events by a nationally projected estimate of the number of patients exposed to a suspect drug during a specified calendar time under consideration. Thus, the resulting rate is adjusted for number of patients but not follow-up time. This approach is good for comparing across drugs that are used in the short term and the event occurs within a short time after the start of exposure to a drug (e.g., anaphylaxis). A *prescription-based approach* uses estimated national projected number of prescriptions as the denominator to adjust for drug utilization. Yet another variation is a *drug-sales-based approach* where drug sales data are used as a crude

surrogate measure of drug exposure. This approach is typically used in comparing across drugs within a class for which there are no data available on drug administration or dispensing (e.g., OTC, contrast agents). Mean therapy days are often used to refine the sales data for use as a measure of exposure. The last variation is a *population-based approach* where US census data are used as denominator to calculate the rate in the absence of drug utilization data. This approach may be useful for comparison of rates across geographic regions. All the above approaches produce proportions, and when used to compare events across products they assume that the products under comparison are in the same therapeutic class and have the same indication, course of therapy (dose, route of administration), and marketing calendar.

### Rate-Based Methods

An epidemiologic modification of the reporting rate “denominator” as used in the proportion-based approach employs an estimate of the total person-time of exposure to the drug in the general population rather than the total number of dispensed prescriptions. This prescription-time-based approach uses a person-time denominator that is a sum of the total days of therapy of dispensed prescriptions in a defined population during a time-period of follow-up. Cumulative days’ supply of the prescriptions dispensed or the number of prescriptions dispensed and mean days of therapy are used to estimate the total days of therapy (person-time). This approach is particularly applicable for chronically used drugs.

### Comparison Between Drugs in a Class

The reporting rate of an event can be compared between different products within the same class and indication. A review of case reports identified a signal of pulmonary fibrosis with the anti-androgen nilutamide used in the treatment of prostate cancer. Reporting rates, adjusted for market age and calendar time, were calculated for this product and two other anti-androgens marketed in the USA for the same indication. This analysis found a much higher reporting rate with nilutamide

and led to changes in product labeling (Ahmad and Graham, 2003).

La Grenade *et al.* (2005) compared reporting rates for Stevens–Johnson syndrome and toxic epidermal necrolysis associated with the use of selective COX-2 inhibitors. The analysis found reporting rate for valdecoxib (49 cases per million person years) that was eight to nine times higher than for celecoxib (6 cases per million person-years) and approximately 25 times higher than background rate.

### Comparison with Background Rates: Observed-to-Expected Analysis

An observed-to-expected analysis is often used as a signal refinement approach. This method needs an estimate of the background rate for the adverse event of interest in the general population obtained from published literature or other sources, such as the US National Center for Health Statistics (La Grenade *et al.*, 2000). This information is sometimes supplemented by the use of extramural databases that provide access to large, automated claims data from population-based healthcare plans (Graham *et al.*, 2000). For reporting rate calculation, the rate-based approach described earlier can be used to estimate the denominator.

One example is an evaluation of adverse event reports for clozapine that found 47 reports of myocarditis and cardiomyopathy, with a sizable proportion occurring within the first few months of starting therapy. A literature review produced a population-based estimate for fatal myocarditis of 4 per million person-years (Murray and Lopez, 1992). To determine the total US exposure-time to clozapine, FDA epidemiologists turned to the US National Clozaril Registry and obtained the number of patients ever treated with the drug (Honigfeld *et al.*, 1998). The cumulative patient-time for the first month of drug use was calculated and an estimate of the expected number of fatal cases of myocarditis derived. This analysis showed a 321-fold excess in fatal reports of myocarditis in the first month of clozaril use (La Grenade *et al.*, 2001).

This method works best when the background rate for the clinical event of interest is very low. In

the above examples, the background rates were in the range of a few per 100 000 to a few per 1 000 000 per year. With more common events, such as myocardial infarction or asthma, the expected number of cases becomes large, thereby greatly reducing the signal-to-noise ratio. Because of the presence of large-scale underreporting of ADR cases, the lack of an excess number of reports over the number expected cannot be interpreted by itself as invalidating the signal. However, the strength of the method is demonstrated in those situations where the reported number ("observed") is close to or exceeds the expected number. Because of underreporting, the actual level of risk may be much greater than that obtained. In such instances, one has moved beyond signal towards establishing an association.

### Interpretation of Reporting Ratios

Reporting rates must be interpreted carefully because they are not incidence rates. True incidence rates incorporate the element of time and depend upon the complete ascertainment of all new events being measured within a defined population (Clayton and Hills, 1993). More specifically, the denominator should be comprised of the sum total of the length of time at risk for each member of the population at risk during the observation period. The population at risk and the exposure time on drug are often unknown and can only be approximated from the drug utilization database. These requirements do not hold for reporting ratios. Using person-time rather than prescription number as the denominator of the reporting rate still does not give rise to an incidence rate because of the problem of underreporting of adverse events, and hence the reporting rate may seriously underestimate the true incidence.

## MANAGEMENT OF SAFETY SIGNALS, INCLUDING RECOMMENDATIONS FOR REGULATORY ACTION

As described in the previous sections, the FDA evaluates potential safety signals identified from spontaneous case reports in AERS, published lit-

erature cases, and other data sources by integrating the following to serve as the basis for benefit-risk assessments:

- spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;
- background rate for the event in general and specific patient populations, if available;
- relative risks, odds ratios, or other measures of association derived from pharmacoepidemiologic studies, if available;
- biologic effects observed in preclinical studies and pharmacokinetic or pharmacodynamic effects;
- safety findings from controlled clinical trials; and
- general marketing experience with similar products in the same pharmacologic class.

Based on an analysis of available data, including knowledge of pre-approval clinical trial findings and other available scientific information before and after approval, the FDA considers all available regulatory actions to minimize the identified risk, which are communicated to the product manufacturer. Potential actions include a requested or required safety labeling change, required postmarketing study or clinical trial, required implementation of a risk evaluation and mitigation strategy (REMS) with or without new restrictions for use, issuance of a drug safety communication and/or removal of the product from the US market.

In many instances, modification of product labels to include new safety information is adequate to communicate and reduce risk of harm from exposure to a drug. However, for some products, additional safety plans or strategies beyond product labeling may be needed in order to minimize risk while preserving access to and the potential benefits from use of a product. The FDA issued guidance for industry on risk minimization action plans (RiskMAPs), which were developed for products that had risks that required additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required safety reporting (FDA, 2005c). The Food and Drug Administration Amendments Act of

2007 (FDAAA) (Public Law 110-85) gave the FDA the authority to mandate a REMS when needed to ensure the safe use of a drug such that its benefits outweigh its risks. A REMS has essentially replaced RiskMAPs; the REMS will be described in further detail in the next section (FDA, 2009a).

The FDA issues Drug Safety Communications (DSCs) to provide drug safety recommendations and information to patients and healthcare providers. In general, a DSC includes separate sections for the safety announcement, general information for patients, additional information for healthcare professionals, and a summary of scientific data, including AERS data, with a list of literature references (where applicable) (FDA, 2010a, 2011d).

## **PHARMACOVIGILANCE AND PRODUCT SAFETY IN THE USA: CURRENT AND FUTURE INITIATIVES**

Following the passage of the FDAAA (FDA, 2009a), the FDA has been pursuing various initiatives to improve drug safety and strengthen its pharmacovigilance capabilities. Core provisions of the FDAAA include enhanced authority regarding postmarket drug safety, improved postmarket surveillance, and strategies to enhance risk evaluation, mitigation, and communication.

If criteria are met, the FDA may require postmarketing studies, clinical trials, or safety labeling changes related to serious risks. The FDA may require a REMS to ensure that the benefits of a drug outweigh its risks. A REMS may include a medication guide if it meets requirements in the regulations, a patient package insert if the FDA determines that it may help mitigate a serious risk of a drug, a communication plan to healthcare providers that may require distribution of information directly or through professional societies if it may support implementation of the REMS, elements to assure safe use (ETASU) if the drug has been shown to be effective, but is associated with a serious adverse event and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate the specific serious risk(s) listed in the labeling of the product.

The FDAAA also includes a provision that impacts on the FDA's pharmacovigilance. It requires development of methods and establishment of a system to conduct active postmarketing safety surveillance and analysis based on federal health-related electronic data, health insurance claims data, and patient survey data. In response to this mandate, the Sentinel Initiative was launched in May 2008 (FDA, 2011f). Because the Sentinel Initiative is a complex endeavor, the FDA has launched several pilot projects designed to help develop the eventual Sentinel System, including two pilot initiatives: Mini-Sentinel and the Federal Partners' Collaboration. Mini-Sentinel (<http://mini-sentinel.org/>) leverages privately held electronic databases of claims and administrative data, enabling the FDA to query electronic healthcare data and to develop the scientific operations needed for the Sentinel Initiative. The Federal Partners' Collaboration uses the scientific capabilities of other federal government agencies, including the Veterans Health Administration at the Department of Veterans Affairs, the Department of Defense, and the Centers for Medicare & Medicaid Services, for active medical product surveillance.

The need for drug safety communication was also addressed in the FDAAA; in response, the FDA developed a CDER website for "Postmarket Drug Safety Information for Patients and Providers." Among the links included under "Latest Safety Information" are the AERS website, a website listing potential signals of serious risks identified from AERS, and a website containing postmarketing safety summaries of recently approved products.

The FDA has supported multiple initiatives designed to enhance pharmacovigilance and risk communication activities. The three recent initiatives include Safety First, Safe Use, and Sentinel.

The Safety First Initiative involves integrated, multidisciplinary safety-issue teams that assess significant safety issues, recommend actions, and monitor sponsors' activities (FDA, 2010b). The Safe Use Initiative is a collaborative effort of the FDA with other healthcare partners (including other federal agencies, professional societies, healthcare professionals, patients, and consumers) to identify and reduce preventable injuries from

medication use through interventions such as consumer education information and improved product labeling (FDA, 2011e).

In addition to the above initiatives, the FDA collaborates with other federal agencies in programs designed to augment surveillance for postmarketing drug safety issues. The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project is a collaborative effort of the US Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, US Consumer Product Safety Commission, and the FDA to collect data on the types and frequencies of adverse drug events reported from a representative sample of hospital emergency departments in the USA that are part of the National Electronic Injury Surveillance System – All Injury Program (Budnitz *et al.*, 2005; CDC, 2005).

The Drug-Induced Liver Injury Network was established by the National Institute of Diabetes and Digestive and Kidney Diseases in collaboration with five clinical centers as a registry of individuals who experienced serious liver injury associated with marketed drugs, OTC products, and dietary supplements (DILIN, n.d.).

An emerging area of interest at the FDA relative to drug safety is pharmacogenomics, which involves the study of the relation of genetic variations (polymorphisms) to a drug's efficacy and adverse reaction profile. Through the use of pharmacogenomic methodology, advances have been made in the understanding of genetic polymorphisms in drug-metabolizing enzymes (such as variants in the cytochrome P450 gene family) and drug transport proteins and their associated safety biomarkers for certain drugs (Amur *et al.*, 2010).

## CONCLUSION

Through the pharmacovigilance practice activities and safety initiatives, the FDA aims to enhance signal detection and management to better characterize the benefit–risk profile of the approved products. The FDA is exploring scientific methodologies to support the rapidly escalating number of spontaneous adverse event reports, increase the effi-

ciency of data mining strategies, and enhance analysis of safety signals for effective risk management. Globally, the FDA maintains extensive interactions with other international regulatory agencies to exchange information on safety on medical products. Efforts continue to foster collaboration between the FDA, academia, application holders, and the pharmaceutical industry on all activities related to safe use of the products. These may include facilitating collaboration with the general public through education campaigns, improved prescribing practices, and enhanced health literacy to reduce medication errors and promote safe use.

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## 14b

# Spontaneous Reporting in Mexico

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## ORGANIZATION AND OPERATION

Mexico has been a member of the Programme for International Drug Monitoring coordinated by World Health Organization since 1999, through the Pharmacopeial and Pharmacovigilance Executive Direction, which is part of the Commission of Evidence and Risk Management, a branch of the drug national agency, named COFEPRIS (as per its acronym in Spanish, Federal Commission for Protection Against Sanitary Risks), reporting directly to the Minister of Health.

The national program is specifically regulated by the Mexican Official Norm 220-SSA1-2012, *Pharmacovigilance Installation and Operation*, which points out as mandatory the notification of adverse drug reactions and the NOM-240-SSA1-2012, intended for medical devices, which was launched in October 2012, both involving institutions of public and private sectors of the National Health System, as well as healthcare professionals, the

owner of marketing registry or their legal representative, establishments dedicated to the sale and supply of medicinal products, and clinical research units.

A complementary regulation for establishing the procedures and tests for demonstrating that a drug is interchangeable and a biotechnological product is a biosimilar is being reviewed in a common document entitled Mexican Official Norm 177-SSA1-2013, which also involves pharmacovigilance activities for diverse parties.

Any spontaneous report can be sent directly to the health authority or through entities that collect and register the reports, known as state-centers, or pharmacovigilance institutional centers, the pharmaceutical industry, and clinical research units, who, as well as health professionals and medications' users, provide information to the health authority.

The analyses of the quality and causality of reports using the Naranjo algorithm are executed

by the pharmacovigilance centers/units and health authority to input information into the national database, which, to date, is in an improvement process in order to have a standardized coding procedure. At some point, joint auditing processes to ensure data reliability for decision making should be added.

## RESULTS

The health authority describes the general compiled data (Figure 14b.1) annually, which globally includes adverse drug reactions reports, adverse events following immunization, cases related to medical devices, to hemovigilance, and adverse events in pharmacological clinical research trials. The specific number of reports with sufficient causality to establish association with the suspected drug and other descriptive information are not normally opened. For a population of 112 337 million inhabitants (INEGI, 2011), Mexico should generate at least 22 000 useful notifications each year. The fact is that this goal has not been achieved due to the bad quality of the reports and to the lack of feedback to the reporters. From 1999 until November 2010, Mexico's contribution to the international program has been limited to a total of around 50 000 notifications, which represents less than 1% of the global base, in spite of Mexico occupying second place in the Latin American pharmaceutical

market, after Brazil, with a population highly prone to self-medication practices with prescription drugs due to extensive advertising in the mass media.

As an example, in 2009 there were 26 640 notifications reported, but only 11 284 became useful reports (Becerril, 2010). The origin of the reports involved the pharmaceutical industry (58%), state centers (11%), institutional centers (3%), healthcare professionals directly to health authority (0.5%), medication consumers (0.5%), and adverse events coming from clinical research (27%) (not necessarily associated with drugs). Unfortunately, the quality of information issued by the pharmaceutical industry was not appropriate in 77% of the cases (the date of the reaction was not described, nor the drug involved), a situation related to the collection of data by secondary or tertiary sources.

In a recent publication, deficient quality of spontaneous reports reached 20–66% of the total number that was collected in 2007 and 2008 by the National Pharmacovigilance Program (Sánchez-Sánchez *et al.*, 2012). Criteria for acceptance are now being promoted.

Other results of the national program include qualitative signals detection or in accordance with the alerts issued in other countries. The national database is not designed to make quantitative estimates, nor has it access to the number of subjects exposed. Mexico has published some descriptive studies or cohorts in small groups (vulnerable populations) (Rosete *et al.*, 2008), and with specific medicinal products (Hernández-Hernández *et al.*, 2002; Rodriguez-Fragoso *et al.*, 2008), but to date there are no initiatives based on pharmacoepidemiological designs or safety monitoring in health programs involving drugs.

Decision making of the health authority is focused on actions such as modifying the pharmaceutical prescribing information simultaneously with the international information issued by other health authorities. Other actions, such as restricting or expanding indications, contraindications, or issuing product recalls, are barely carried out.

Adverse events following immunization are issued through CENSIA (per its acronym in Spanish: National Center for the Health of Children and Adolescents) and COFEPRIS is also informed, but there is no a communication strategy

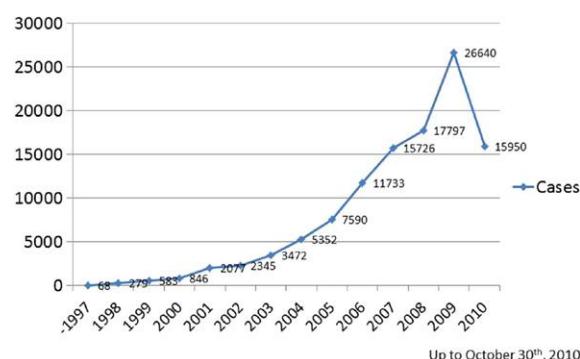


Figure 14b.1 Global reporting is informed annually; it includes useful and nonuseful adverse drug reactions, adverse events following immunization, and adverse events related to clinical research and medical devices.

intended for encouraging reporting, nor a joint database, and it reached 1764 cases from January to October 2009.

In a complementary way, other communication tasks such as issuing announcements and newsletters are seldom performed.

## STRENGTHS

Mexico has a national center operating with 30 people dedicated full time, standard operating procedures, a database, and continued support from the Uppsala Monitoring Centre and Spain; in order to improve the operation, recent updating of the regulation has been focused on active pharmacovigilance projects, which will require educational scientific strategies (pharmacoepidemiological methodology) for all the parties. Interaction with the international program has increased and has had favorable results, although it is still to grow. From 2009 to date, it has activated the notification of adverse events following vaccination, in cooperation with PAHO and UMC.

## OPPORTUNITIES

In a high percentage of the notifications, the quality of the information is not good and the lack of feedback has not allowed improvement.

Despite the tasks performed having evolved, they still fail to have an impact on public health, so it is a priority to strengthen health authority decision

making in cooperation with multidisciplinary advisory groups of a high technical-scientific level, the active participation of all the stakeholders, escalating the pharmacovigilance application to national health policies and pharmaceutical policies, besides achieving drug consumers' education, as well as favoring the interaction with drug prescribers to move all the system to one of higher impact on public health, providing vital information for the better use of health resources.

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## 14c

# Pharmacovigilance in Argentina: A Lot Done, A Lot To Do

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In order to understand the organization of the Argentina's pharmacovigilance system and how it works, this chapter will give you overview of the Argentina's healthcare system, Argentina-based pharmaceutical industry's main features, and how National drug regulation has been established in this South-American federal country.

Argentina's health system is a complex mixture and overlapping of national and provincial government assistance healthcare systems and private healthcare institutions. Argentina's 40 million inhabitants have universal access to governmental primary and hospital care and the main basic medicines. In spite of this, marked differences exist between social classes regarding health care quality and access, according to their economic income, geographic location and working status. Private health institutions and facilities provide healthcare services to private health insurance systems and union workers' insurance, meanwhile governmental

institutions can also give health care services to union workers' and private health insurance. Some conditions (such as HIV infection and AIDS and hemophilia) are fully supported by national health programs. Regrettably, this system is periodically affected by national or regional economic turbulences and crises that affect mainly the poorest social classes.

Argentina's pharmaceutical industry can be roughly classified in three groups: multinational laboratories, which have to fulfill the same quality-product standards as in the originator countries because of their internal organization; a national pharmaceutical industry, which manufactures high-quality standard products (mainly similar or generic products with few or no investigational drugs); and a national pharmaceutical industry with less advanced technology, which elaborates mainly similar products. The first two groups have usually high prices, the latter has lower prices and

their products are widely distributed in hospitals. Most of the reports of suspected substandard quality mention medicinal products manufactured by less technically equipped laboratories.

Until 1992, Argentina's drug legislation was limited to bureaucratic procedures. The situation was "chaotic" because of the system's inefficiency, lack of informatics technology and no ad-hoc facilities: medicinal products' registrations took more than 4 years and 4 months (Bazerque, 2013). Dr Pablo Bazerque was charged to organize a regulator National office in order to set up a system allowing accelerating drug evaluation and marketing authorization. In 1992, a diethylene glycol massive intoxication, caused by a glycerine contaminant included in propolis candies, killed more than 25 adults (Bazerque, 2013; Herrera Comoglio, 2012), and prompted the creation of the National Food, Drug and Medical Technology (ANMAT) agency. In 1993, the ANMAT Pharmacovigilance Department was created and Dr Estela Giménez, who had participated in the investigation about propolis candies' intoxication, was in charge of it.

ANMAT Pharmacovigilance system was conceived as a central office with staff professionals, and "peripheral nodes" that report suspected adverse reaction on a voluntary basis. Since its creation, the number of reports has increased step by step. Some signals generated by the evolving pharmacovigilance spontaneous reporting system were reports of mibepradil and oxybutinin. In 1994, Argentina joined the WHO Pharmaceutical Vigilance Programme.

First, one of the more evident problems was the one related to products' quality. Many reports mentioned suspected lack of efficacy, mainly in anesthetic products. Antiretroviral and anticonvulsive agents were also a source of frequent efficacy and safety concerns. In 1995, there were an increased number of claims of lack of efficacy or prolonged neuromuscular blocking in anesthetic and muscle relaxant products purchased by the Córdoba Ministry of Health and used in public hospitals (Alesso and Herrera, 2002; Alesso, 2007). These claims elicited a pharmacovigilance survey, and quality tests were performed on product samples. Chemical analysis showed consistent differences in the strength of principal pharmaceutical with respec-

tively lower or higher concentrations than those specified in the *Pharmacopeia* (Alesso and Herrera, 2002; Alesso, 2007). Such products were considered substandard. These results provided the basis for structured administrative requirements for wholesalers and laboratories in order to purchase medicines. Suspected lack of efficacy was then explicitly included in the national Yellow Card scheme as a drug-related event. In 1999, ANMAT required bioequivalence (BE) studies for some therapeutic groups or specific drugs with narrow therapeutic index (i.e. anticonvulsants, digoxin, cyclosporine, etc.) (Bolaños, 2012; ANMAT 1999). The adherence of the different local manufacturers to this first requirement was slow. Antiretroviral agents were included as products requiring BE studies in 2001. In 2006, ANMAT published "Good Practices for Bioequivalence studies", in 2007 BE studies were required for other immunosuppressant agents, in 2012 new drugs were added to the list of agents that require BE studies, and in 2013, Good Laboratory Practices for BE studies were specifically regulated.

In past years, the important problem of circulation of fake medicines in Argentina was tackled throughout the creation of the National Investigation Programme on Illegitimate Medicines, created in 1997 and directed by Dr Carlos Chiale. Many fake and substandard medicines, as well as adulterated, stolen, and expired products, have been detected because of the activity of this department (ANMAT, 2004; Alesso *et al.*, 2008; WHO, 2008a,b). Some of these counterfeit products were also detected throughout the Pharmacovigilance system: in December 2004, at least one pregnant woman died, another woman presented acute liver failure and had to be transplanted, and many other patients suffered severe intoxications because of the administration of a fake parenteral iron product in a public hospital (Bologna *et al.*, 2005; HerreraComoglio, 2007). This illustrated a continuing problem with the regulation and control of purchasing in the public hospitals and some governmental health structures (Alesso *et al.*, 2005, 2008).

A recent approach is the "ANMAT Federal": Since ANMAT belongs to the federal (national) government, and each province has its own regulation for pharmaceutical products manufactured

and sold within their territorial borders, in 2010 ANMAT started a federal program in order to establish collaboration between provincial health ministries and national drug administration ([www.anmat.gov.ar](http://www.anmat.gov.ar)). This program aims to control inter-provincial drug trade and transport, thereby tackling fake and substandard medicines.

ANMAT also set specific requirements for pharmaceutical industry, which is required to have a pharmacovigilance-qualified person in order to liaise with ANMAT. For approved new drugs (chemical or biological entities) a risk management plan is required. Some intensive pharmacovigilance programs are in force, such as for thalidomide, lenalidomide, and for clozapine.

Reporting is increasing year on year, with 6100 reports in 2011, and 7182 in 2012, (174 reports/million inhabitants), adverse events are mainly reported by the pharmaceutical industry (69% in 2011 and 80.7% in 2012) (ANMAT, 2013). Several university and hospital pharmacovigilance centers actively collaborate with the National Spontaneous Reporting System, as a substantial part of non industry reporters. Patient reporting is still low (1.7% in 2012). The new ANMAT federal program also proposed a hospital sentinel pharmacovigilance center in each province, but the efficiency of this part of the system might be hampered because of the administrative nature of these centers. A system of electronic reporting has been recently made available (ANMAT, 2013).

In conclusion, many efforts have been made in order to clean up the market of substandard, fake and illegitimate medicine, and this constitutes an invaluable premise for the availability of good quality and more controlled medicinal products. Although substandard legitimate products are still a concern (22% of reports of suspected lack of efficacy in 2012), no reports involving suspected counterfeit medicines have been sent to the Pharmacovigilance National system in 2012. University and hospital pharmacovigilance centers should be more active, but they are deeply under-resourced and understaffed in Argentina. Peripheral nodes should be funded by the national reporting system in order to enhance their performance and efficiency. The number of centers should be increased and communication improved; peripheral nodes

should have access to the National database. Pharmacovigilance should be included in Schools of medicine's curricula. The inclusion of all peripheral nodes in a structured and well-funded system at national level will allow better harmonize all individual efforts and standardize procedures and methods. We have to work for a more clinical and more active pharmacovigilance, with the contribution of health care professionals and patients, in protection of patients' health.

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## **Part II: PHARMACOVIGILANCE SYSTEMS**

### **Pharmacovigilance in Asia**

**15a**

# **Pharmacovigilance and Risk Management in Japan**

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## **INTRODUCTION**

Pharmacovigilance in Japan has been characterized by complex post-approval safety procedures in which the drug company has many duties in addition to collecting suspected adverse drug reactions (ADRs) to report them to the regulatory body. For example, the drug company has long had the legal duty to conduct a “drug use investigation” (DUI), which involves physicians registering thousands of patients treated with a newly launched product to monitor and report suspected ADRs (Tanaka *et al.*, 2002). Furthermore, early-phase postmarketing vigilance (EPPV) was introduced as an additional requirement in 2001. In 2005, the international guideline on the pharmacovigilance planning (PVP) agreed at the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was implemented in Japan. It may, however, take some

more time till DUIs are reorganized as studies with the scientific standards that the PVP guideline requires. The risk minimization action plan (risk MAP) will also be incorporated into Japanese risk management plan (RMP) guidance, which was implemented in April 2012. In addition to these guidelines and guidance, the next amendment of the Pharmaceutical Affairs Law (PAL) was enacted in 2013 to strengthen pharmacovigilance and modernize other regulatory activities for drugs and medical devices.

## **SPONTANEOUS REPORTING SYSTEM IN JAPAN**

The Japanese spontaneous reporting system (SRS) has been in operation since 1967. The performance of the Japanese SRS was rather poor till the 1990s. As shown in Table 15a.1 (PMDA, 2011a), the

Table 15a.1 The number of domestic spontaneous reports sent to the SRS in Japan.

Fiscal year	From companies	From health professionals
1966	— <sup>a</sup>	3
1967	— <sup>a</sup>	44
1968	— <sup>a</sup>	595
1969	— <sup>a</sup>	293
1970	— <sup>a</sup>	200
1971	— <sup>a</sup>	338
1972	— <sup>a</sup>	271
1973	— <sup>a</sup>	360
1974	— <sup>a</sup>	285
1975	— <sup>a</sup>	336
1976	— <sup>a</sup>	416
1977	— <sup>a</sup>	456
1978	— <sup>a</sup>	530
1979	— <sup>a</sup>	712
1980	388	669
1981	383	816
1982	455	822
1983	751	766
1984	1 072	767
1985	1 183	803
1986	1 562	890
1987	1 669	854
1988	1 672	1 025
1989	2 357	1 332
1990	2 523	1 374
1991	3 823	1 451
1992	6 540	1 667
1993	8 440	1 505
1994	12 980	1 615
1995	14 288	1 859
1996	16 831	1 914
1997	17 504	3 730
1998	18 466	4 882
1999	20 031	5 502
2000	22 326	5 297
2001	22 451	4 094
2002	24 221	4 195
2003	28 004	5 399
2004	25 448	4 594
2005	24 751	3 992
2006	26 560	3 669
2007	28 500	3 891
2008	32 306	3 816
2009	30 928	3 721
2010	34 677	3 656

<sup>a</sup>A small number of reports sent to the SRS are not shown.

Source: Data from PMDA (2011a) <http://www.pmda.go.jp/guide/hyougikai/23/h231220gijishidai/file/siryo2-1.pdf>. [Accessed 31 December 2011]; <http://21jsphcs.jtbc.com.co.jp/pdf/symposium/27.pdf>; [http://books.google.co.jp/books?id=rdAlPjX88boC&pg=PA22&lpg=PA22&dq=%E8%87%AA%E7%99%BA%E5%A0%B1%E5%91%8A%E6%95%BA%0%E3%80%80%E5%BA%4%E6%AC%A1%E6%8E%8A%E7%A7%BB&source=bl&ots=MHMMUctzNx&sig=86yKl8skSvUN\\_2wUb8Vwp8WE8g&hl=ja&sa=X&ei=dHciT42eAadiAfW0MznBA&ved=0CD4Q6AEwBQ#v=onepage&q=%E8%87%AA%E7%99%BA%E5%A0%B1%E5%91%8A%E6%95%BA%0%E3%80%80%E5%BA%4%E6%AC%A1%E6%8E%8A%E7%A7%BB&f=false](http://books.google.co.jp/books?id=rdAlPjX88boC&pg=PA22&lpg=PA22&dq=%E8%87%AA%E7%99%BA%E5%A0%B1%E5%91%8A%E6%95%BA%0%E3%80%80%E5%BA%4%E6%AC%A1%E6%8E%8A%E7%A7%BB&source=bl&ots=MHMMUctzNx&sig=86yKl8skSvUN_2wUb8Vwp8WE8g&hl=ja&sa=X&ei=dHciT42eAadiAfW0MznBA&ved=0CD4Q6AEwBQ#v=onepage&q=%E8%87%AA%E7%99%BA%E5%A0%B1%E5%91%8A%E6%95%BA%0%E3%80%80%E5%BA%4%E6%AC%A1%E6%8E%8A%E7%A7%BB&f=false). Courtesy of Mr Kawahara, former officer in MHLW and PMDA.

number of reports from health professionals was less than 2000 per annum, mainly because the reports were sent from a limited number of “designated” medical institutions and pharmacies before 1997 when the Ministry of Health and Welfare (MHW, renamed the Ministry of Health, Labour and Welfare (MHLW) in 2000) changed the policy and received around 5000 reports per annum from all of the doctors and pharmacists. In the amendment of the PAL in 2002 (2002 PAL amendment), doctors, dentists, pharmacists, and other health professionals had a legal duty to report an ADR when judged to be necessary to prevent the onset or spread of the risk of harm to public health or hygiene. The number of domestic reports via drug companies was also very small initially (less than 500 per annum) till 1979, when the ministerial ordinance made drug companies duty bound to send the ADR reports to the MHW. The reports via drug companies then increased and exceeded 10 000 per annum in 1994. The number has consistently been around 30 000 per annum since 2007.

Following the 2002 PAL amendment, the definition and standards for expedited reporting of post-approval ADR reporting via drug companies was revised in 2005 when more emphasis was placed on recording the serious reactions in line with the implementation of ICH-E2D guideline in April 2005. Under the new regulations, nonserious reactions have been excluded from those requiring the expedited reporting. On the other hand, when the marketing authorization holder (MAH) is aware that a domestic case has experienced an expected and fatal ADR, the reaction should be reported within 15 calendar days as for unexpected serious ADRs. In addition, all the expected serious reactions should be reported within 15 calendar days during the EPPV and during the first 2 years after the approval of a new chemical entity. In line with the enhancement of the safety measures for biological products in the 2002 PAL amendment, mentioned in the next section, the revision in 2005 required that all the expected and unexpected serious cases of infection due to the use of any kind of drug be reported within 15 calendar days and nonserious unexpected domestic cases of infections be also reported within 15 calendar days.

In January 2011 a pilot study was started to ascertain whether spontaneous reports directly from patients via the Internet may work in Japan (PMDA, 2011b). During the first 6 months of the pilot study, 160 patients reported a total of 716 suspected ADRs. The scheme of patient reports was formally incorporated into Japanese regulatory activities from early 2012.

## ENHANCEMENT OF THE POSTMARKETING SAFETY MEASURES

Japan introduced a system for the “re-evaluation” of marketed drugs since 1971 and that for “re-examination” since 1979. The “re-examination” system involves a reassessment of the usefulness of all new drugs after a fixed period of time (8 years for usual products, 4–10 years for some other drugs) following the first approval. In the re-examination, the submission of the findings obtained by the DUI is normally required. Unless the results of the re-examination indicate that the product has no major problem, the manufacturer is no longer allowed to market the product. On the other hand, the quality, effectiveness, and safety of the approved drug may be subject to re-evaluation based on the advancement of medical and pharmaceutical sciences. Since April 1997, the basic plan of postmarketing studies is required to be submitted at the approval stage of the new products.

The periodic safety update report (PSUR) of the ICH-E2C guideline was introduced to Japan in April 1997, where the manufacturer was obliged to submit a PSUR together with summary of the ongoing postmarketing studies and other documentation to the MHW. As an additional regulation, the EPPV was introduced in 2001, which is unique to Japan. Under this regulation, the MAHs are required to encourage health professionals to report ADRs for the first 6 months after launch.

In the 2002 PAL amendment, new regulations to ensure the safety of biological products were introduced. In the 1990s it became clear that many hemophiliacs with HIV infection contracted the virus from plasma products prepared in the 1980s. Similarly, many patients suffering from hepatitis C contracted the virus from blood and plasma

preparations made around 1980. In the 2002 PAL amendment, “specified biological products” were defined for some blood and plasma preparations requiring special regulations, including long-term record retention covering manufacturing, distribution, and administration.

The Pharmaceutical and Medical Device Agency (PMDA) was established in April 2004 under the Law of the Incorporated Administrative Agency – Pharmaceutical and Medical Devices Agency enacted in December 2002. The role of the PMDA to secure drug safety now encompasses collecting, analyzing, and distributing the safety data of drugs obtained from spontaneous reports and medical databases, as illustrated later.

## GOOD POSTMARKETING STUDY PRACTICE AND ICH E2E GUIDELINE

The DUI has long been regarded as the major tool for collecting drug safety information in Japan. Thousands of patients who were prescribed a new product are registered by their physicians and followed usually for up to 6 months, depending on its usual administration term. The predecessor of the DUI, known as the “side effect investigation,” was formed in the late 1960s. Between 1973 and 2000, out of 874 side effect investigations or DUIs, a total of 7180188 patients or an average of 8215 (range 37–111810) patients per study were monitored (Tanaka *et al.*, 2002). Since the mid 1990s, the DUIs and other post-approval procedures have been regulated by the “Good Post-Marketing Surveillance Practice” (GPMSP) first made as a notice in 1994 and legislated as a ministerial ordinance in 1997. In 2004, the GPMSP was divided into the Good Postmarketing Study Practice (GPSP) and the Good Vigilance Practice (GVP). The GVP is a ministerial ordinance that the MAH must follow without exception covering spontaneous reports (via drug companies) and EPPV. The GPSP, being different from the GVP, is not license rules but a ministerial ordinance stipulating duty rules for post-approval investigations. In the GPSP, the investigations and trials are, as in the former GMPSP, divided into three categories: DUI, DUI

of special population, and postmarketing clinical trial.

In the notices from the MHW given before and after the GPMSP, the methodological requirements for the side effect investigation and DUI, including the number of patients being monitored, have altered many times. However, one of the main objectives of the DUIs was consistently defined as “the detection of unknown serious reactions.” For example, in the notice issued in March 1997, the target number of patients to monitor in the DUI was said to be 3000. The reasoning for this regulation was explained by using the “rule of 3” (Bégaud and Tubert-Bitter, 1993) and the notice read “the target number of the subjects should be decided according to the characteristics of the drug, but it should be normally set as 3,000 in order to detect, with 95% confidence, unknown ADRs with the 0.1 % or more of the frequency” (Notice No. 34 from the Safety Division of the MHW, in 1997). As mentioned in the earlier section, until the 1990s the number of domestic spontaneous reports of ADRs was small, and one of the consistent roles of the DUI was to complement the SRS. The DUI does not normally have the comparator group and ADRs are assumed to be suspected, evaluated, and reported by participating physicians as in the SRS.

In November 2004, an agreement between the EU, USA and Japan was reached for the guideline of “Pharmacovigilance planning (PVP)” (also known as the “E2E guideline”) in the ICH. The guideline was then incorporated into Japanese regulation rules as the notice issued from the MHLW in September 2005. According to the E2E guideline (ICH, 2004), “when choosing a method to address a safety concern, sponsors should employ the most appropriate design.” On the other hand, the DUIs have been conducted irrespective of whether the drug had any “special concerns.” In the amendment of the GPMSP in 2000, it was stated that the DUI was no longer a uniform requirement and was carried out according to the characteristics of the drug. However, the DUI with the traditional methodology still prevailed in 2011 as opposed to more optimistic forecasts made by Kubota and Koyama (2007) in Chapter 31 of the second edition of *Pharmacovigilance*.

## THE INVESTIGATIONS USING PHARMACOEPIDEMIOLOGIC METHODS IN JAPAN

Although the DUIs with the traditional methodology still prevail, some investigations using pharmacoepidemiologic methods are gradually emerging in Japan. For example, the study to examine the association between gefitinib for non-small-cell lung cancer and interstitial lung disease (ILD) conducted as a DUI of Special Population was a nested case-control study (Kudoh *et al.*, 2008). In this study, all of the patients in participating hospitals were registered if the patient had already been treated by one or more regimens of chemotherapy for non-small-cell lung cancer, irrespective of the treatment eventually selected for the patient. In addition to obtaining the relative risk of ILD with gefitinib, the study examined other risk factors of ILD, including genetic factors (Nyberg *et al.*, 2011).

Although not carried out as research under the regulation of the GPSP, a case-control study on the association between nonsteroidal anti-inflammatory drugs (NSAIDs) and upper gastrointestinal bleeding (UGIB) was the case-control study using community controls (Sakamoto *et al.*, 2006). The method of the case-control study with community controls was also used in the study on the effectiveness of pertussis vaccine (Okada *et al.*, 2009).

These examples and other studies, such as a cross-sectional study to examine the association between pergolide/cabergoline and cardiac regurgitation (Yamamoto *et al.*, 2006), a study to examine the background incidence of ILD in Japanese patients with malignant mesothelioma (Nojiri *et al.*, 2011), and a case-cohort study to compare some of ADRs associated with statins in the Japanese population (Kageyama *et al.*, 2010), suggest that a study using the standard design for pharmacoepidemiology is feasible in Japan. These studies may act as a prototype of the postmarketing studies, fulfilling the standard for the comparative observational studies given in the ICH E2E guidelines. In the final report issued in the late 2011 from the advisory committee on the next amendment of the PAL and other system revisions of pharmaceutical affairs, it is recommended to introduce a new rule

where the re-examination period may be extended when the MAH conducts a legitimate pharmacoepidemiologic study. Another recommendation is to develop a mechanism to secure a proper relationship between researchers and funding bodies while assuring transparency (Advisory Committee for the MHLW, 2011).

## DATABASES IN JAPAN

Since around 2000, several commercially available databases have emerged in Japan, as in the list provided by Japanese Society for Pharmacoepidemiology (JSPE) (JSPE Task Force on Pharmacoepidemiology and Database, 2011). Those databases are relatively small, but two large databases are emerging. One is the database called the national database (NDB) containing the data of the health-care claims covering the whole Japanese population (about 130 million people) since 2009 and some of test results (blood pressure, plasma lipid, and fasting blood sugar) obtained in health screenings conducted under the "Act on Assurance of Medical Care for Elderly People" (enacted in 2010) where all the insurers had to provide an opportunity for health screening to insured persons aged 40 to 74. The MHLW published the guidelines on the use of the NDB for secondary purposes in March 2011 (MHLW, 2011a). According to the guideline, all the personal identifiers in the NDB are encrypted and the user should not attempt record linkage between the NDB and other data sources to protect privacy. The MHLW started a scheme to provide the NDB data for secondary purposes from April 2011. The period between April 2011 and March 2013 is defined as the "pilot study period," where the provision of the data is restricted to academia and central and local governments. In November 2011, six institutions (one central government, one local government, one national cancer center and three universities) were allowed to use the data extracted from the NDB for the first time.

Another large electronic health record (EHR)-type database is currently constructed also by the MHLW. The database will eventually organize data covering 10 million patients from hospital groups

in five areas in Japan and will be used initially by the PMDA to develop the system to find and examine signals for new drug–adverse event associations (PMDA, 2011c).

## NEW TRENDS IN PHARMACOVIGILANCE BY THE REGULATORY BODY

Traditionally, the contribution of the regulatory body to drug safety has mainly been achieved through regulating the drug companies, though there have been some exceptions, including collecting spontaneous reports directly from health professionals. However, in these several years, some activities for pharmacovigilance and risk management directly conducted by the regulatory body are emerging. For example, as mentioned earlier, the web-based system for patient reporting has been operated by the PMDA from early 2012 following the 1-year pilot study period in 2011 (PMDA, 2011b). Other activities include the development of “Japan Drug Information Institute in Pregnancy” ([www.ncchd.go.jp/kusuri/index.html](http://www.ncchd.go.jp/kusuri/index.html)) run under contract with the MHLW by the National Center for Child Health and Development (NCCHD) in collaboration with the “Motherisk program” in the hospital for sick children in Toronto, Canada (PMDA, 2007). After the 4-year enterprise of compiling the “ADR manuals” from 2005 to provide the information related to the serious ADRs to health professionals and patients, 75 manuals in 19 system organ classes are currently publicly available (MHLW, 2006). The medication guides for patients regarding the drugs which need special attention have been developed under the leadership of the regulatory body, and currently more than 1500 medication guides on various drugs are publicly available (PMDA, 2011d).

Another new activity in the PMDA is the “Medical Information for Risk Assessment Initiative” project, also called MIHARI (meaning monitoring or watching in Japanese) project (Endo *et al.*, 2010, 2011; PMDA, 2011e). The project was started in 2009, being stimulated in part by the Sentinel Initiative by the US Food and Drug Administration. In the project, using several kinds of electronic health information, pharmacoepidemiologic

methodologies to evaluate the risk of ADRs and methods to measure the impact of regulatory actions are developed. The methodologies developed in the MIHARI project will be used when the EHR-type database covering 10 million patients currently being developed by the MHLW (PMDA, 2011c) becomes ready for use.

## RISK MANAGEMENT PLAN AND RISK MINIMIZATION ACTION PLAN IN JAPAN

In April 2011, the MHLW made public the draft for the RMP guidance in Japan to ask for public comment on the draft by the end of October 2011 (MHLW, 2011b). The whole structure of the draft RMP guidance is similar to the EU-RMP published in 2005 (European Medicines Agency, 2005). For example, in the draft RMP guidance, the safety specification is regarded as the basis for both of the PVP and risk MAP as in the EU-RMP. However, being different from the EU-RMP, in the draft RMP guidance in Japan, the traditional DUI methodology is raised as an example of the methods to be used in the PVP in addition to the legitimate epidemiological designs like cohort study and case-control study.

In the draft guidance, tools for the risk MAP are classified as (1) provision of the additional information to health professionals as needed, (2) medication guide for patients, (3a) restriction of the drug use, including restriction of prescribers or institutions, (3b) mandatory registration of doctors and pharmacists for drugs with teratogenicity or other possibly serious reactions, (3c) careful selection of patients, informed consent from patients, and specific laboratory test as the condition of the drug use, and (4) other tools, including special display, container, and package of the drug. The draft guidance also requires a periodic report on the activities of the PVP and risk MAP and periodic reappraisal of the benefit–risk balance.

Several risk MAPs are already in operation in Japan. For example, thalidomide was approved for the treatment of multiple myeloma in October 2008 on the condition that the manufacturer implemented a risk management program designated the Thalidomide Education and Risk Management

System (TERMS) to manage the risk of teratogenicity of the drug (TERMS, 2008). TERMS is a facsimile-based system, but it is designed to incorporate all of the elements of the Systems for Thalidomide Education and Prescribing Safety (STEPS) (Uhl *et al.*, 2006). The procedures in TERMS have been modified many times since its introduction in 2008 according to the conclusion reached at the "TERMS evaluation committee," consisting of stakeholders, including those representing the MHLW, patients with multiple myeloma, thalidomide victims, and hematologists.

Another risk MAP currently in operation is called "RevMate" (RevMate, 2010), for lenalidomide, another teratogen, approved for the treatment of multiple myeloma and myelodysplastic syndrome, which is slightly different from "RevAssist" in the USA (RevAssist, 2007). For example, in RevMate, a mobile terminal device is used mainly by pharmacists to communicate with the center operated by the manufacturer, while in RevAssist the telephone is used as a major tool for communication between users (patients, doctors, pharmacists) and the center. In addition, the MHLW requires that RevMate and TERMS may be operated according to the same principle. For example, as in TERMS, lenalidomide is dispensed by the same hospital where the patient sees the doctor, and in this regard, RevMate is different from RevAssist, which assumes that lenalidomide is dispensed at the community pharmacies in the USA.

As in the USA and UK, for clozapine approved in 2009 in Japan, a system called the Clozaril Patient Monitoring Service (CPMS) (CPMS, 2009) has been introduced to minimize the risk of agranulocytosis and impaired glucose tolerance. In the CPMS, the web system operated by the manufacturer provides a tool where two or more of three participants (doctor, coordinator, and pharmacist) confirm each step needed to secure that the blood test is performed, and the test result does not preclude the prescription of clozapine.

For thalidomide, a system called the "Safety Management System for Unapproved Drugs" (SMUD) is operated by the Drug Safety Research Unit Japan under a contract with the MHLW (SMUD, 2009). Though SMUD was developed when thalidomide was not approved and imported

by individual doctors, SMUD was started in March 2010 more than 1 year after thalidomide was approved and TERMS was implemented. As the name indicates, SMUD may become a system for unapproved drugs in general, but currently the main roles of SMUD are restricted to registering patients and providing some functions of risk MAP for thalidomide, which is still imported by individual doctors even after the approval of thalidomide. Thalidomide approved in October 2008 has been used by patients with multiple myeloma only, and the off-label use of thalidomide has been strictly prohibited. Though there is no firm evidence for the efficacy of thalidomide for the treatment of diseases other than erythema nodosum leprosum (Sheskin, 1965) and multiple myeloma (Singhal *et al.*, 1999), thalidomide is still used for solid tumors and other diseases like Crohn's disease and Behcet's disease. Some patients with multiple myeloma are also treated by thalidomide imported by the individual doctors by various reasons, including that the qualified hematologist is not available in the hospital. The MHLW decided to operate SMUD even if it was developed originally as a temporary system for thalidomide under the circumstance where thalidomide was not approved. During the period of 14 months between March 2010 and May 2011, 485 patients were registered to SMUD, while 5575 patients were registered to TERMS during the period of 38 months between October 2008 and December 2011 (TERMS, 2008). Although the patients registered to SMUD are relatively minor compared with those registered to TERMS, those registered to SMUD are often a female patient of childbearing potential. As of May 2013, the fraction of the female patients with childbearing potential when registered to SMUD was 1.3% (1/79) in female patients with multiple myeloma, 10.8% (16/148) in those with other malignancies, and 34.8% (16/46) in those with nonmalignant diseases (SMUD, 2013). Since October 2010, the MHLW started to distribute a brochure with the information for safety use of thalidomide to the patients registered to SMUD. However, SMUD is a weak tool for risk minimization compared with TERMS. For example, the current SMUD does not have a mechanism to monitor the results of pregnancy tests on a real-time basis.

It is becoming increasingly easy for patients to obtain information via the Internet on a new drug that is not approved in their own country. In Japan, the approval of a new drug can often take several years after the original approval somewhere else in the world. Indeed, this is currently a major social issue in Japan. Although the regulatory body is making every effort to improve the situation, in particular by promoting clinical trials, the changes are being introduced slowly, mainly because improvements in the infrastructure needed to conduct the clinical studies are not yet well in place. The double standard for the risk MAP of thalidomide in Japan (Ooba *et al.*, 2010) may be resolved in finding the general measures to cope with problems associated with the delay of the new drug approval and the subsequent phenomenon that unapproved drugs are imported by individual doctors.

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# 15b

## Pharmacovigilance in Hong Kong

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### INTRODUCTION

Pharmacovigilance involves monitoring the safety of drugs and formulating effective strategies to reduce risks and maximize benefits associated with their use. It is the challenge of every drug regulatory authority to ensure that drugs in the market are safe, effective, and of good quality. National strategies to promote rational use of drugs are also required.

### REGULATION OF PHARMACEUTICAL PRODUCTS IN HONG KONG

In Hong Kong, regulation of pharmaceutical products is essentially provided by the Pharmacy and Poisons Ordinance (Cap 138) (PPO) and implemented through a two-tier monitoring system consisting of pre-marketing and post-marketing regulatory control.

For pre-marketing regulatory control, it is stipulated in the PPO that all pharmaceutical products in Hong Kong must be registered with a statutory body, the Pharmacy and Poisons Board (PPB), before sale. The PPB will ensure that only products which are safe, efficacious, and of good quality will be registered.

### PHARMACOVIGILANCE IN HONG KONG

Pharmacovigilance and territory-wide programs to promote the safe, rational, and effective use of medicines require the collaborative efforts among the government, healthcare professionals, Hospital Authority (HA), pharmaceutical industry, and academia.

In the past, pharmacovigilance focused mainly on the spontaneous reporting of adverse drug reactions (ADRs). In the 1980s, the Department of Clinical Pharmacology of the Chinese University

of Hong Kong started to promote ADR reporting in a general teaching hospital, and the scheme was later extended to other hospitals and the community (Chan and Critchley, 1993). Unfortunately, the reporting rate remained low despite active promotion (Chan and Critchley, 1994).

A survey in the 1980s revealed that few pharmacies in the public and private hospitals coordinated ADR reporting (Ho *et al.*, 1998).

In 2002, the HA introduced an electronic medication incident reporting system in the public hospitals and advised the frontline staff to report all medication incidents and ADRs (Cheung and Wang, 2002). Important drug safety information would be disseminated to their staff through regular newsletters and alerts.

The Department of Health (DH) established an ADR monitoring system in 2005. Healthcare professionals including doctors, Chinese medicine practitioners, dentists, and pharmacists are encouraged to report ADRs. The reports will be analyzed by professional staff for appropriate follow-up actions. Important information will be referred to the PPB for regulatory actions, such as restriction in use, introduction of specific warnings on the product label, or even product withdrawal.

## THE REORGANIZATION OF THE DRUG REGULATORY OFFICE IN HONG KONG

Following a number of incidents concerning pharmaceutical products in Hong Kong in 2009, the Government set up the Review Committee on Regulation of Pharmaceutical Products to review the existing drug regulatory regime and map out long-term measures to strengthen drug regulation.

As recommended by the Committee, the government reorganized the Pharmaceutical Service of the DH into the Drug Office in September 2011 to enhance its capability in drug regulation. The Pharmacovigilance and Risk Management Division was established under the Drug Office to strengthen pharmacovigilance in Hong Kong. The Division plans pharmacovigilance strategies, conducts risk analysis of ADR reports, and derives risk management plans. The ADR reporting system has been enhanced by introducing online reporting and pro-

moting ADR reporting among healthcare professionals and the pharmaceutical industry. Awareness of ADR reporting amongst pharmacists increased after the DH launched the ADR monitoring system (Hui and Lui, 2012).

## OTHER PHARMACOVIGILANCE ACTIVITIES IN HONG KONG

Nowadays, the scope of pharmacovigilance has been broadened to cover traditional and complementary medicines, substandard and counterfeit drugs, toxic exposures, and poisoning. In Hong Kong, the Trade Description Ordinance (cap 362) protects the consumers by prohibiting the trade of counterfeit products.

The following systems are also used to identify possible hazards caused by drugs:

**1 Drug Surveillance Program** Locally registered pharmaceutical products are subject to risk-based sampling by the DH for testing and compliance checking against their registered particulars. Furthermore, surveillance against health products in the local market for adulteration with undeclared medicines is also conducted. If problematic products are found, the DH will take appropriate actions, including in-depth investigation, instructing the traders to conduct product recall, and prosecution against the relevant parties.

**2 Toxicovigilance Program** In 2007, the Hong Kong Poison Control Network was jointly established by the DH, the HA, and the Chinese University of Hong Kong to adopt a proactive and coordinated approach in the prevention and control of poisoning incidents in Hong Kong. The Toxicovigilance Section was also set up in the DH to enhance epidemiology surveillance for identification of poisoning risk in the community and to strengthen investigation of poisoning incidents with public health significance referred from the HA so as to implement control measures in a timely manner.

**3 Monitoring of Drug Information from Overseas Authorities** To keep abreast of the latest global drug safety information, the DH keeps vigilant

to the announcements of various international and national health authorities. The DH will notify healthcare professionals, initiate investigation, and strengthen the regulatory measures as appropriate.

- 4 *Intelligence from the Public* The community is always an important source of intelligence on drug safety data. The DH maintains a hotline and an e-mail contact to receive drug-related complaints from the public and healthcare professionals.
- 5 *Communication with Stakeholders* When new drug safety information is identified, the DH issues letters to healthcare professionals and makes public announcement as appropriate. Drug safety information will also be summarized in a monthly bulletin, *Drug News*, as a reference for relevant stakeholders.

## FUTURE DEVELOPMENT

The pharmacovigilance system in Hong Kong will continue to be strengthened. The DH will set up a

pharmacovigilance advisory body to provide expert advice and technical assistance.

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# Pharmacovigilance in China

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## INTRODUCTION

Medication safety is closely related to the maintenance of rights and interests of public life and health. The Chinese Government pays great attention to medicine safety monitoring, and has constructed a pharmacovigilance system to ensure the safe use of medicines by the following works.

## CONSTRUCTION OF A NETWORK FOR REPORTING AND MONITORING ADVERSE DRUG REACTION

China officially joined the WHO Collaborating Center for International Drug Monitoring in 1998. The Measures on Administration of Monitoring of Adverse Drug Reactions (for Trial Implementation) were published in 1999, which defined the system of reporting and monitoring adverse drug

reactions (ADRs). In 2004, Measures on Administration of Reporting and Monitoring of Adverse Drug Reactions were published by the China Food and Drug Administration (CFDA). A national monitoring center, 34 provincial monitoring institutions, and 333 regional monitoring centers or stations for ADRs have been set up until 2011. A nationwide information network for monitoring of ADRs has been constructed, fulfilling electronic reporting and online real-time reporting. Since 2000, China has made significant progress in ADR reporting. The National Center for ADR Monitoring has received more than 3.15 million reports until December 2010, and issued 44 bulletins of ADRs by the end of January 2012, involving more than 80 kinds of drugs. This demonstrated the institutionalization of monitoring ADRs, as well as analyzing and evaluating drug safety signals in China; it also indicated the initial establishment of a pharmacovigilance system.

## CHINA ATTACHES IMPORTANCE TO RE-EVALUATION OF MARKETED DRUGS

On the basis of ADR monitoring, the drug administration departments have focused on a number of marketed drugs and launched special monitoring and retrospective analysis on them. Based on this re-evaluation, risk management has been implemented. To ensure the public drug safety, the drug administration departments have revised the directions for a number of drugs that were showing risks, such as puerarin, potassium dehydroandrograplide succinate and sodium bisulfite andrographolide injections; they have suspended the sale and use of drugs like herba houttuyniae injection, and abolished the manufacturing permission for those drugs with high risk and low therapeutic value, such as bimolane. Since 2007, China has carried out the re-evaluation of the safety of traditional Chinese medicine injections, and double checked the quality standard of traditional Chinese medicine injections, in order to promote the steady enhancing of the quality standard of traditional Chinese medicine injections. According to the applications of production enterprises, CFDA has canceled the brands and revoked the drug standards of Yanduqing injection and Ginseng stem leaf total saponin injection in 2007 and 2008, respectively. During the risk investigation of production and quality control of traditional Chinese medicine injections, those production enterprises unable to control product risk took the initiative to stop production; in addition, a few enterprises took the initiative to write off the certificate of approval of related traditional Chinese medicine injections. This indicated the interactive process of Chinese medicine production enterprises and drug administration departments during the application of pharmacovigilance.

## CHINA ATTACHES IMPORTANCE TO THE DEVELOPMENT OF LAWS AND REGULATIONS SYSTEM OF PHARMACOVIGILANCE

In 1984, the Drug Administration Law of the People's Republic of China was adopted in China. It

was for the first time that the research, production, management, and application of medicines were regulated by laws, and the legal responsibility of producing and selling counterfeit and inferior drugs was clearly defined, which indicated the entering of the legal track of Chinese medicine surveillance. This law was revised in 2001 and became the legal guarantee of strengthening medicine surveillance, ensuring medicine quality and protecting public rights of medication. According to the Drug Administration Law of the People's Republic of China, a series of regulations have been formulated by the national drug regulatory department, including Provisions for Drug Recall, Provisions for Drug Registration, Good Laboratory Practice for Non-clinical Laboratory Studies (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), Provisions for the Drug Distribution Licenses, and Good Supply Practice (GSP). The national drug regulatory department has also jointly issued provisions with the health, industry and commerce, and customs authorities, including Provisions for Adverse Drug Reaction Reporting and Monitoring, Standards for the Examination and Publicizing of Drug Advertisements, Provisions for the Examination of Drug Advertisements, Provisions for the Import Drugs, and Provisions for the Import and Export of Protein Assimilation Preparations and Peptide Hormones (Provisional).

These provisions came from the 30 years of work experience in drug surveillance and pharmacovigilance after China's reform and opening up, and played a great role in the maintenance of the normalization of drug research, production, distribution, and employment and in the guarantee of drug safety. The further improvement of current regulations and provisions of medicines is the foundation stone for constructing a long-term mechanism of Chinese drug risk management.

## CHINA PAYS ATTENTION TO THE SUBJECT SYSTEM CONSTRUCTION AND ACADEMIC EXCHANGE OF PHARMACOVIGILANCE

The *Chinese Journal of Pharmacoepidemiology* started publication in 1992; the first Conference on

Pharmacoepidemiology was held in China in 1995, with the first monograph for pharmacoepidemiology published in China in 1996; the Committee of Pharmacoepidemiology of the Chinese Pharmaceutical Association was set up in 2003; the *Chinese Journal of Pharmacovigilance* started publication in 2004; the first Asia Conference on Pharmacoepidemiology was jointly hosted by the International Society for Pharmacoepidemiology and the Committee of Clinical Drug Evaluation, and the Shanghai Society for Pharmacology in Shanghai, China in 2006; the first International Symposium on China Pharmacovigilance was jointly hosted by the National Center for ADR Monitoring and the Chinese Pharmaceutical Association in 2007; Proposed by the member of the Chinese Academy of Engineering Hong-Hao Zhou, jointly organized by the Chinese University of Hong Kong and the

Division of Medicine and Health, the Chinese Academy of Engineering, the Central South University, the University of London and the University of Bordeaux, the International Conference on Pharmacovigilance and Drug Safety has been held yearly in Changsha and Hong Kong since 2008.

The International Academic Communications on Pharmacovigilance is held by the Faculty of Medicine, Chinese Academy of Engineering regularly in China; the 6th Asia Conference on Pharmacoepidemiology was jointly hosted by the International Society for Pharmacoepidemiology and the Chinese Pharmaceutical Association in Beijing, China in 2011. These academic activities have improved the recognition of pharmacovigilance by Chinese medicine practitioners, promoted the publicity of pharmacovigilance methodology, and contributed for ensuring public drug safety.



# 15d

## China

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### INTRODUCTION

The National Center for Adverse Drug Reactions (ADR) Monitoring was initiated, with the support of the Ministry of Health (MOH), as early as 1988 (Yan-Min, n.d.) “to perform drug safety surveillance programs in 10 regional medical organizations within several cities and provinces in China.”

The National Center became a member of the World Health Organization (WHO) International Drug Monitoring Program in 1998. Since 1999 the National Center for Adverse Drug Reactions (ADR) Monitoring reports to the State Food and Drug Administration (SFDA), a division of the MOH.

China expected to accomplish 400 (adverse drug reaction) ADR monitoring centers (Yan-Min, n.d.) situated all throughout the country by the end of 2010.

Effective July 2011 (Du *et al.*, 2008) the “Adverse Drug Reaction Reporting and Monitoring Provi-

sion,” a drug safety surveillance-specific regulation under the Drug Administration Law of the People’s Republic of China, was revised by the MOH. As well as the original provisions on the ADR reporting process, the analysis, evaluation, and investigation of ADRs are now mandatory under the revised rule in order to establish a risk-based management system.

### ADVERSE DRUG REACTIONS REPORTING SCHEME

In accordance with Chapter 5 of the Drug Administration Law, it is mandatory for market authorization holders (MAHs) and healthcare professionals to monitor and report all ADRs and adverse drug events. Spontaneous reporting by consumers, on the other hand, can be filed by phone, fax, or online. A standardized form is available at [www.cdr.gov.cn](http://www.cdr.gov.cn) or [www.adr.gov.cn](http://www.adr.gov.cn).

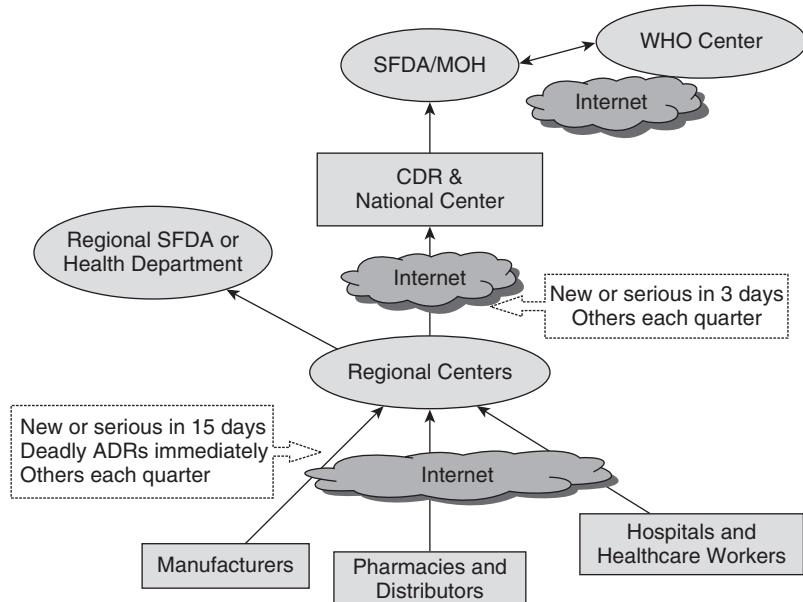


Figure 15d.1 ADR monitoring and reporting scheme in China. Source: Du *et al.* (2008). Reproduced with permission of Elsevier.

Reports made to the provincial centers will be analyzed and transmitted to the National Center for Adverse Drug Reactions (ADR) Monitoring at the SFDA. The SFDA will then implement regulatory actions as appropriate. Possible outcomes include modification of package inserts, conversion of over-the counter (OTC) drugs to prescription drugs, and suspension of sales and use of some drugs.

Under the international monitoring program, these reports are submitted to the Uppsala Monitoring Center (UMC) in Sweden for inclusion into the WHO database – VigiBase.

An overview of the monitoring and reporting scheme in China is shown in Figure 15d.1.

## ACTIVITIES

A total of 692 904 reports (*China Pharmaceutical Newsletter*, 2011), 84.7% of which were sent in by healthcare professionals, were received in 2010. The current population of China is 1 338 299 511 (The World Bank, n.d.). Compared with the 170 000

cases reported in 2005, the rapid increase is attributed to the establishment of an organized ADR system resulting in the increase in the utilization rate of reports over the last 20 years.

Traditional Chinese medicine (TCM) products are regulated as drugs in China; thus, all related ADRs are also reported. Of the 3 150 000 reports received by the National Center for Adverse Drug Reactions (ADR) Monitoring from 1988 to 2010, 13.8% (Zhang *et al.*, 2012) represent TCM.

A nationwide computerized ADR surveillance information system was established in 2003 in order to facilitate public safety communications. The website registered 40 826 users<sup>5</sup> in 2010, 53.4% of whom were medical institutions, 39% were MAHs, and 7.6% were consumers.

In 2011, the National Center for Adverse Drug Reactions (ADR) Monitoring at the SFDA and the UMC signed an agreement on a 2-year project entitled “Standardization Study and Application of Adverse Drug Reaction Monitoring” (UMC, 2011). The five-part study aims to enhance data exchange from China’s ADR monitoring database and the WHO global database. Part of the challenge is to

translate the large Chinese-language database into English for global harmonization of safety analysis.

The National Center for Adverse Drug Reactions (ADR) Monitoring has two publications: the *ADR Information Bulletin* and the *Chinese Journal of Pharmacovigilance*. The former publishes warnings and signals generated by the national ADR database, while the latter covers a wide range of drug safety issues, such as developments in pharmacovigilance. Ten volumes of the *ADR Information Bulletin* were released in 2010 (*China Pharmaceutical Newsletter*, 2011). Furthermore, safety information regarding foreign drugs was disseminated through 15 volumes of the *Drug Alerts Newsletter*, also released in 2010 (*China Pharmaceutical Newsletter*, 2011).

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**15e**

# Malaysia

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## INTRODUCTION

The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) was established under the Drug Control Authority (DCA) Ministry of Health Malaysia “to ensure the safety of Malaysians through the continuous assessment of the safety profiles of drugs registered for use in this country” (NPCB, n.d.). In 1990, the National Drug Safety Monitoring Center was accepted as the 30th member of the World Health Organization (WHO) International Drug Monitoring Program. Both MADRAC and the National Drug Safety Monitoring Center are under the National Pharmaceutical Control Bureau (NPCB), a division of the DCA.

In accordance with Section 28 of the Control of Drugs and Cosmetics Regulations 1984 (MOH, n.d.), Sale of Drugs Act 1952 (revised 1989), it is mandatory for market authorization holders to submit reports of all encountered adverse drug reactions (ADRs) to the DCA. Although ADR reporting by healthcare professionals is on a voluntary basis, submission of ADR reports is highly encouraged through the provision of the standardized ADR reporting forms with prepaid postage.

Consumers and other concerned individuals may also report ADRs through the NPCB website (<http://www.bpfk.gov.my>), by simply clicking the “Reporting medication problem” icon on the bottom of the page and then selecting the appropriate reporter type icon. An online form can then be downloaded and submitted either electronically or through the post. In response, a letter of acknowledgment with its corresponding MADRAC database case report number will be sent to the reporter.

The report is then evaluated by the MADRAC and feedback is given to both the reporter and the DCA for appropriate action. Once the case is proven to require a regulatory action, a policy is then prepared for implementation by the DCA. Possible outcomes include labeling changes, usage restrictions, control on sale of products, or drug recall and product withdrawal.

In agreement with the WHO, all ADR reports that have been received and screened by MADRAC

are forwarded to the Uppsala Monitoring Centre (UMC) in Sweden for inclusion into the WHO database – VigiBase.

## ACTIVITIES

A total of 7079 reports, 84.4% of which were sent in by healthcare professionals from the government sector, were received in 2010 (NPCB, n.d.). The current population of Malaysia is 28401017 (The World Bank, n.d.). Compared with the number of reports received in year 2009, there is a notable 21% increase in submissions. MADRAC, composed of a chairman, a secretary, and 10 members, met six times over the same year and reviewed 5615 cases.

The committee participates and also conducts nationwide pharmacovigilance seminars to increase awareness of the importance of reporting adverse events of drugs and vaccines, and to improve the quality of ADR reports submitted. There is an observed increase in reporting by healthcare professionals from both the government sector (from 4698 reports in 2009 to 5976 in 2010) and private sector (144 reports in 2009 to 248 reports in 2010).

In addition to an annual report, MADRAC also publishes an ADR newsletter three times a year that discusses regulatory matters, safety issues of current interest, and other updates. Both are accessible through the website.

## CONTACTS

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# Philippines

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## INTRODUCTION

Pursuant to Department Order 345-Is of the Department of Health (DOH) and jointly supported by the Australian Agency for International Development, the National Adverse Drug Reaction Advisory Committee (NADRAC) was created in 1994 (Hartigan-Go, 2002). It was established to assist the Philippine Food and Drug Administration (FDA), then known as the Bureau of Food and Drugs, in matters related to adverse drug reactions (ADRs) monitoring. The Adverse Drug Reaction Monitoring Programme, now renamed the National Pharmacovigilance Center (NPC-FDA), was accepted as the 42nd member of the World Health Organization (WHO) International Drug Monitoring Program in 1995. Since then, the Philippines has contributed 9809 individual case safety reports (ICSRs) to the database, on May 2012 (Uppsala

Monitoring Centre, [www.who-umc.org](http://www.who-umc.org), personal communication).

The Philippine FDA Act of 2009 and its Implementing Rules and Regulations (FDA, n.d.a) marked several initiatives to strengthen the agencies' postmarket surveillance system. Currently, a policy (FDA, n.d.b) on the NPC-FDA is being institutionalized to meet future challenges presented by ADR monitoring.

## ADVERSE DRUG REACTION REPORTING SCHEME

As mandated by law, market authorization holders (MAHs) submit reports of encountered ADRs and provide standard operating procedures for handling ADRs to the FDA. Healthcare professionals and consumers, on the other hand, may submit

ADR reports through a standardized ADR reporting form available online ([https://www.fda.gov.ph/sysFDA\\_WorkFlow/en/classic/63866899151ef25b75f7f59042808866/ADR\\_Form.php](https://www.fda.gov.ph/sysFDA_WorkFlow/en/classic/63866899151ef25b75f7f59042808866/ADR_Form.php)). This newly installed Adverse Drug Online Reporting System reflects the implementation of the Department of Health's program on Pharmacovigilance (FDA, 2012).

The NPC-FDA shall then receive, encode on the database, and consolidate all reports. Relevant serious reports will be forwarded to the regulators after analysis by the Advisory Committee, after which the necessary recommendations on regulatory measures will be implemented as appropriate. Anticipated outcomes include regulatory actions like revision of package inserts, drug withdrawal, and/or public information campaigns, such as the ADR newsletter or "Dear Doctor" letters. Consequently, feedback and relevant information will be provided to the end-users.

Under the international monitoring program, these reports are submitted to the Uppsala Monitoring Centre in Sweden for inclusion into the WHO global ICSR database system – VigiBase.

## ACTIVITIES

In addition to online drug alerts and through the media, the NPC-FDA also releases *Signals* – a twice yearly ADR newsletter (Hartigan-Go, 1998; DOH, n.d.). Though not country specific, *Signals* provides the public with the latest international drug safety alert information.

The control of local traditional (herbal and alternative) medicines (TMs) is still not covered under the revised postmarketing surveillance system of the NPC-FDA. In the Philippines, it is highly unlikely for those who practice TM to participate in ADR reporting, unlike Western-trained doctors (Hartigan-Go, 2002). There are even products used in this practice that are not fully evaluated for quality, efficacy, and safety.

From 2007–2008, a pilot study on consumer reporting was conducted in Davao City by the FDA with the support of the WHO Western Pacific Regional Office (Lim, n.d.). The study proved the

significant contribution of consumer reporting not only for drug-related issues, but also on unauthorized practices by drug sellers; 68% of the reports received were found accurate.

In 2010, a series of training on pharmacovigilance as provided by the FDA to equip health workers in the recognition, monitoring, reporting and management of ADRs specifically in government hospitals. This aims to improve the low reporting rates observed from health care professionals relative to the 93 261 000 (The World Bank, n.d.) population of the country.

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# 15g

## Singapore

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### INTRODUCTION

The Vigilance Branch (VB), formerly known as the Adverse Drug Reaction Monitoring Unit, was established under the Health Sciences Authority (HSA) of Singapore in 1993 ([www.hsa.gov.sg](http://www.hsa.gov.sg)) “to collate and review adverse drug reaction (ADR) reports”. Singapore was accepted as the 40th member of the World Health Organization (WHO) International Drug Monitoring Program in 1994. A Pharmacovigilance Advisory Committee (PVAC), appointed by the HSA, performs major drug safety assessments and advises the HSA on corresponding appropriate regulatory actions.

### ADVERSE DRUG REACTION REPORTING SCHEME

Spontaneous reports from healthcare professionals are received online, by mail, or by fax. Periodic safety reports, on the other hand, are mandatorily submitted by pharmaceutical companies every 6 months for the first 2 years of marketing in Singapore, annually for the subsequent 3 years, and at the first renewal of the product license. A standardized ADR reporting form is available at [www.hsa.gov.sg](http://www.hsa.gov.sg).

These reports are then screened and captured into the national ADR database for aggregate

analysis. VB also uses other postmarketing risk assessment approaches, such as literature review and exchange of regulatory information with other international drug regulatory bodies. Possible outcomes include product label amendments, product withdrawals, and suspensions.

Under the international monitoring program, these reports are submitted to the Uppsala Monitoring Centre (UMC) in Sweden for inclusion into the WHO database – VigiBase.

## ACTIVITIES

A steady rate of over 500 ADR reports per million inhabitants per year has been maintained by Singapore for the past 5 years (HSA, 2011). A total of 29 769 reports (*Adverse Drug Reaction News*, 2011) were received in 2010, of which 54.4% and 39.4% were sent in by healthcare professionals from the government clinics and public hospitals, respectively. The current population of Singapore is 5 076 700 (The World Bank, n.d.). Singapore was ranked second in terms of ADR report submission by the WHO Collaborating Center for International Drug Monitoring at the UMC – a significant six-spot climb from its eighth position in 2009. The increase was attributed to the addition of nonserious adverse event (AE) terms (e.g., rash, watery eyes) received from the national electronic medical record exchange, known as the Critical Medical Information Store (CMIS), to the AE database (*Adverse Drug Reaction News*, 2011). The CMIS initiative serves “to facilitate the incorporation of quantitative signal detection and data mining tools.”

Several initiatives to strengthen risk communication and safety assessment for medical devices, traditional medicines, cosmetics, vaccines, and cell and tissue therapies were also implemented by the HSA in 2010. A total of 214 risk assessments (HSA, 2011) on health products were carried out which led to regulatory changes.

Outreach programs and seminars for healthcare professionals were conducted by the HSA to further promote AE report submissions. Together with the WHO and UMC, the HSA Health Products Regulation Group hosted a five-day Basic Pharma-

covigilance Training Course in 2010 (HSA, 2010). The course equipped participants from ASEAN countries with the necessary skills to strengthen pharmacovigilance capabilities in their respective countries. The event featured local and international pharmacovigilance experts and offered a curriculum that included the management of traditional medicines and ADR reporting.

In addition to a published annual report, VB also provides information to end-users through the *ADR News Bulletin* published thrice yearly, Dear Healthcare Professionals Letters, and Drug Alerts (*Adverse Drug Reaction News*, 2011).

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# 15h

## Thailand

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### INTRODUCTION

The Thailand National Pharmacovigilance Center was established by the Ministry of Public Health (MOPH), under the responsibility of the Thai Food and Drug Administration (TFDA), in 1983 (MOPH, n.d.a). The center, with a mandate to collect and interpret reports of adverse events from health products, is the 26th member of the World Health Organization (WHO) International Drug Monitoring Program.

Following the Eighth National Social and Economic Development Plan (1997–2001), product monitoring was further expanded to include narcotic drugs, foods, cosmetics, medical devices, and toxic substances for home use with the creation of the Health Product Vigilance Center (HPVC). From an initial 19 regional centers in 1992, there are currently 23 centers all over the country.

### ADVERSE PRODUCT REACTIONS REPORTING SCHEME

Within the adverse product reactions (APRs) reporting scheme (MOPH, n.d.a,b; SIAPS 2013), a standardized reporting form can be requested from the HPVC, the *Medical and Health Product Journal*, or downloaded from <http://thaihpvc.fda.moph.go.th/thaihvc/index.jsf>.

Reports are assessed and submitted voluntarily by healthcare professionals to the regional centers established within hospitals throughout Thailand. Consumers are currently not allowed to directly report adverse product reactions (APRs) (Jarernsirisopornkul *et al.*, 2009a). The regional centers, in turn, will then file and evaluate these reports before sending them to the national pharmacovigilance center located at the TFDA. Feedback is provided at the national level.



Active ICSRs in the WHO global ICSR database per million inhabitants and year  
Period covers 2007-05-08 and 2012-05-08

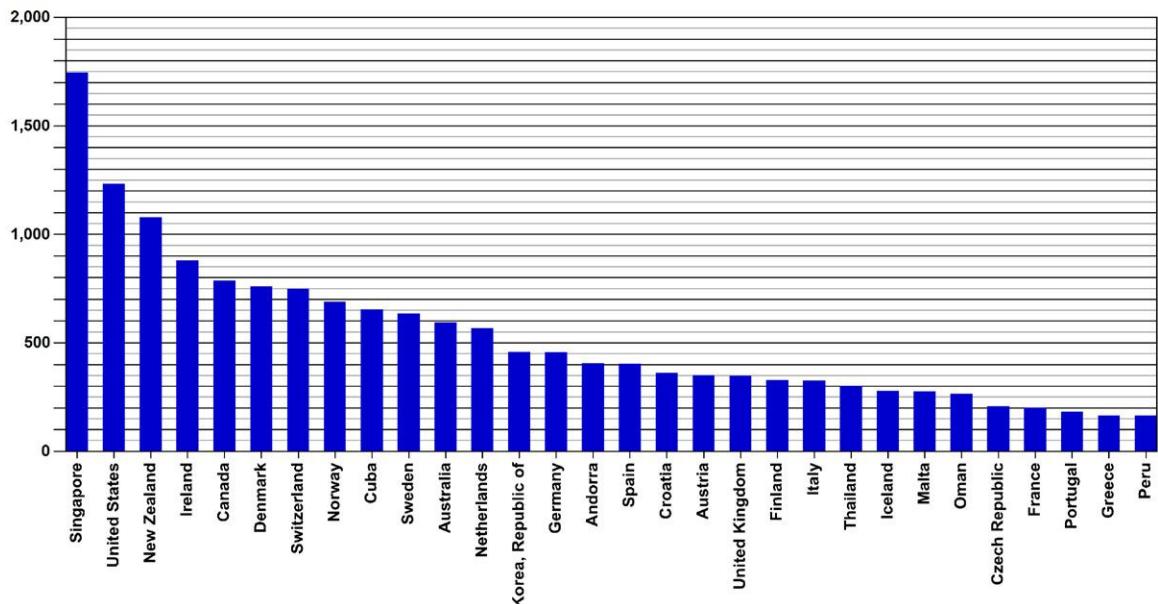


Figure 15h.1 Active ICSRs in the WHO global ICSR database per million inhabitants and year for the period May 2007 to May 2012. Source: Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, through personal correspondence.

Reports are evaluated using epidemiologic data and appropriate statistical tools. Possible outcomes include appropriate regulatory changes and the dissemination of information to the consumers.

Under the monitoring program protocol, all reports collected and analyzed by the national center will be submitted to the Uppsala Monitoring Centre ([www.who-umc.org](http://www.who-umc.org)) in Sweden for inclusion to the WHO global individual case safety report (ICSR) database system – VigiBase.

## ACTIVITIES

Thailand is consistently among the top 10 contributors globally for adverse drug reaction reports. This is based on the total ICSRs submitted into Vigi-

Base for a prescribed period of time since the year 2000 (Lindquist, 2008; UMC, personal communication). For a country with a population of 69 122 000 in 2010 (The World Bank, n.d.), the country contributed 187 944 ICSRs in May 2012 alone. Figure 15h.1 shows the active ICSRs in VigiBase per million inhabitants and year for the period May 2007 to May 2012 (UMC, personal communication).

Starting in 1989, postmarketing surveillance for newly licensed drugs is done through the Safety Monitoring Program (SMP) (Jarernsiripornkul *et al.*, 2009a; MOPH, n.d.a). Additional product labels, such as “Must Monitor”, “For Health Care Agency Use Only” or “For Hospital Use Only,” are required to facilitate APR reporting of doctors during the first 2 years of product use. SMP find-

ings are regularly published in annual professional conferences for both manufacturers and hospital staff (Jarernsiripornkul *et al.*, 2009b).

As a supplement to the Hospital Accreditation Program launched by the MOPH, a standard protocol regarding the ADR Prevention Program was launched in 2000 to prevent recurrent adverse drug events. Although the quality assurance program was found effective, further policies are still recommended to improve its sustainability (Chaikoolvattana *et al.*, 2006).

In addition to an annual report distributed to healthcare professionals throughout the country, drug newsletters and other health information are also provided to hospitals and government healthcare offices every 3 months.

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### **INTRODUCTION**

The Adverse Drug Reaction (ADR) Monitoring Center in Vietnam was accepted as the 56th member of the World Health Organization Adverse Drug Reactions on International Drug Monitoring Program in 1998. To further strengthen pharmacovigilance activities in the country, the National Center for Drug Information and Adverse Drug Reactions Monitoring (DI & ADR) was established under the Vietnam Drug Administration Department of the Ministry of Health (MOH) in accordance with Decision 991/QS-BYT of 2009 (DI & ADR, n.d.).

The center functions to help the MOH (1) build up and update the drug database, (2) provide information on pharmacovigilance, (3) conduct training, (4) conduct research, (5) provide guidelines to health establishments at different levels, (6) practice international cooperation and consultancy, and (7)

provide other services in the field of drug information and pharmacovigilance. As of January 2010, all adverse drug reaction (ADR) reports from regional and local monitoring centers are sent to the National Center for DI & ADR.

### **ADVERSE DRUG REACTION MONITORING SCHEME**

It is mandatory for market authorization holders in Vietnam to report ADRs to the MOH. However, current regulations do not require ADR reporting from research and treatment facilities (Thu Thuy, 2011). Voluntary reporting by both healthcare personnel and consumers can be done online through <http://canhgiacduoc.org.vn/en/CanhGiacDuoc/ADROnline.aspx> (in Vietnamese). Completed ADR forms can also be sent to the DI & ADR by post, e-mail, or fax.

After receipt and classification of the ADR reports, a consultation group then evaluates the reports. Feedback is subsequently given, as appropriate, to both the MOH and the reporters.

Under the monitoring program, all ADR reports that have been received and screened by the National Center for DI & ADR are submitted to the Uppsala Monitoring Center (UMC, [www.who-umc.org](http://www.who-umc.org)) in Sweden for inclusion into the WHO global individual case safety report (ICSR) database system – VigiBase.

From the period 2009–2010, reports received were in the vicinity of 2000 (DI & ADR, n.d.), for a population of 86 928 000 (The World Bank, n.d.). And for the period 2007–2012, the country ranked 60th in the active ICSRs in VigiBase per million inhabitants and year. Vietnam contributed 9602 ICSRs in May 2012 (UMC, personal communication).

## ACTIVITIES

Vietnam National Center for DI & ADR also focuses on providing education and training for healthcare professionals in the country, with 10 classes conducted per year from year 2001 to 2006. Information (such as health advice) is shared with the public via telecommunication media and through posters and publications.

A sentinel site-based pilot active surveillance pharmacovigilance in the Vietnam Antiretroviral (ARV) Therapy Program (Joshi and Stergachis, 2010) was proposed by the Strengthening Pharmaceutical Systems Program and United States Agency for International Development in cooperation with the local government in 2010. The activity, targeted specifically at the use of ARV regimens, aims to develop, implement, and demonstrate a practical and sustainable active medicines surveillance system across the country. In connection with the project, several capacity trainings to build operational efficiency for the center staff were conducted.

Other groups that have contributed to knowledge and practices on pharmacovigilance include the

World Health Organization and the International Society of Pharmacovigilance. In 2009, these groups conducted a pharmacovigilance training program in coordination with the Hanoi University of Pharmacy (Hartigan-Go, 2009).

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# Pharmacovigilance in India

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## INTRODUCTION

India is a vast country with a pharmaceutical industry valued at \$18 billion and growing at the rate of 12–14% per annum and exporting nearly 40% of generic medicines worldwide. India is also emerging rapidly as a hub for global clinical research and a destination for drug discovery and development with several outsourced projects in pharmacovigilance. In addition new chemical entities are being introduced into the country, which is reflected by the increased total number of applications received and processed, which doubled from 10 000 in 2005 to 22 806 in 2009 at the Central Drugs Standard Control Organization (CDSCO), HQ, New Delhi.

In a vast country like India, with a population of over 1.2 billion and with vast ethnic variability, different disease prevalence patterns, the practice of

different systems of medicines, and different socio-economic status, it is important to have a standardized and robust pharmacovigilance and drug safety monitoring program for the nation.

## HISTORY OF PHARMACOVIGILANCE IN INDIA

In India, consideration for the surveillance of adverse drug reactions (ADRs) developed relatively late, as traditionally there was no concept of surveillance of medicines in India. Even though pharmacovigilance is still in its infancy, it is not new to India. It was not until 1986, when a few physicians, mainly from academic institutions, called for greater attention to be devoted to the potential adverse effects of prescription medicines and rational prescribing of medicines. This led to

formation of the first ADR monitoring program consisting of 12 regional centers, each covering a population of 50 million, but was unsuccessful (Kulkarni, 1986).

Nothing much happened until a decade later when, in 1997, India formally joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Program based in Uppsala, Sweden. Three centers for ADR monitoring were identified, mainly based in the teaching hospitals: a National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi, and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs to medicines marketed in India. However, they were non-functional, as information about the need to report ADRs and about the functions of these monitoring centers never reached the prescribers and there was lack of funding from the government. This attempt was also unsuccessful; hence, again from January 1, 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program (NPVP) for India was made operational (CDSCO, 2004).

The NPVP, established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based at CDSCO. Two zonal centers – the south-west zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the north-east zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi) – were to collate information from all over the country and send it to the committee as well as to the Uppsala Monitoring Centre in Sweden. Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center in turn would have several peripheral centers (24 in total) reporting to it. The program had three broad objectives: the short-term objective was to foster a reporting culture, the intermediate objective was to involve a large number of healthcare professionals in the system in information dissemination, and the long-term objective was for the program to be a benchmark

for global drug monitoring. However, this program also failed (Biswas and Biswas, 2007).

## **THE CURRENT PHARMACOVIGILANCE PROGRAM IN INDIA**

Recognizing the need to restart the NPVP, in a brainstorming workshop jointly organized by Department of Pharmacology, AIIMS and CDSCO in late 2009, the framework of the new and current program was formulated. The program now rechristened as the Pharmacovigilance Programme for India (PvPI) was operational from mid July 2010 (CDSCO, n.d.a). This program was coordinated by the Department of Pharmacology at AIIMS as a National Coordinating Centre (NCC). With an aim to monitor the benefit and risk profile of medicines, the Union Ministry of Health recently appointed the Indian Pharmacopoeia Commission (IPC) as the NCC for PvPI. The main aim of the NCC at the IPC will be to generate independent data on the safety of medicines that will be on a par with global drug safety monitoring standards.

## **FRAMEWORK OF THE NEW PROGRAM**

The center at the IPC will focus on developing India's own database on drug information and ADRs so that India will not have to be dependent on data from other countries to take decisions relating to banning and suspension of drugs. As of now, India does not have a strong database on ADRs and has to depend on information from Western countries. So far, only 2823 ADRs have been reported since September 2010 under the current PvPI, which is very small to draw any meaningful conclusion implicated for any particular signal. It is being envisaged that all the medical institutions, hospitals, colleges, and public health programs in the country, both government and private, will take part in the PvPI and report ADRs to the IPC so that all the data generated will be collated and analyzed at one place.

The program will be administered and monitored by

- 1 a steering committee and
- 2 a working group.

Technical support will be provided by

- 1 a signal review panel
- 2 a core training panel, and
- 3 a quality review panel.

The ADR reports will be collected from the following centers:

- 1 Medical Council of India (MCI)-approved medical colleges and hospitals;
- 2 private hospitals;
- 3 public health programs; and
- 4 autonomous institutions (Indian Council of Medical Research, etc.).

The *mission* of the program is to safeguard the health of the Indian population by ensuring that the benefits of use of medicine outweigh the risks associated with its use, while the *vision* is to improve patient safety and welfare in the Indian population by monitoring drug safety, thereby reducing the risk associated with use of medicines.

The objectives of the program are:

- to create a nationwide system for patient safety reporting;
- to identify and analyze new signals (ADR) from the reported cases;
- to analyze the benefit/risk ratio of marketed medications;
- to generate evidence-based information on safety of medicines;
- to support regulatory agencies in the decision-making process on use of medications;
- to communicate safety information on use of medicines to various stakeholders to minimize risk;
- to emerge as a national center of excellence for pharmacovigilance activities;
- to collaborate with other national centers for the exchange of information and data management;
- to provide training and consultancy support to other national pharmacovigilance centers.

The program was envisaged to be rolled out in three phases. Phase I would include 40 ADR monitoring centers (AMCs) to be rolled out in 2010. The program would be expanded in phase II to include up to 140 MCI-recognized medical colleges by 2011. Until the end of 2011 a total of 60 AMCs only were included. Phase III was ultimately intended to cover the entire healthcare system by 2013. The AMCs will get operational and logistic support from the respective zonal CDSCO centers, situated at Ghaziabad, Kolkata, Mumbai, and Chennai. The zonal CDSCO centers will be under administrative control of the CDSCO headquarters at New Delhi.

## **ADVERSE DRUG REACTION DATA FLOW**

ADR reports will be collected at the AMC by the pharmacovigilance staff, who will check for validity of the report and conduct provisional causality assessment. The ADR forms will then be dispatched to the coordinating center. The AMC staff will maintain a log of all the center activities, and selected AMCs will also carry out focused ADR monitoring of drugs as per the watch list.

The coordinating center will conduct causality assessment and upload the reports into the pharmacovigilance database. The coordinating center will prepare a consolidated report of ADRs collected at defined time intervals and will implement and integrate pharmacovigilance activities into public health programs involving mass usage of drugs. Lastly, the integrated ADR data will be transmitted through the Vigiflow interface into the Uppsala Monitoring Centre ADR database, where signal processing can be carried out.

## **ENSURING QUALITY OF ADVERSE DRUG REACTION DATA**

A quality review panel has been constituted for maintaining quality assurance in the program. All the centers will be assessed based on performance metrics criteria, completeness of reports, training imparted, and other parameters mentioned in the

pharmacovigilance program protocol. Following this assessment, performance-based incentives will be provided to the centers.

## **IMPLEMENTATION OF THE PHARMACOVIGILANCE PROGRAMME FOR INDIA**

The IPC understands the need for establishing local hospital-based centers across the nation for better patient safety. In a vast country like India, with a huge population and vast ethnic variability, different disease prevalence patterns, the practice of different systems of medicines, and different socio-economic status, it is important to have a standardized and robust pharmacovigilance program for the nation. The IPC is also working towards having good business relations with other international monitoring bodies to ensure that India has a greater role in reporting of ADRs.

## **PROGRAM VISIBILITY, COMMUNICATION, AND FEEDBACK**

A website dedicated to pharmacovigilance will be created by CDSCO. In phase II of the program there will be a provision of online reporting of ADRs by healthcare professionals not covered under the program. The CDSCO headquarters in collaboration with the NCC will publish a quarterly *Medicine Safety Newsletter* comprising 4–16 pages. Approximately 3000 copies will be printed for circulation to healthcare institutions across the nation. A Medicine Safety Card will be included in the *Medicine Safety Newsletter*, and in national medical journals, to ensure that healthcare professionals not covered under the program can report ADRs directly to any of the centers. This will create awareness about the program and ensure reporters get adequate feedback and remain motivated. In addition, to enhance the awareness and visibility of the program, focused workshops, symposia, and group meetings on ADR reporting and causality assessment will be carried out at regular intervals by all the centers.

## **PHARMACOVIGILANCE REGULATIONS IN INDIA**

### **SCHEDULE Y**

Legislative requirements of pharmacovigilance in India are guided by specifications of Schedule Y of the Drugs and Cosmetics Act 1945. Schedule Y also deals with regulations relating to preclinical and clinical studies for development of a new drug as well as clinical trial requirements for import, manufacture, and obtaining marketing approval for a new drug in India. Schedule Y was revised and amended, on January 20, 2005, as continued commitment of Drug Controller General of India (DCGI) to ensure adequate compliance of pharmacovigilance obligations of pharmaceutical companies (CDSCO, n.d.b). An attempt has been made in the amended Schedule Y to better define the roles and responsibilities of pharmaceutical companies for their products as well as relating to reporting of adverse events from clinical trials.

### **SPONTANEOUS ADVERSE DRUG REACTIONS**

Schedule Y specifies that all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant, with follow-up information provided. Individual adverse reaction reports should be included in the next periodic safety update report, and not necessarily in an urgent manner. However, further details regarding the capture, evaluation, and follow up of adverse reactions have not been addressed in Schedule Y. Pharmaceutical companies in India, therefore, rely on the guidance from ICH E2D for handling of spontaneous reports for marketed products.

### **SAFETY REPORTING DURING CLINICAL TRIALS**

As per amended Schedule Y, the sponsor's responsibilities include reporting of serious adverse events as follows:

Any unexpected serious adverse event (SAE) (as defined in GCP guidelines) occurring during a clinical trial should be communicated promptly

(within 14 calendar days) by the sponsor to the licensing authority and to other investigator(s) participating in the study (Appendix XI).

However, Schedule Y does not provide any guidance on the procedure to determine the expectedness of an adverse event.

Also, as per Schedule Y, during the conduct of a clinical trial or its follow up, it is the responsibility of an investigator to ensure adequate medical care to the subjects suffering with adverse events. Regarding reporting responsibilities of the investigators, Schedule Y states that:

Investigator(s) shall report all serious and unexpected adverse events to the sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol with seven working days of their occurrence.

However, Schedule Y does not specify the rules regarding the reporting of foreign cases from multinational trials and lacks further details on the procedures for unblinding, coding, data monitoring committees, annual safety reports, and handling of the adverse events associated with placebo or comparator drugs.

## CONCLUSION

Pharmacovigilance is a complex process, and robust systems are essential to undertake the activity. The foundation for building a robust pharmacovigilance system has already been laid by the DCGI. However, the system needs to be refined with the help of pharmacovigilance experts in collaboration with information technology. With more and more clinical research and pharmacovigilance outsourcing work now being conducted in India, it will be worthwhile for the DCGI to invest in a robust pharmacovigilance system, to enable assessors and decision makers to analyze safety data and take regulatory decisions without the need to depend on other countries. The DCGI should take some tough decisions and make commitments to make pharmacovigilance mandatory and start the culture of pharmacovigilance inspections.

Pharmaceutical companies will need to show both regulators and consumers that they are doing everything possible to assure drug safety, while finding more effective approaches to manage drug safety data.

Reporting of ADRs should be actively encouraged and should involve concerned stakeholders. To enhance and facilitate this, a culture of learning about pharmacovigilance should start early in the professional training of healthcare students. This will help healthcare professionals to understand the subject and also create awareness by giving adequate information to patients at the start of any treatment about the potential benefits and risks of the therapy.

The DCGI has shown its commitment to ensure safe use of drugs by establishing the NPVP. More and more clinical trials are now being conducted in India, and business process outsourcings based in India are now also undertaking pharmacovigilance projects. Healthcare professionals, consumer groups, nongovernmental organizations, and hospitals should appreciate that there is now a system in place to collect and analyze adverse event data. They should start reporting adverse events actively and participate in the NPVP to help ensure that people in India receive safe drugs.

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## **Part II: PHARMACOVIGILANCE SYSTEMS**

### **Pharmacovigilance in New Zealand and Australia**

# **16a**

## **Pharmacovigilance in New Zealand**

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### **INTRODUCTION**

New Zealand (NZ) is a small country of approximately 4 million people that has developed pharmacovigilance systems which have been “admired and envied” by international experts in medicines safety (Herxheimer *et al.*, 2004). Pharmacovigilance in NZ began in 1965 when a national spontaneous reporting program was implemented following the thalidomide tragedy in the early 1960s (McBride, 1961). In 1968, NZ was one of the founding members of the World Health Organization (WHO) International Drug Monitoring Programme and over 40 years later remains an active contributor to it.

### **ORGANIZATION OF PHARMACOVIGILANCE IN NEW ZEALAND**

The organization of pharmacovigilance in NZ is shown in Figure 16a.1.

Medsafe, the NZ medicines and medical devices safety authority (<http://www.medsafe.govt.nz/>), has overall responsibility for pharmacovigilance in NZ. Medsafe is a regulatory unit of the Ministry of Health and applies international guidelines to its pre- and postmarket medicines evaluation processes for medicines, including assessment of risk management plans, conducting risk–benefit reviews, and publishing product data sheets and consumer medicine information.

Unlike most other countries, Medsafe does not collect and review individual case safety reports (ICSRs) but rather contracts the New Zealand Pharmacovigilance Centre (NZPhvC) at the University of Otago to operate nationwide postmarketing data collection, analyses, and surveillance programs (see below) on its behalf. Collection of patient data by the NZPhvC is in line with the Health Information Privacy Code 1994 (<http://privacy.org.nz/health-information-privacy-code/>).

Medsafe and the NZPhvC teleconference regularly to plan work programs, review selected ICSRs, and identify potential issues. Medsafe utilizes

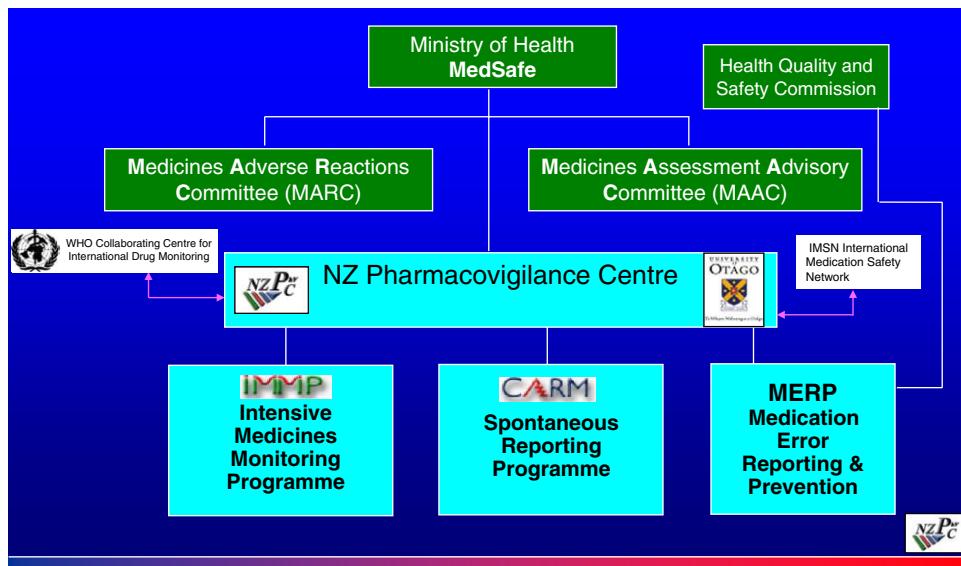


Figure 16a.1 Organization of pharmacovigilance in NZ.

summaries of ICSRs and analyses provided by the NZPhvC to determine whether further investigation or regulatory action is required. An enhanced spontaneous reporting scheme ( $M^2$ ) is promoted to stimulate reports to Centre for Adverse Reactions Monitoring (CARM – see below) on specific potential signals of concern. Medsafe is advised by an expert committee on medicines safety, the Medicines Adverse Reactions Committee (MARC).

## THE NEW ZEALAND PHARMACOVIGILANCE CENTRE

The NZPhvC operates several monitoring programs that operate in an integrative and synergistic manner to enhance detection of adverse drug events (ADEs) in the NZ population (Kunac *et al.*, 2008). The main programs are as follows.

### THE CENTRE FOR ADVERSE REACTIONS MONITORING

The spontaneous reporting program in NZ, CARM, operates on the same principles as other countries' systems in encouraging the voluntary

reporting of ICSRs. CARM accepts reports for all therapeutic products, including vaccines and complementary and alternative medicines, without barrier to the type or source of reporter. Whilst encouraging use of a standard report form, in a paper or online option, other modalities that may be suited to the reporter, such as email or telephone, are accepted. CARM and Medsafe have also developed an electronic ADE reporting tool that has been integrated into the practice software of approximately 90% of GP practices in NZ. Where opportunities are identified, CARM also links reporting options to professional networks or programs that may be a source for ICSRs.

All reports are assessed by a clinician at the NZPhvC and a personalized response is composed with appropriate feedback (Kunac *et al.*, 2008). Reactions reported suggesting further use of a medicine may expose a patient to risk are entered onto the National Medical Warning System maintained by the Ministry of Health for Health Care Providers. Reports recorded in the CARM database are accessible to the public through an online Suspected Medicine Adverse Reaction Search (SMARS) tool hosted on the Ministry of Health (Medsafe) website.

The inclusive approach to reporting, the direct contact with reporters, and the synergy of the center's programs are considered to contribute to NZ being the leader in reporting rate (per million population) for well over a decade until 2010 (Biriell, 2010).

### THE INTENSIVE MEDICINES MONITORING PROGRAMME

The Intensive Medicines Monitoring Programme (IMMP) is a national program for proactively monitoring specific medicines using prescription event monitoring (PEM) methods (see Chapter 22, Prescription event monitoring in New Zealand). Patient cohorts for monitored medicines are established from dispensing data collected directly from community and hospital pharmacies throughout NZ. The IMMP is the only nationwide program that can collect dispensing data on any prescription medicine dispensed in NZ, regardless of whether or not it is subsidized.

Patients dispensed the monitored medicines are followed up by multiple "intensive" methods. Questionnaires requesting information on all new clinical events since the patient started the medicine are sent to prescribing doctors. Additional information is obtained from spontaneous reports sent to CARM (see above) and in order to identify deaths and ADEs resulting in hospitalisation, the IMMP also undertakes record linkage to the NZ National Collections databases (see Chapter 22).

The IMMP has identified numerous new adverse drug reaction (ADR) signals (Clark and Harrison-Woolrych, 2006) and performed many studies in NZ populations as outlined in Chapter 22. Several IMMP studies have had significant clinical outcomes, including investigations of enuresis with atypical antipsychotic medicines (Harrison-Woolrych *et al.*, 2011; Barnes *et al.*, 2012), psychiatric events associated with varenicline (Harrison-Woolrych, 2010; Harrison-Woolrych and Ashton, 2011), and gastrointestinal dysmotility with clozapine (Palmer *et al.*, 2008).

The IMMP lists the currently monitored medicines, information for pharmacists, updates for prescribers, and all other relevant information

relating to the program on its website: <https://nzphvc.otago.ac.nz/immp/>.

The methods of the IMMP were used as the model for the Intensive Vaccine Monitoring Programme, which operated at the NZPhvC between 2004 and 2006 and monitored adverse events to the meningococcal B vaccine in near to real time (Tatley *et al.*, 2008).

In December 2013 the IMMP was disestablished due to insufficient funding and is no longer operational.

### MEDICATION ERROR REPORTING AND PREVENTION SYSTEM

The NZPhvC has led the development and piloting of a Medication Error Reporting and Prevention (MERP) system, a web-based, voluntary, non-punitive, and confidential reporting system for primary care.

Historically, pharmacovigilance center activities have focused on ADRs; however, more recently, pharmacovigilance centers have recognized an emerging role in the identification of medication errors. The NZPhvC initiated MERP to contribute to this international initiative from a NZ perspective.

The aim of MERP is to coordinate the capture and analysis and dissemination of timely information on medication errors in primary care, to enhance the safety of medication use for New Zealanders.

MERP has been developed to accommodate both "organization" and "individual healthcare professional" reporting. Acknowledging that useful sources of medication error data exist elsewhere, the "organisation" reporting component allows anonymized medication error data generated in other organizations to be securely uploaded to MERP. During the pilot, batched data extracts were received from the National Poisons Centre, and reports to CARM which document an underlying medication error are directed to MERP. Individual healthcare professionals report medication errors using a web-based reporting form that captures information about the event, including factors that may have contributed to the error and actions taken to prevent future similar errors. Reports may be submitted anonymously if preferred.

Following the successful pilot of a MERP system prototype, a second phase of development is currently underway to demonstrate greater utility and value of the MERP system.

## RISK COMMUNICATION IN NEW ZEALAND

Communication of safety information to health-care workers and patients is an important part of pharmacovigilance in NZ. The NZPhvC works collaboratively with Medsafe, the NZ Health Quality and Safety Commission (HQSC), and other committees and professional organizations in NZ to ensure risk is communicated appropriately. In its role as the regulatory body, Medsafe may ask sponsors to update product data sheets when new risk–benefit evidence (from the NZPhvC and/or other sources) has been reviewed.

For spontaneously reported ADEs, clinical assessors in the CARM and IMMP respond to individual reporters directly, including summaries of the NZ and international data on the issue where relevant. IMMP sends regular updates on the monitored medicines to pharmacists and prescribers (usually general practitioners) and also communicates information about the monitoring studies via its website. For medication errors, a mechanism has been established where the MERP data concerning serious medication errors can be communicated to the HQSC Medication Safety Programme through its advisory group to allow dissemination of warnings or precautions.

Summaries of issues identified by the NZPhvC are presented in local publications, including Medsafe's *Prescriber Update*, the HQSC *Medication Safety Watch* bulletin, and other professional magazines, including *NZ Doctor* and *Pharmacy Today*. Research papers from the NZPhvC are published in peer-reviewed international journals (see Chapter 22 for examples). Significant findings are also communicated to professional organizations, including the International Society of Pharmacovigilance (ISoP), the WHO Uppsala Monitoring Centre, the International Medication Safety Network (IMSN), regulators in other countries, research groups, and the general public where appropriate.

## CONCLUSION

In summary, NZ has had effective systems of pharmacovigilance for over 40 years and continually aims to improve and expand its activities. The key difference to pharmacovigilance in other countries is the operation of multiple synergistic programs operating within the NZPhvC to enhance patient safety in this country.

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## 16b

# Pharmacovigilance: Australia

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The reporting of cases of thalidomide embryopathy from Australia (McBride, 1961) served as a powerful motivator for the early establishment by the national Department of Health of an expert committee to assess the safety of new medicines and a scheme for the spontaneous reporting of suspected adverse reactions (McEwen, 2007). The Australian Drug Evaluation Committee (ADEC) first met in July 1963, and under its aegis the reporting scheme commenced in August 1964, with the distribution of report forms to doctors. Initially, ADEC provided the expert clinical review of incoming reports. Australia was one of the 10 countries that participated in the pilot program that led to the establishment of the WHO Program for International Drug Monitoring and has been a contributing member ever since. By 1970, increasing numbers of reports led to the establishment of the Adverse Drug Reactions Advisory Committee (ADRAC) which, despite its name, was a subcommittee of ADEC. ADEC, and through it ADRAC,

provided advice to the Department of Health. Analysis of spontaneous reports has provided numerous alerts about new safety problems and confirmations that problems detected in other countries were also occurring in Australia (Mackay, 2005).

In August 1989 the national activities to do with medicines and medical devices were designated as the Therapeutic Goods Administration (TGA), which is organizationally a division of the Department of Health and Ageing. The TGA is funded solely through assessment, registration and license fees paid by the industry.

A new organizational structure of the TGA was implemented on July 1, 2010. An important element relevant to pharmacovigilance was the creation of separate pre-marketing and postmarketing groups. The pre-marketing evaluation of medicines and medical devices is a responsibility of the Market Authorisation Group. Concerning prescription medicines, this group is advised by the Advisory

Committee on Prescription Medicines, which is a successor to ADEC. Pharmacovigilance and device problem monitoring are undertaken by the Office of Product Review (OPR) within the Monitoring and Compliance Group. Concerning medicines and vaccines, this office is advised by the Advisory Committee on the Safety of Medicines (ACSom) and the Advisory Committee on the Safety of Vaccines (ACsov). Importantly, ACSom and ACSov are established as statutory expert committees reporting directly to the TGA, and no longer is the medicines safety advisory committee reporting through the evaluation committee. OPR produces the Medicines Safety Update, published each 2 months in the *Australian Prescriber* journal.

Pharmacovigilance in Australia remains largely dependent on spontaneous reporting by healthcare professionals and obligatory reporting by pharmaceutical companies. Reporting options have been expanded from the blue card introduced in 1971 to include fax, email, and via an online facility. Reports from consumers have been accepted for more than 20 years. Consumers may report for the price of a local phone call to the Adverse Medicines Event Line funded by the National Prescribing Service, which relays relevant reports to the TGA's OPR.

A risk management plan has been required since April 2009 as part of almost all types of applications to register or extend the use of prescription medicines. The plans are assessed by the OPR, which may take advice from ACSom, in parallel with the evaluation undertaken in Market Authorisation Group and may lead to the imposition of requirements for additional postmarketing pharmacovigilance activities by pharmaceutical companies.

Australia (population approximately 23 million) has a single national Pharmaceutical Benefits Scheme (PBS) for the subsidization of medicines supplied through community pharmacies, in private hospitals, and to patients at discharge from public hospitals (Anon., 2011). Patients pay a co-contribution for each dispensed item. The PBS reimbursement database captures details of dispensings of subsidized items for individual patients only when the cost of a medicine exceeds the co-contribution. Extent of capture is much more comprehensive for pensioner and concessional patients

(whose co-payment is lower) than for other patients. Capture of all dispensings of PBS items have occurred, however, from April 2012.

PBS dispensing data have been quite widely used for studies of drug utilization – for example, see McManus *et al.* (1999) and Ostini *et al.* (2008). The linking of PBS data to other health administrative datasets for pharmacovigilance research purposes has been very uncommon, in part because of concerns about data privacy. Linkage of PBS data to administrative health data in the State of Western Australia has been demonstrated to be feasible (Colvin *et al.*, 2009). Data linkage has also been undertaken using the separate administrative data of the Department of Veterans Affairs, which covers approximately 320 000 principally elderly veterans (Caughey *et al.*, 2010).

## CONTACT

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**Joint Statement Regarding the Formation  
of a Joint Australian and New Zealand  
Regulatory Agency**

On June 20, 2011, the Prime Ministers of Australia and New Zealand signed a Statement of Intent to implement progressively over a period of up to 5 years a joint regulatory agency for medicines, medical devices, and other therapeutic goods. The agency is to be known as the Australia New Zealand Therapeutic Products Agency (<http://www.anztpa.org/>). This initiative reactivated negotiations that commenced in 2003 but which were suspended in 2007. Early manifestations of the renewed cooperation are the Joint Adverse Event Notification System and the Trans-Tasman early warning system of safety concerns with medicines and medical devices. Other implications for pharmacovigilance activities await policy decisions as part of the renewed negotiations.



## **Part II: PHARMACOVIGILANCE SYSTEMS**

### **Pharmacovigilance in Africa**

**17**

# **Pharmacovigilance in Africa**

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## **INTRODUCTION**

Pharmacovigilance (PV) is new to Africa, and most PV systems in Africa are in their infancy. Prior to 2000, only five national PV centers in Africa were members of the WHO Programme for International Drug Monitoring. Several reasons account for this, including the absence of national drug regulatory authorities, destabilizing civil and political strife, and lack of human and financial resources. The last 20 years, however, have seen seismic shifts in the political, civil, and healthcare environment in Africa. The 55 countries that constitute geographical Africa are now committed to democratic principles, and the global community has increased its support towards strengthening national health systems. Initiatives like the Global Fund against HIV/AIDS, TB and Malaria, the United Nations AIDS Programme (UNAIDS), and UNITAID

have brought huge financial resources to improve access to life-saving medicines and health commodities in Africa. The Global Alliance for Vaccines and Immunization (GAVI) and UNICEF have also leveraged resources to provide vaccines for infants. In addition to these resources have been the billions of dollars provided by the Bill and Melinda Gates Foundation, the (US) President's Emergency Plan For AIDS Relief (PEPFAR/Emergency Plan) and the President's Malaria Initiative (PMI) towards providing medicines for HIV/AIDS, malaria, and tuberculosis. This huge influx of resources has dramatically increased access to medicines for millions of people in Africa, and this has highlighted the need for strong and effective health systems to ensure that these health commodities are used rationally and that they are safe and of good quality. The need for PV could not be more obvious.

## PHARMACOVIGILANCE IN AFRICA

Currently, 33 national pharmacovigilance centers in Africa are full members of the WHO Programme for International Drug Monitoring, whilst another six are associate members, working to fulfill the technical requirements needed to become full members. It is important to note that 17 countries joined the WHO Programme for International Drug Monitoring in the past 5 years alone, showing the young nature of the various systems, most of which are in their infancy and require support in data collection, management, analysis, and in decision making. A recent analysis by Olsson *et al.* (2010) showed the challenges facing African PV centers, including lack of human and financial resources. A survey by the Strengthening Pharmacovigilance Systems (SPS) Program (2011) showed similar results. A recent publication by Isah *et al.* (2012) provides an excellent background and overview of PV in Africa and charts nicely PV evolution in Africa. The article bemoans the absence of PV policies and legislation across Africa, the low reporting of ADRs to the World Health Organization (WHO) database, the poor financial and human resources available for PV, and the low participation of industry in national PV efforts. The important role of genetics in drug safety and the expanding field of pharmacogenetics and its relevance to drug safety in Africa are also described. In Africa, few countries currently have PV guidelines for industry, though there are general guidelines for spontaneous reporting and for undertaking active post-registration studies. Most countries do not require mandatory reporting of adverse drug reactions (ADRs) by the pharmaceutical industry, though this may change soon. The total number of spontaneous reports from African countries is extremely low even for drugs that are used heavily within the region; for example, antimalarials (Stergachis *et al.*, 2010; Kuemmerle *et al.*, 2011). Despite this low reporting, a safety signal – that is, extrapyramidal reactions with the antimalarial drug combination of amodiaquine + artesunate – has been generated entirely due to PV efforts in Africa (McEwen, 2012), showing the benefits of PV in Africa. With the support of the WHO, PV in Africa is being incorporated into public health programs,

and methods like cohort event monitoring and targeted spontaneous reporting are being used in addition to routine spontaneous reporting (Isah *et al.*, 2012).

## THE FUTURE

PV in Africa is evolving, and key stakeholders like the pharmaceutical industry are being brought on board. Indicators for PV exist (Strengthening Pharmaceutical Systems (SPS) Program, 2009) or are being developed and a PV toolkit is available ([www.pvtoolkit.org](http://www.pvtoolkit.org)). The establishment of the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance ([www.who-pvafrica.org](http://www.who-pvafrica.org)) at the University of Ghana Medical School in Accra, in addition to the Africa office of the Uppsala Monitoring Centre (UMC-Africa, [www.who-umcafrica.org](http://www.who-umcafrica.org)) in Accra, is providing the needed focus and regional hub for technical and advocacy support to countries in Africa. The pharmaceutical industry and other stakeholders in Africa no longer have to deal with the frustration of not knowing the PV framework or guidelines in individual African countries as the WHO Collaborating Centre maintains an updated list of contacts as well as requirements for PV across the continent. PV in Africa is new, but the future looks bright. Detailed information on PV systems in each African country, including key personnel, is available on request by email at [info@pvafrica.org](mailto:info@pvafrica.org). More information is also available from the WHO ([www.who.int](http://www.who.int)), Uppsala Monitoring Centre ([www.who-umc.org](http://www.who-umc.org)) and UMC-Africa ([www.pvafrica.org](http://www.pvafrica.org)) websites.

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## **Part III**

# **SIGNAL DETECTION/GENERATION IN SPONTANEOUS REPORTING PROGRAMS AND OTHER SOURCES: FROM SPONTANEOUS REPORTING TO PHARMACOEPIDEMIOLOGY**



# 18

## Vaccine Safety Surveillance

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### INTRODUCTION

In general, clinical trials are designed and powered to evaluate efficacy, not safety. Owing to a relatively small number of subjects, short period of follow-up, limited number of concomitant vaccines administered, and relatively healthy population in vaccine clinical trials, prelicensure trials usually cannot detect rare adverse events, and imbalances in more common adverse events might not be statistically significant. Therefore, postmarketing surveillance is necessary to ensure that safety is continually monitored.

Vaccines are different from other pharmaceuticals, in ways that influence safety considerations. Vaccines are given to healthy people, including infants and children, whereas many drugs are administered to adults with multiple chronic ill-

nesses. Highly effective and extremely safe, vaccines are a foundation of public health disease prevention programs. Schools and some employers require proof of immunization. Because vaccination campaigns have eradicated or largely reduced the burden of certain infectious diseases, the public often no longer perceives those illnesses as a substantial threat and is, instead, more concerned about the possible side effects of vaccines.

### VACCINE SAFETY SURVEILLANCE IN THE USA

#### VACCINE ADVERSE EVENT REPORTING SYSTEM

The National Childhood Vaccine Injury Act of 1986 was established to address vaccine liability and other concerns. The scope of the act is limited to universally recommended childhood vaccines. The act mandated the establishment of vaccine

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<sup>1</sup>Deceased, 2012.

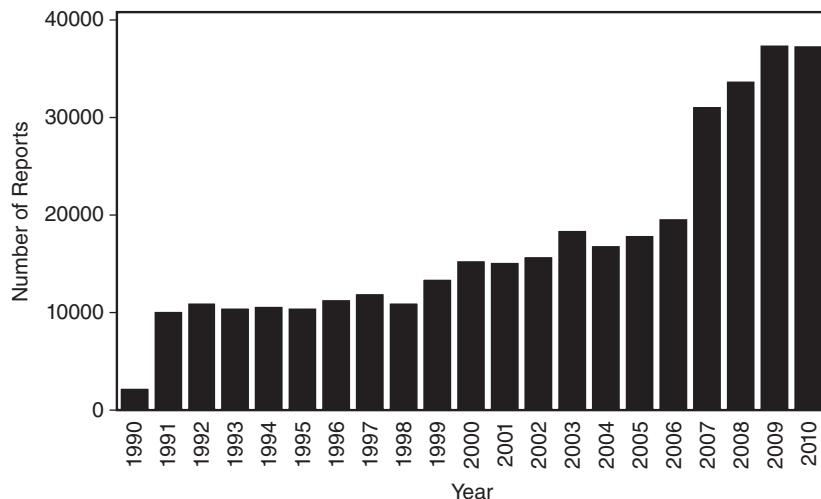


Figure 18.1 Number of VAERS reports, by year. Source: <http://vaers.hhs.gov/index>.

safety infrastructure in the USA, including the National Vaccine Program Office, National Vaccine Injury Compensation Program (Vaccine Excise Tax and Vaccine Injury Table), Vaccine Information Statements, Institute of Medicine review committee, and Vaccine Adverse Events Reporting System (VAERS).

VAERS is a national system for passive surveillance of adverse events following vaccination (Zhou *et al.*, 2003). Established in 1990, VAERS is jointly managed by the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). Anyone can submit a report to VAERS, including vaccine manufacturers, physicians, state and local public health clinics, vaccine recipients, and their parents or caregivers. Reporting to VAERS is mandatory for manufacturers within 15 days for serious, unexpected events. Manufacturers must also report adverse events occurring outside the USA if the vaccine contains any or all of the same components as a vaccine that that manufacturer is licensed to distribute in the USA; therefore, VAERS contains both US and foreign reports. Reporting is largely voluntary for health-care providers; however, reporting is mandatory for any event that the package insert lists as a contraindication to further doses of the vaccine or any event in the Vaccine Injury Table (<http://www.hrsa.gov/vaccinecompensation/vaccinetable.html>)

that occurs within the specified time period after the immunization. The table lists medical conditions that are presumed to be caused by certain vaccines (within specified intervals post-vaccination) and may make it easier for some individuals to receive compensation for vaccine-related injuries. Under US federal regulations (CFR, 2013), a serious adverse event is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect; important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of these outcomes. Medical officers at the FDA review all reports of death and other serious adverse events after vaccination; hospital discharge summaries, laboratory results, and autopsy reports are also requested and reviewed. Since its inception in 1990, VAERS has grown considerably, and in recent years it has received more than 30 000 reports per year (Figure 18.1), of which approximately 14% are

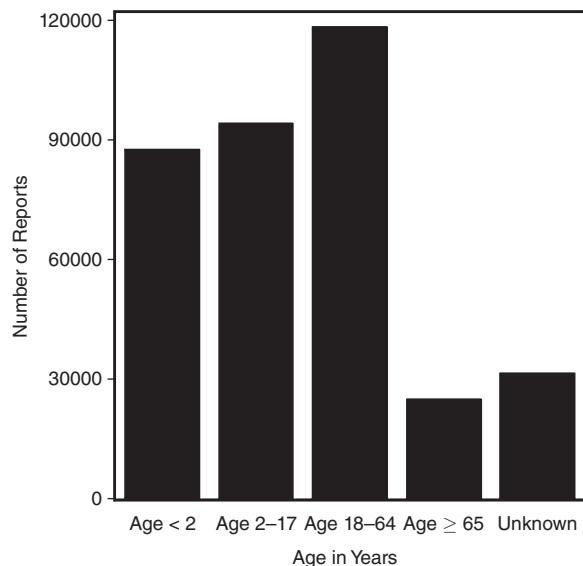


Figure 18.2 Age of vaccinees – VAERS 1990–2010. Source: <http://vaers.hhs.gov/index>.

serious. In contrast, more than 90% of Adverse Event Reporting System reports for blood products and therapeutic biologic products are serious. Half of all VAERS reports pertain to individuals under 18 years of age (Figure 18.2).

Surveillance systems like VAERS perform a critical function by generating signals of potential problems that may warrant further investigation. A safety signal refers to a concern about an excess of adverse events compared with what would be expected to be associated with a product's use (Szarfman *et al.*, 2002). Monitoring and analysis of reports, including in-depth medical review, data mining techniques, and analysis of reporting rates (number of adverse events/number of doses distributed), are designed to detect serious events that occur at higher rates than expected. Priorities for analysis of VAERS data include evaluating new vaccines for unexpected adverse events, reports of death and other serious adverse events, and prevention of adverse effects. Analysis of VAERS data has identified important safety issues, such as intussusception after live rotavirus vaccine in infants (Zanardi *et al.*, 2001), vasovagal syncope and injury after injected immunizations in adolescents (Braun

*et al.*, 1997; Woo *et al.*, 2005; Slade *et al.*, 2009), and thrombocytopenia after vaccination (Woo *et al.*, 2011). However, routine monitoring of VAERS has also revealed numerous potential safety concerns of unclear significance, such as alopecia after routine immunizations (Wise *et al.*, 1997), Guillain–Barré syndrome after meningococcal conjugate vaccine (FDA/CDC, 2005), and thromboembolic events after human papillomavirus virus vaccine (Slade *et al.*, 2009). Because no numerical threshold can be applied to define causality and severity of adverse events following immunization, clinical judgment and multidisciplinary review are critical components of the ongoing regulatory process, which can include safety notifications, public health advisories, “Dear Healthcare Provider” letters, changes in the manufacturer’s package insert, and even market withdrawal of the vaccine. Contributions to public health include publications in medical journals, presentations at professional and scientific conferences, presentations to advisory committees, and responses to inquiries from Congress, the public, and other parties.

Strengths of VAERS include the detection of rare adverse events, timely availability of data, national and international coverage, and ability to generate hypotheses (Chen *et al.*, 1994; Zhou *et al.*, 2003; Varricchio *et al.*, 2004). Moreover, in some cases, lot-specific safety analyses or investigations may also be performed, if there is concern about the possibility of inconsistency in the manufacturing process or of other lot-specific problems. Limitations of VAERS include uncertainty about denominators (the number of vaccine doses that have been distributed is known, but the number of doses that have been administered is not), under-reporting, incomplete and inaccurate reporting, biased or stimulated reporting (e.g., influence of news media), limited resources for follow-up, and lack of an unbiased comparison group (Chen *et al.*, 1994; Zhou *et al.*, 2003; Varricchio *et al.*, 2004). Because of these limitations, analysis of VAERS data does not usually allow determination of a causal relationship between a vaccine and an adverse event. Nevertheless, VAERS data have been used to describe a range of potential vaccine side effects and to look for unexpected patterns in demographics and clinical characteristics that

might lead to hypotheses about relationships between vaccines and adverse events that can be tested with epidemiologic or laboratory studies.

Empirical Bayesian and proportional reporting ratio are data mining methods that attempt to identify adverse events that are reported more commonly after one vaccine than others. In routine use at the FDA, data mining analyses in VAERS have identified events of interest after smallpox (McMahon *et al.*, 2005a), human papillomavirus (Slade *et al.*, 2009), seasonal influenza (McMahon *et al.*, 2005b), H1N1 influenza (Vellozzi *et al.*, 2010), and hepatitis A and B combination (Woo *et al.*, 2006) vaccines. VAERS data have also been stratified (Woo *et al.*, 2008) in order to adjust for potential confounders, such as age and sex. In addition, analysis of individual strata may reveal important patterns, particularly if there is a large imbalance in the administration of vaccines or in the baseline susceptibility to a given condition.

#### REGULATORY PROCESSES RELATING TO POSTMARKETING SAFETY SURVEILLANCE

In accordance with Title IX, Section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), postmarketing evaluations are performed 18 months after approval of the product (or expanded indication) or after its use by 10 000 individuals, whichever is later (FDA, 2013). Physicians at the FDA review the relevant data, summarize findings, and, when necessary, develop a plan to investigate potential new safety issues. The evaluations are performed to determine whether there are any new serious adverse events that were not previously identified during product development, known side effects that have been reported with unusually high frequency, or potential new safety concerns that have emerged since the product was introduced to the general population. This information is intended to improve the transparency of information about drugs and biologics, and to provide patients and healthcare providers better access to specific types of safety information. Postmarketing safety evaluation findings include potential new safety concerns that are identified during the evaluation and should not be viewed as a summary of all safety issues addressed since the

product's approval. The FDA assesses information from many sources, including the pre-approval safety data, the current US prescribing information, VAERS reports, manufacturer-submitted periodic safety reports, medical literature, product utilization databases, and data from post-approval clinical trials and other studies (when available). The FDA also presents a safety summary to an independent pediatric advisory committee, who will assess the reviews and make recommendations for action. To date, the FDA has completed 915 reviews for the following vaccines: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *Haemophilus b* conjugate vaccine (Pentacel), diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine (Kinrix), rotavirus vaccine, live oral (Rotarix), *Haemophilus b* conjugate vaccine (Hiberix), and human papillomavirus vaccine bivalent (types 16 and 18) vaccine (Cervarix).

Under Title IX, Subtitle A, Section 901 of FDAAA, the FDA may require the submission of a risk evaluation and mitigation strategy (REMS) to manage a known or potential serious risk associated with a drug or biological product, if the FDA finds that a REMS is necessary to ensure that the benefits of the drug or biological product outweigh the risks of the product (FDA, 2009a). A REMS can include a medication guide, patient package insert, communication plan, elements to assure safe use, and an implementation system, and must include a timetable for assessment of the REMS. For smallpox (vaccinia) vaccine, live (ACAM2000), there is a REMS to manage the risks of eczema vaccinatum, exposure of pregnant women to vaccinia, secondary transmission of live vaccinia, and autoinoculation (FDA, 2008).

Title IX, Subtitle A, Section 901 of FDAAA also empowers the FDA to impose a postmarketing requirement (PMR) at the time of product approval, or after approval, if the FDA becomes aware of new safety information (FDA, 2012). Specifically, clinical trials or other studies may be required to assess a known serious risk related to the use of the product, to assess signals of serious risk related to the use of the product, or to identify an unexpected serious risk when available data indicate the

potential for a serious risk. The FDA imposed a PMR to assess the risk of spontaneous abortion in women who become pregnant around the time of vaccination with human papillomavirus vaccine bivalent (types 16 and 18) vaccine (Cervarix) (FDA, 2009b). This postmarketing requirement was based upon clinical trial data that identified higher rates of spontaneous abortion among Cervarix recipients than control subjects.

#### INTEGRATION OF VACCINE ADVERSE EVENTS REPORTING SYSTEM AND SAFETY DATA FROM OTHER SOURCES

In addition to VAERS, the FDA conducts near real-time surveillance methods through its Post-licensure Rapid Immunization Safety Monitoring system (PRISM) and Mini-Sentinel Network ([http://mini-sentinel.org/about\\_us/](http://mini-sentinel.org/about_us/)). These systems address key gaps in existing vaccine safety monitoring capabilities by assembling a nationally representative surveillance population of very large size and statistical power, capturing data from sources outside traditional healthcare systems, establishing the operational framework for a claims-based active vaccine surveillance system, conducting initial validation and monitoring of vaccine-outcome pairs, identifying and evaluating complementary data sources, developing a strategic approach to detection of non-prespecified adverse events after vaccination, and developing improved methods for causal inference in sequential analysis, including extension and evaluation of a new sequential regression approach. The CDC participates in two additional projects to monitor the safety of all licensed vaccines. Through their collaborative Vaccine Safety Datalink (VSD), CDC and 10 managed care organizations monitor vaccine safety and address the gaps in scientific knowledge about rare and serious side effects following immunization by conducting careful descriptive epidemiologic and hypothesis-testing studies (CDC, 2013a). The VSD monitors over 8 million people and uses a “rapid cycle analysis” method that repeatedly evaluates rates at which key suspected side effects have developed in vaccinees, so that it will become evident as early as possible should any of these side effects prove to

have a statistical association with vaccination. The Clinical Immunization Safety Assessment (CISA) network is a national network of six medical research centers with expertise in immunization safety (CDC, 2013b). The CISA conducts clinical research on immunization-associated health risks and seeks to explore the role of individual variation in susceptibility to adverse events, to provide clinicians with vaccine-based counsel and empower individuals to make informed immunization decisions, to assist domestic and global vaccine safety policy makers in the recommendation of exclusion criteria for at-risk individuals, and to enhance public confidence in sustaining immunization benefits for all populations.

For example, an integrated and collaborative approach was used to address the H1N1 influenza pandemic. The FDA licensed the first influenza A (H1N1) monovalent vaccines on September 15, 2009. The H1N1 vaccines were available as a live, attenuated monovalent vaccine for intranasal administration and as monovalent, inactivated, split-virus or subunit vaccines for injection. The licensure and manufacturing processes for the monovalent H1N1 vaccines were the same as those used for seasonal trivalent inactivated or trivalent live, attenuated influenza vaccine. To assess the safety profile of H1N1 vaccines in the USA, the FDA and CDC reviewed all VAERS reports (serious and nonserious) for H1N1 vaccines during the 2009–10 influenza season (Vellozzi *et al.*, 2010). No substantial differences between H1N1 and seasonal influenza vaccines were noted in the proportion or types of serious adverse events reported. Simultaneously, federal agencies conducted near real-time surveillance of the safety of monovalent H1N1 vaccines using data from PRISM, VSD, the Epidemic Intelligence Service, the Centers for Medicare and Medicaid Services, the Department of Defense, and the Department of Veterans Affairs. Because the 1976 swine influenza vaccine was associated with Guillain–Barré syndrome, influenza virus vaccines are now routinely monitored for this neurological adverse event. Surveillance for this adverse event has been performed after other influenza vaccines. In some analyses, the risk after monovalent H1N1 vaccines was elevated, but the absence of consistently statistically significant

results suggests that the results may have been due to chance.

## GLOBAL VACCINE SAFETY SURVEILLANCE

In most countries around the world, postmarketing safety surveillance of vaccines is organized in the way it was organized in the USA before VAERS was constituted: the postmarketing safety surveillance unit in the National Regulatory Authority (FDA in the USA) and the National Immunization Program (CDC in the USA) each run separate programs. Thus, within a country, the national regulatory authority (NRA) and national immunization programs (NIPs) often use different reporting forms, terminology, case definitions, databases, and methods for assessing causality.

The NRA and the NIP have complementary responsibilities in vaccine safety surveillance. NRAs are responsible for marketing authorization, licensing activities, and postmarketing surveillance of all licensed vaccines as individual medicinal products. NIPs are responsible for the safe storage, handling, delivery, and administration of vaccines that are used in the immunization program. Safety surveillance of the NIP extends to all relevant aspects of the public health program for immunization, including safe injection practices and the detection, correction, and prevention of program errors. When a response to a reported adverse event following immunization (AEFI) is sought, the immunization program staff who administer vaccines are often the first responders – assessing and treating the adverse event, reporting the adverse event, and participating in any investigation. The NIP is responsible for assuring that health staff respond appropriately to adverse events, report the AEFI, and implement corrective or programmatic action to minimize the risk of AEFIs in the future.

In many countries the NIP shares serious AEFI reports with the NRA in a collaborative manner. A survey at the 2011 annual meeting of national pharmacovigilance centers demonstrated that 30 of 45 NRAs received AEFI reports from the NIP safety surveillance unit; but the extent of this collabora-

tion varies substantially, ranging from none, through incidental joining forces when national vaccine safety issues occur, to full collaboration, including managing a joint database (Labadie, 2012). Unfortunately, collaboration often has been unsustainable because it is partly based on personal relationships, rather than on formalized structures and standardized procedures. Nonetheless, the need for collaboration is widely recognized, and the NRA must have access to all AEFI reports in a country in order to fulfill its regulatory responsibilities regarding vaccines in the postmarketing phase (Letourneau *et al.*, 2008a). This need for collaboration has never been greater, now that vaccines specifically designed and developed to address the infectious disease burden of low- and middle-income countries (LMICs) have been developed (e.g., MenAfriVac™ (WHO, 2010) against meningitis A, which causes seasonal epidemics in Africa's sub-Saharan meningitis belt) or are in advanced stage of clinical development (e.g., malaria vaccine (WHO, 2009)). In the past, vaccines were first introduced in high-income countries (e.g., hepatitis B vaccine (Martin and Marshall, 2003) and *Haemophilus influenzae* type b vaccine (Rossi *et al.*, 2007)) and then in LMICs. LMICs, which often have limited resources to conduct postmarketing safety surveillance of vaccines, benefited from effectiveness and safety data that had already been collected and analyzed during years of use in countries that were better equipped. Vaccines that address the unique infectious disease burden of LMICs will not be implemented on a large scale in high-income countries but rather on a small scale (e.g., in travel clinics but not in NIPs). Consequently, postmarketing safety surveillance of MenAfriVac™ and similar vaccines will need to rely on the surveillance systems of the LMICs where these vaccines are universally or widely administered, in addition to any ad hoc systems created specifically for the launch of these vaccines.

## WORLD HEALTH ORGANIZATION

According to World Health Organization (WHO) assessments in 2010, 48% of the world's population lived in countries with nonfunctional vaccine safety

systems in which the NRA and NIP did not perform basic tasks and did not collaborate effectively (Belgharbi, 2012). Most of these countries are among the least economically developed. The WHO plays an important role in making safe and efficacious vaccines available and in strengthening and harmonizing postmarketing safety surveillance of vaccines through case definitions (WHO, 2004), standards (WHO, 2000), guidelines (WHO, 1999), training, and capacity building. Three particular WHO vaccine-specific initiatives have been instrumental in these efforts: the Expanded Program on Immunization (EPI), prequalification of vaccines, and the Global Advisory Committee on Vaccine Safety (GACVS).

### The Expanded Program on Immunization

Building on the success of the global smallpox eradication program, the EPI was launched in 1974 and seeks to ensure that all children throughout the world benefit from life-saving vaccines. The first diseases targeted by the EPI were diphtheria, whooping cough, tetanus, measles, poliomyelitis, and tuberculosis. By 1990, vaccine coverage for the six EPI diseases was nearly 80% for the world's children. Global policies for immunization include a generic immunization schedule (WHO, 2013a), safe immunization practices (WHO, 2013b), vaccine safety monitoring, and vaccination coverage targets (e.g., children less than 1 year of age should receive at least three doses of diphtheria toxoid, tetanus toxoid, and pertussis vaccine). Most countries, including the majority of LMICs, have added hepatitis B and *Haemophilus influenzae* type b to their routine infant immunization schedules. Increasing numbers of countries are adding pneumococcal conjugate vaccine and rotavirus vaccines to their schedules as well. Safe immunization practices include the use of safe injection materials, including auto-disable syringes. Vaccine safety monitoring includes AEFI reporting and analysis, with emphasis on the detection of AEFI caused by so-called programmatic errors (i.e., adverse events associated with improper storage, transport, handling, preparation, and administration of a vaccine, and not with intrinsic properties of the vaccine; for example, see Box 18.1).

### Box 18.1 Example of a Programmatic Error

In June 2003, three infants, aged 9–11 months, died following routine measles immunization. The three infants developed convulsions and died within minutes of vaccination. Three more infants were given the same vaccine before health workers learned about the deaths and stopped the vaccination session. These three infants developed milder symptoms but survived.

An investigation of the deaths revealed that suxamethonium (a muscle relaxant), instead of the regular diluent, had been used to reconstitute the vial of measles vaccine used to vaccinate the six children. Further, the information provided suggested that, a few days prior to the vaccination session, as a result of a power failure, several vials of vaccine and ampules of diluent were transferred by a health worker from the vaccine refrigerator in the health center to a pharmacy refrigerator where both suxamethonium and synthetic oxytocin were stored (incidentally, these two drugs were noted to have "similar containers"). On the day of vaccination, the vaccines and diluent were transferred back to the vaccine refrigerator. This wrong practice of storing vaccines with other drugs (coupled with lack of proper training for and/or inattention by the healthcare workers involved) subsequently led to the erroneous and fatal use of suxamethonium to reconstitute measles vaccine.

*Source:* Information for health-care workers – managing adverse events. Real-life case histories from the field. URL [http://www.who.int/immunization\\_safety/aefi/managing\\_AEFIs/en/index4.html](http://www.who.int/immunization_safety/aefi/managing_AEFIs/en/index4.html) [accessed on 8 December 2013].

### Prequalification of Vaccines

WHO prequalification is a regulatory step aimed at ensuring that diagnostics, medicines, and vaccines for high-burden diseases meet global standards of quality, safety, and efficacy, in order to optimize the use of resources and improve health outcomes. The prequalification process consists of a transparent

scientific assessment, which includes dossier review, consistency testing or performance evaluation, and site visits to manufacturers. Based on data from studies relevant to the target populations, the WHO evaluates the safety and effectiveness of vaccines for use in NIPs. Prequalified vaccines must meet the specific needs of NIPs in different areas of the world (i.e., potency, thermostability, presentation, labeling, shipping conditions, etc.). The acceptability of vaccines from different manufacturers in different countries must also be established. Vaccines that are evaluated through the prequalification process are distributed to UNICEF and other UN agencies that purchase vaccines for LMICs. A complete list of WHO prequalified vaccines can be found at [www.who.int/immunization\\_standards/vaccine\\_quality/PQ\\_vaccine\\_list\\_en/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html). The program for prequalification of vaccines relies on the NRA of the country in which the vaccine is produced to monitor the production process and quality control methods and to monitor compliance with good manufacturing practices to ensure production consistency. Since prequalification is not possible if the NRA does not meet prespecified standards of performance, the WHO has a separate program to assess NRAs. Immunization postmarketing safety surveillance is an important NRA function that is assessed by WHO. A list of participating National Regulatory Authorities and National Control Laboratories is available at [www.who.int/immunization\\_standards/national\\_regulatory\\_authorities%20/offices/en/index.html](http://www.who.int/immunization_standards/national_regulatory_authorities%20/offices/en/index.html).

#### **Global Advisory Committee on Vaccine Safety**

Vaccine safety is an issue of global importance, since many of the same vaccines are used on all continents. The WHO can assist with case investigation and crisis management. In 1999, the GACVS was established to provide prompt scientific, evidence-based responses to vaccine safety issues of global concern. Its 14 members include international experts in epidemiology, statistics, pediatrics, internal medicine, pharmacology and toxicology, infectious diseases, public health, immunology and autoimmunity, and drug regulation and safety (WHO, 2012). The GACVS advises the WHO in vaccine safety-related issues in the broadest sense:

ranging from assessments of specific vaccine-adverse event associations (e.g., second-generation rotavirus vaccines and intussusception (WHO, 2011a)) to global policies and strategies to enhance and improve vaccine safety (Global Advisory Committee on Vaccine Safety (GACVS)/WHO Secretariat, 2009). The expert committee meets twice a year. Its reports are available on the WHO website ([www.who.int/vaccine\\_safety/en](http://www.who.int/vaccine_safety/en)) and in the *Weekly Epidemiological Record* (<http://www.who.int/wer/en>).

#### **INTERNATIONAL DATABASES**

Postmarketing safety surveillance of vaccines can benefit from pooling individual case safety reports (ICSRs) of AEFI into large international databases. These larger systems can detect safety signals that cannot be recognized in smaller national databases. In addition, international databases provide an impetus and justification for harmonizing case definitions, terminology, and methods. Currently, two such large databases exist: VigiBase™ and EudraVigilance. Both databases receive adverse drug reaction reports from NRAs and national pharmacovigilance centers. As described above, the comprehensiveness of the AEFI reports within these databases depends heavily on the level and quality of the collaboration and sharing of ICSRs among the NRAs and NIPs of the countries that submit ICSRs. If the NIPs do not share ICSRs with the NRA, the NRA may miss important safety information that might have prompted regulatory action. Unlike databases (such as VAERS) that contain ICSRs only for vaccines, both VigiBase and EudraVigilance contain ICSRs for all medicinal products. The inclusion of all pharmaceutical products within a single system presents a challenge with respect to statistical analysis and data mining techniques for identifying vaccine safety signals.

#### **VigiBase**

Developed and maintained by the Uppsala Monitoring Centre (UMC) on behalf of the WHO (UMC, 2013), VigiBase is the largest and most comprehensive adverse reaction data resource in the world. Since 1968, national pharmacovigilance

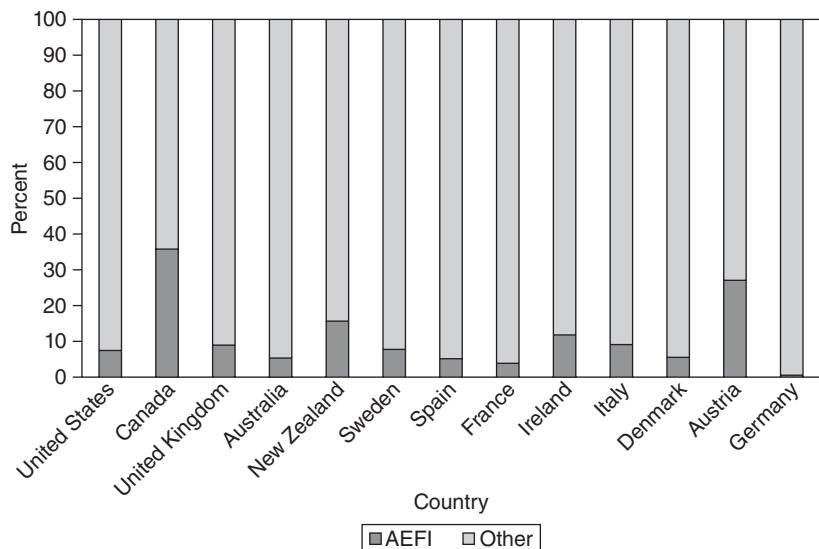


Figure 18.3 Countries with >1000 AEFI reports in VigiBase. Source: Letourneau *et al.* (2008b). Reproduced with permission of Elsevier.

centers of countries that are members of the WHO Program for International Drug Monitoring submit ICSRs to the WHO. Currently, over 105 countries are full members of the program. All these countries submit reports to VigiBase, including the USA, which contributes reports from AERS and VAERS. VigiBase contains over 7 million ICSRs, of which 10% pertain to AEFI (Figure 18.3). These reports include voluntary reports from healthcare professionals and consumers, and mandatory reports from marketing authorization holders to NRAs. Reporting to VigiBase is not mandatory, but national centers are asked to send reports at least quarterly; most national centers adhere to these guidelines, and several report more frequently. Periodic analysis of VigiBase data is performed, as part of UMC's routine signal detection process, to find previously unrecognized adverse drugs or vaccine reactions. These signals are published in the *WHO Pharmaceuticals Newsletter*.

### EudraVigilance

In the European Union (EU) two major agencies contribute to vaccine safety monitoring: the European Center for Disease Prevention and Control

(ECDC) and the European Medicines Agency (EMA). All 27 member countries within the EU collaborate in the EMA. The EMA's central database, EudraVigilance, was created in December 2001. The NRAs of all member states are required to submit ICSRs, including AEFI reports. Reports are also received from pharmaceutical companies. Vaccine pharmacovigilance is guided by the "Guideline on the conduct of pharmacovigilance for vaccines for pre- and post-exposure prophylaxis against infectious diseases" (EMA, 2009). Under the EU's new pharmacovigilance legislation, marketing authorization holders will be required to report nonserious suspected adverse drug reports to the EMA within 90 days of becoming aware of the adverse events. A 15-day time frame is already in force for serious suspected unexpected adverse drug reports (EC, 2008).

The ECDC is mandated to act as an authoritative source of scientific advice, to facilitate the development and implementation of standards for data collection and communication, and to collect and share relevant information at the EU level (Figure 18.4). Decision making, organization, and implementation of vaccination programs fall within the exclusive mandate of the national public health

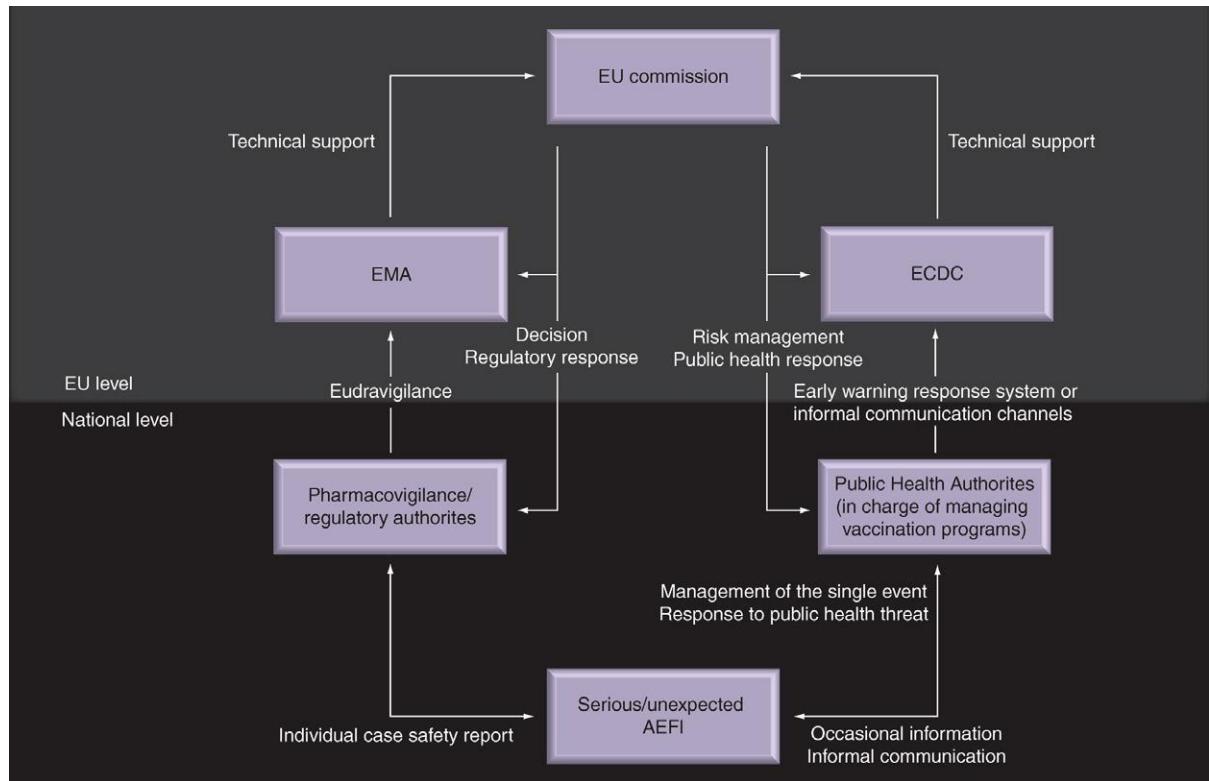


Figure 18.4 Communication flow and responsibility levels in Europe for adverse events following immunization. Source: Lopalco *et al.* (2010). Reproduced with permission of Expert Reviews Ltd.

authorities of the member countries. The ECDC is not directly involved in pharmacovigilance activities, such as the spontaneous reporting systems in EU member states and the EudraVigilance system. However, both agencies collaborate closely: ECDC observers are invited to the EMA Vaccine Working Party meetings, and EMA observers are invited to the ECDC Advisory Group on Vaccination meetings.

#### Safety of New Vaccines Network

One of the newer international initiatives is the Safety of New Vaccines (SAN-EVA) network, which includes Argentina, Brazil, Mexico, Panama, and Venezuela. Since 2006, these nations have collaborated to improve their vaccine pharmacovigilance systems by strengthening all aspects of their passive vaccine safety surveillance systems and by

developing active surveillance systems (SAN-EVA, 2011).

#### Global Network for Post-Surveillance of Newly Prequalified Vaccines

The goal of this WHO initiative is to establish standardized postmarketing surveillance of the safety of vaccines that are newly prequalified and introduced, or expanded, into routine immunization programs. Twelve countries (including China and India) from all six WHO regions were selected to pilot strategies and tools for postmarketing surveillance of vaccines.

#### Global Vaccine Safety Blueprint Project

The Global Vaccine Safety Blueprint Project (WHO, 2011b) is a WHO-led analysis of the current

performance of vaccine pharmacovigilance systems in LMICs, and of existing inter-country and global support mechanisms. Based on an analysis of infrastructure, the blueprint is designed to define the indicators of a minimal capacity for ensuring vaccine safety and to propose a strategic plan for enhancing global vaccine safety activities. This strategic plan intends to assist all LMICs to develop at least a minimal capacity to monitor vaccine safety and respond to safety signals and to enhance the level of active surveillance of vaccine safety in countries that introduce new vaccines. Furthermore, the project aims to foster international collaboration and encourage strategic planning, to ensure that adequate safety surveillance will be conducted for all vaccines, and that safety information will be shared internationally.

## CONCLUSION

As this overview of global of vaccine safety surveillance illustrates, many important strides have been made in the area in recent years. Multiple national, regional, and global initiatives are underway, and many others are being planned. The evaluation of vaccine safety is ideally conducted through a network of diverse, yet integrated, activities that begin during product development and licensure and then continue as long as the vaccine is available for public use. This approach of “safety throughout the life cycle” includes not only national regulatory and public health authorities, but also international organizations, local governments, academia, industry, healthcare providers, professional organizations, third-party payers, managed care organizations, and others. Ensuring that vaccines are as safe as possible is the goal of these collective endeavors. Given the large number of vaccines in development, postmarketing safety surveillance will be an essential component of future public health efforts.

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# How We Assess Causality

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## INTRODUCTION

Drugs and other medicinal products are used to produce a beneficial effect. However, these products can also be associated with adverse events (AEs) that can cause illness, injury, and even death. A certain number of expected AEs are accepted within the clinical risk–benefit equation. However, serious, unknown or unexpected events that occur with product use, often discovered only after marketing, must be assessed to determine if the events were caused in part or in full by the drug product.

Making such an assessment is often complex. In reality, a particular event is either *caused or not caused* by a particular drug. But drug-associated AEs vary greatly, and thus may make assessment a difficult task. Adverse drug events mimic almost the entire range of human pathology, and new drug-related pathologies have even emerged (e.g., kidney stones consisting of drug crystals and the

oculomucocutaneous syndrome caused by pravastatin). AEs vary in the time latency between exposure and symptom onset, as well as in the symptoms produced. Furthermore, challenges arise when applying assessment tools for causality because, in fact, the event may have multiple causal factors – and the event may have resulted from any one or a combination of those factors.

Even though many methods and algorithms for causality assessment have been developed, essentially none of them ever achieves a *definitive* determination of causality. Still, public health needs and some regulatory bodies demand that estimates of causal association be used by drug developers, drug manufacturers, drug regulators, and clinicians to assess whether (and which) AEs are causally associated with a drug product.

The most commonly utilized tools are related to the original Koch postulates, published in 1890, as well as to the early work of Irey (1966–1968) and

Karch and Lasagna (1976). They are based upon consideration of some specific features of the event of interest: (1) timing of the event relative to exposure; (2) change of the event when the exposure is removed (usually termed “de-challenge”); (3) return of the event on re-exposure (“re-challenge”); and (4) consideration of the role of other possible causes or confounding factors. The application of these principles is generally divided into three types of causality assessment methods: (1) expert judgment/global introspection; (2) algorithms; and (3) Bayesian or other probabilistic methods. This chapter discusses the strengths and weaknesses of these methods in assessing possible drug product safety problems.

## CLINICAL CHALLENGES

A clinical event, drug-related or otherwise, does not occur in a vacuum. It occurs following multiple possible contributory causal factors that range from an illness, medicines, foods, environmental, and/or other factors. The primary task is to conduct a differential diagnosis and evaluate the degree to which the occurrence of the event is linked to one or more suspect causal agent, in this case a drug or other medicinal agent. There are similarities in evaluating causality in chronic disease epidemiology and in individual or groups of AEs; however, epidemiologic disease causality generally relates to events in one or more defined population studies (e.g., cancer in smokers versus nonsmokers).

Assessing causality from case reports of suspected AEs typically received by pharmaceutical manufacturers and regulators is more challenging. Data in these reports are often very incomplete. Furthermore, a report often represents a clinician's suspicion of a causal association. Therefore, an *implicit* judgment of causality has been made, and this may affect the data provided to support the clinician's hypothesis.

Single reports often have several attributes that represent obstacles to unbiased causality assessments. Specifically:

- 1 The reporter generally *suspects* an association between the event and exposure to a drug or

other medicinal product. This suspicion can often lead to less rigorous collection and examination of data needed to evaluate other possible causes.

- 2 Data on exposure to the suspect and concomitant drugs are often incomplete, often missing precise information on duration, actual dose ingested, and past history.
- 3 Available data on the AE, including its onset, characteristics, and time course, are typically incomplete, partly because the suspicion is usually retrospective and desired data (e.g., baseline laboratory data) are often not available at the initial report.
- 4 Complete data on concomitant diseases and other confounding conditions – diet and lifestyle – are typically not available, often because reports are made based upon the specific suspicion of a medicinal product cause, rather than upon a differential diagnosis.

Adverse reactions to drugs can be acute, subacute, or chronic, can be reversible or not (e.g., death and birth defects), and can be rare or common. They can be pathologically unique (e.g. the oculomucocutaneous syndrome associated with propranolol, Amos, *et al.*, 1978) or identical to known diseases (e.g., myocardial infarction associated with Vioxx (rofecoxib); Mukherjee *et al.*, 2001). Thus, defining general data elements and criteria for assessing causality that will apply to most types of suspected adverse reactions is challenging. For example, for irreversible events such as birth defects or death, data on drug de-challenge and re-challenge are irrelevant.

The task of evaluating whether there is a causal relationship between a drug exposure and an event is linked to the reporter's motivation for that assessment and the impact of that inference on their actions. For example, if the assessment is perceived to have little impact on future actions relating to either a patient in a clinical setting or to product labeling in the regulatory environment, the assessment might be less rigorous. Conversely, if, for example, continuation of a clinical trial or drug development program depends upon the assessment, the reliability of the method of assessment becomes more critical.

There continues to be an increasing focus on adverse drug reactions, and the concept of causality assessment has been incorporated into more drug regulatory language. For example, all reported AEs in France are subjected to the French Method (Dangoumau *et al.*, 1978), and the US Food and Drug Administration's (FDA's) clinical trials reporting regulations mandate the reporting of AEs from clinical trials determined to be "reasonably" associated with a drug (21 CFR § 312.22).

## THE METHODOLOGIES

### EXPERT JUDGMENT/GLOBAL INTROSPECTION: ASSESSMENT BY EXPERTS

Since the mid 1960s, and continuing to the present day, it has generally been the practice of many dealing with AEs suspected to be associated with drugs that they would be reviewed by one, two, or more experts who are often specialists in the AE disorder of interest. They would carefully evaluate a case or several cases to determine if the AEs were likely caused by the drug or occurred due to other reasons. As has been noted in the later literature on causality, these judgments drew upon the particular sphere of knowledge of the expert and might be subject to various biases, notably information bias. For example, if one expert were a pharmacologist who knew the metabolic pathway of a particular drug, it might prompt consideration of this factor as a likely explanation for the relationship (e.g., blocking of a cytochrome 3A4 pathway can result in abnormally elevated levels of the drug which can cause the effect). Another expert, not aware of this pathway, might not invoke this scenario, but instead focus on confounding factors that might also cause the event.

More commonly in assessment of suspected AEs, however, an event is considered as "possibly associated with the drug" when multiple similar reports are received by manufacturers and/or regulatory bodies. Important considerations of pharmacologic plausibility, dose-response, and timing may or may not be included. Expert judgment/global introspection assessments are generally expressed in terms of a *qualitative* probability scale;

for example "definite," "probable," "possible," "doubtful" or "unrelated."

However, more structured approaches have been sought for several decades. Yerushalmy and Palmer (1959), in part drawing upon Koch's postulates, and from what was later published as Bradford Hill's criteria relating to causality in chronic disease, proposed five criteria for evaluating the causal nature of an association: (1) consistency; (2) strength; (3) specificity; (4) temporal relationship of the association; and (5) coherence or biological plausibility. These criteria continue to be generally used in chronic disease epidemiology. A more structured approach that was described for assessing population-based data but still drew on global introspection was that of Sir Austin Bradford Hill.

### BRADFORD HILL

This structured approach was described in a speech by Sir Austin Bradford Hill and published years later (Hill, 1965). He outlined a systematic approach for using scientific judgment to infer causation, and listed nine issues to be considered when judging whether an observed association has a causal relationship. It is important to emphasize that these factors were primarily directed to assessing causation based upon large population studies, not spontaneous reports. The categories include:

- 1 strength – as quantified through statistical analysis;
- 2 consistency – through replication of the event and outcome;
- 3 specificity – through isolation of the cause to a single outcome; and in modern epidemiology, through mathematical elimination of alternative causes;
- 4 temporality – where the cause must precede the outcome;
- 5 biologic gradient – in which an increase in dose evokes a corresponding increase in response;
- 6 plausibility – the cause–effect agrees with current biological understanding and possesses statistical strength;
- 7 coherence – an inverse extension of plausibility in which the evidence does not conflict with the known natural history of disease;

- 8 experimental evidence – usually epidemiological studies – an aspect that is rarely available for analysis of AEs; and
- 9 analogy – in pharmacoepidemiology this is often referred to as an effect within pharmacologic class of drugs.

It must be emphasized that the Bradford-Hill criteria are *not* a causation checklist, but a guideline for categorizing the evidence for rational thinking. It was primarily directed to evaluation of population-based data in clinical trials or, usually, observational studies. The Bradford Hill criteria have been refined in an effort to develop an effective method for assessing causality from specific case and spontaneous reports of AEs (spontaneous reports). When applied to assessing causality in single AEs, the Bradford Hill criteria have in some cases been useful; in others it is questionably appropriate.

### EARLY ORIGINS OF ALGORITHMIC METHODS

In the mid 1960s, Nelson Irey, a US Armed Forces Institute pathologist, and slightly later two clinical pharmacologists, Karch and Lasagna, drew upon the specific criteria in Koch's postulates and Yerushalmey's framework to propose *ordered criteria* to assess suspected AEs associated with drugs. Both approaches apply the following basic data elements:

- 1 timing (relative to exposure);
- 2 presence/absence of other factors that might also cause the event;
- 3 result of de-challenge of the drug;
- 4 result of re-challenge the drug; and
- 5 other data supporting an association (e.g., previous cases).

Irey's and Karch and Lasagna's more streamlined methods spurred development of assessment methods that included these five basic elements: algorithms, decision tables, and a diagrammatic method. These methods are described in greater detail below.

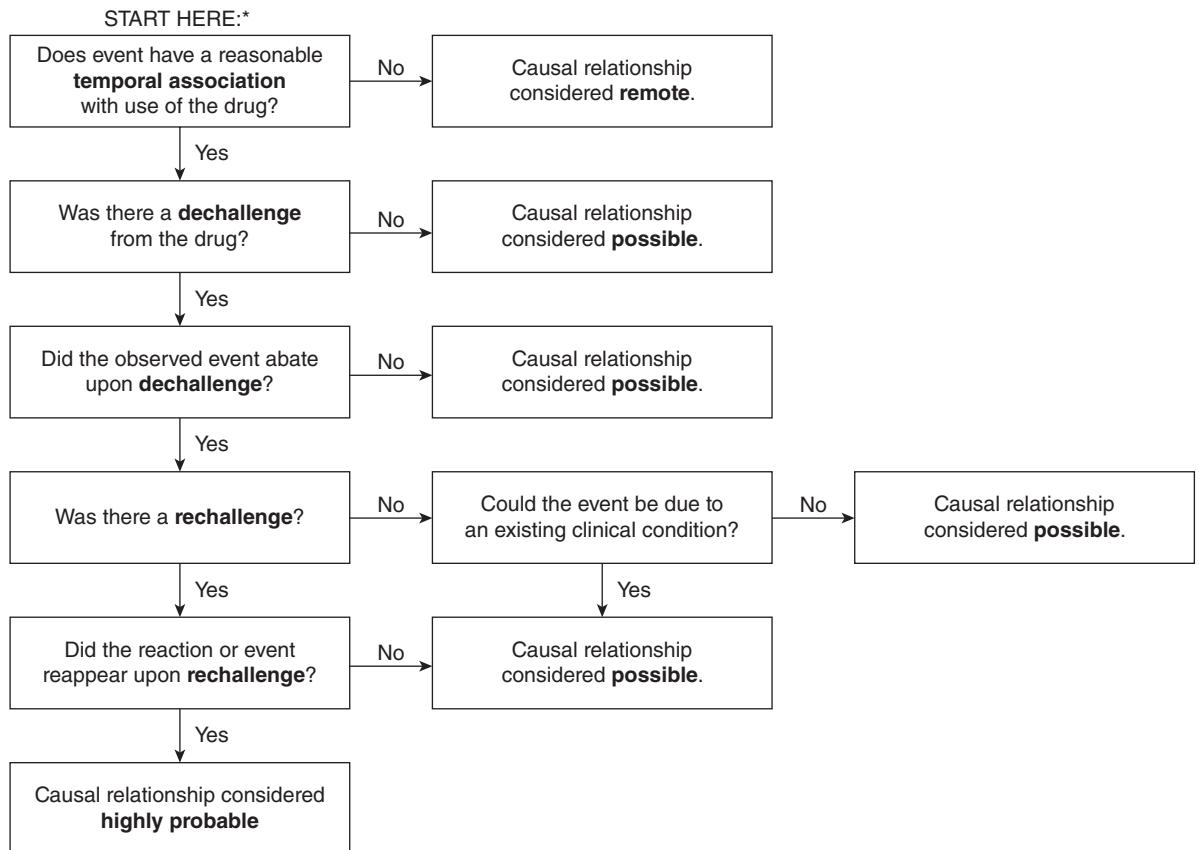
### ALGORITHMS

Algorithms are questions arrayed in sequential and hierarchical fashion that serve to eliminate nonrel-

evant items relating to a question at hand. Thus, if a person's exposure to a drug occurs after an event, this fact alone eliminates consideration of a causal relationship with that drug. Both Irey and Karch and Lasagna essentially developed algorithms presented in an ordered table based upon the criteria above. These approaches were soon adopted by Jones and Turner (Turner *et al.*, 1983; Turner, 1984) at the FDA as possible methods of triaging the large number of AEs received from all manufacturers, and the criteria were arrayed in a sequential order allowing designation of relative levels of certainty ("Possible," "Probable," "Definite" (later changed to "Highly Probable"), or "Not Related," but with no scores (see Figure 19.1). Contemporaneous to this was the development of a number of different algorithms; some, like the FDA's, contain judgmental conclusions. Others use a scoring system; the most widely used of these was developed by Naranjo (Naranjo *et al.*, 1981), which is still widely used today (see Figure 19.2). Naranjo's method is a series of 10 questions incorporating Irey's and Karch and Lasagna's five criteria. It also assesses (1) previous conclusive reports, (2) whether the AE appeared after drug administration, (3) if the drug was detected in bodily fluids in toxic concentrations, (4) the patient's experience with previous exposures, and (5) any objective evidence that confirms the AE. Based on the scoring, the probability that the AE was caused by the drug was classified as definite (score of  $\geq 9$ ), probable (5–8), possible (1–4), or doubtful  $\leq 0$ ). For a comprehensive review of these algorithms, see Agbabiaka *et al.* (2008).

### BAYESIAN OR OTHER PROBABILISTIC METHODS

In 1983, a conference was held in Arlington, Virginia, to promote discussion of available assessment tools and to determine if a "gold standard" could be designated (Herman, 1984). Out of this discussion, a Bayesian approach to causality was proposed within the framework of whether an event could be caused ("Can it?"), or was caused ("Did it?") by a particular drug or, if the drug could predictably cause the event in the future ("Will it") (Lane, 1984). Thus, an application of the Bayes



\*Each drug is carried through independently; if > 1 drug was dechallenged or rechallenged simultaneously causality for all is  $\leq$  possible.

#### QUESTIONS:

1. Did the reaction follow a reasonable temporal sequence?
2. Did the patient improve after stopping the drug?
3. Did the reaction reappear on repeated exposure (rechallenge)?
4. Could the reaction be reasonably explained by the known characteristics of the patient clinical state?

Figure 19.1 The FDA's causality algorithm. Source: Turner, W.M. The Food and Drug Administration algorithm. Special workshop – regulatory. *Drug Inf J*, 1984; 18, 259–266. Reproduced with permission of SAGE Publications.

theorem was developed to assess the probability of an event occurring in the presence of a drug, relative to the probability of that event occurring in the absence of the drug (see Figure 19.3).

Estimation of this overall probability, the “posterior probability,” is based on two components:

- 1 what is the known prior to the event, the “prior probability,” based on clinical trial and epidemiologic data;

- 2 what the likelihoods are for drug causation of *each* of the components of the specific case, including history, timing, characteristics, dechallenge and its timing components, re-challenge, and any other factors, such as multiple re-challenges.

The Bayesian method is considered more robust than the other methods because it requires more detailed knowledge of the clinical event, its

epidemiology, and specific information about the event. Causality assessments have been published using the Bayesian method for different types of adverse drug events, including agranulocytosis, ampicillin-associated colitis, Guillain–Barré syndrome, lithium dermatitis, renal toxicity, and Stevens–Johnson syndrome.

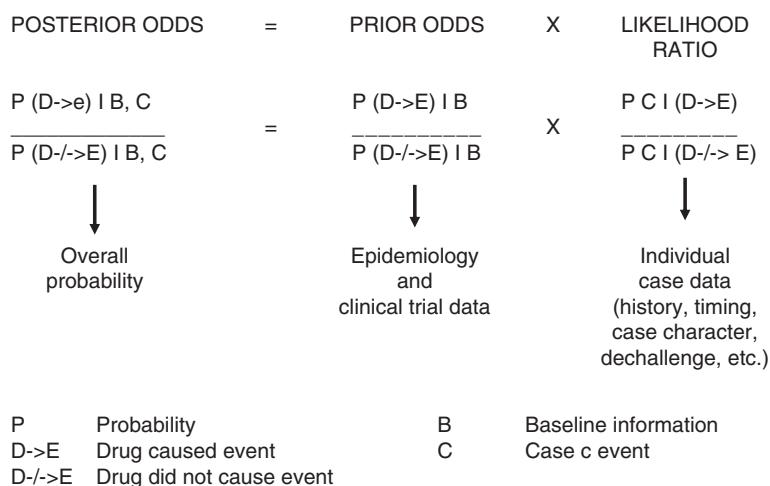
CAUSALITY ASSESSMENT NARANJO SCORED ALGORITHM			
QUESTION	ANSWER		SCORE
	Yes	No	Unk
Previous reports?	+1	0	0
Event after drug?	+2	-1	0
Event abate on drug removal?	+1	0	0
+ Rechallenge?	+2	-1	0
Alternative causes?	-1	+2	0
Reaction with placebo?	-1	+1	0
Drug blood level toxic?	+1	0	0
Reaction dose-related?	+1	0	0
Past history of similar event?	+1	0	0
ADR confirmed objectively?	+1	0	0
<b>Total Score</b>			_____

Naranjo CA, Bustos U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239-45.

Figure 19.2 Causality assessment.

The Bayesian method is generally most widely used when standard statistical methods are inadequate to evaluate causality, because of, among other reasons, small sample size. As a result, the Bayesian method is useful primarily for the analysis of the perplexing first events in new drug clinical trials, serious spontaneous adverse reaction reports, and possibly rare events discovered in cohort studies.

Inadequate data on AEs submitted as spontaneous and case reports limit use of the Bayesian method to the uses noted above. When assessing AEs, the absence of data pertaining to historical risk factors, the time course, and specific characteristics of the drug-associated conditions, as opposed to naturally occurring conditions, makes application of this method more difficult. Data on the incidence of events, along with whether they occur (1) in the *presence of* and (2) in the *absence of* most drugs (the required information for the prior probability) further limits use of this method. In spite of its limitations, however, further use and development of the Bayesian method would represent establishing a framework for structuring further understanding as well as an important challenge. As a result, there appear to be several advantages



Adapted from: J. K. Jones. Bayesian approaches to evaluation of adverse drug reactions. In: *Psychopharmacology Bulletin*, Anonymous 1987; 23: 395-99.

Figure 19.3 Bayesian method. Adapted from Jones (1987).

of using this method for the analysis of suspected drug-associated events which could only add to our ability to correctly evaluate the causal connections between drugs and events. Under the Bayesian method, when appropriately applied to cases where there are sufficient data for assessment, there are also benefits:

- 1 All judgments must be explicit and quantified, which permits better explanations of the degree of uncertainty about each component of information. Further, this approach makes maximum use of the available information and follows the basic rule of not discarding information.
- 2 Since each component is analyzed separately, a sensitivity analysis of each information component can estimate its overall contribution to the final posterior odds or probability estimate. This, in turn, can be used to determine which information is pivotal. For example, if a 10-fold difference in the estimate of the timing does not materially modify the overall posterior odds estimate, further efforts to determine the “best” estimate would not be worthwhile.
- 3 Because of the multistep approach to a judgment, combined with a lack of the prejudged weighting present in most other methods, this approach resists the tendency to achieve a result expected on an *a priori* global judgment. This is quite important in evaluating events with multiple causes.
- 4 This approach can provide an extensive summary of the information needed and areas needing further research and data compilation. Thus, the Bayesian approach ultimately provides a “map” to define the information most critical for understanding drug-induced disease and serves to help formulate the most critical questions to be researched. As disease natural histories and drug-induced diseases are now being described in large population databases, it will be essential to link these two types of analyses.

An elegant combination of tools was published by Zapater *et al.* (2002). They applied the Bayesian method with an additional complimentary method developed by Begaud *et al.* (1985) using the Poisson method for estimating the probability of

rare events in populations. Zapater *et al.* nicely demonstrated the feasibility of utilizing both clinical trial and population data to estimate the posterior probabilities of association in complex cases of ticlopidine-associated hepatitis.

## COMPARISON OF METHODS

Even today there is no consensus about the best methodology to assess causality of drug AE reports. Each methodology has considerable limitations, and there is a great deal of literature examining the usefulness and usability of them.

Pere *et al.* (1986) published an excellent and detailed evaluation of six representative algorithmic methods, identified standard evaluation criteria, and evaluated 1134 adverse reactions using the various methods. Significantly, they found only moderate agreement between all pairs, and considerable disagreements on weightings of three of the major criteria – timing, de-challenge, and alternate etiologies – which tends to underline the lack of considerable information on the events and their characteristics.

These finding were similar to those of Macedo *et al.* (2006). Others have stated that experts, working independently without a framework, frequently disagree on causality assessments because they have the same limitation (subjectivity), which leads to poor reproducibility and to different conclusions. This lack of consensus by experts exists regardless of the AE type examined, (e.g., vaccines, hypersensitivity reactions, or hepatotoxicity).

Agbabiaka *et al.* (2008) assessed 34 different methods and affirmed that there is still no universally accepted method. In addition, they showed that there is no agreement on what factors should be included in making assessments of causality. Agbabiaka *et al.* compiled a table that lists 13 possible factors that are examined in different assessment tools (Table 19.1).

*No single factor is included in all of the tools.* However, based upon frequency of inclusion in the different methods, the most vital elements to consider were “Time to Onset,” “Re-Challenge,” “Response Pattern to Drug,” and “Drug level/evidence of overdose.” “Alternate Etiology” and

Table 19.1 Factors included in 34 causality assessment methods. Adapted from Agbabiaka *et al.* (2008).

Factor	No. of methods that use factor	Percentage of all methods (%)
Time to onset (TTO)/temporality	26/34	76
Re-challenge	24/34	70
Response pattern to drug	22/34	65
Drug level/evidence of overdose	17/34	50
Alternative etiology candidates	16/34	47
Confirmation by lab evidence	16/34	47
Previous experience with drug/drug info	13/34	38
De-challenge	12/34	35
Background epidemiological/clinical information	8/34	23
Concomitant drugs	7/34	20
ADR characteristic/mechanism	7/34	20
Challenge	6/34	18
Other (unspecified)	6/34	18

“Confirmation by Lab Tests” were considered in the same number of methods. There was also no uniformity in how many factors should be examined in these tools; the majority of them assessed causality based on five or six of the 13 factors.

## CHOOSING THE MOST APPROPRIATE TOOL

Given the current state of affairs, where a number of published methods exist, the choice of a method for use in evaluating individual adverse effects will likely be determined by a number of practical factors. These include:

- 1 *How the evaluation will be used.* This refers to both its short-term use (e.g., a rating suggesting more-than-possible association may be needed to result in a “signal”) and long-term use (e.g., will a single highly probable case in a file, not otherwise acted upon, be a source of liability for the evaluator?).
- 2 *The importance of the accuracy of the judgment.* If this evaluation will determine either a specific clinical outcome or, for example, the continuation of a clinical trial or the continued marketing of a drug, then the accuracy of the judgment may be critical and use of a quantitative algorithm or the Bayesian method would be

more appropriate. Conversely, if little hinges upon the judgment, less robust estimates and methods may suffice.

3 *The number of causality evaluations to be made.* The above considerations must also be weighed against the time required to make judgments on large numbers of reports. This dilemma is especially relevant for regulatory agencies and manufacturers, where the need for accurate judgments is pitted against the volume of evaluations to be considered. The FDA has resolved this issue to a great extent by its approach wherein it identifies high-priority problems according to their newness, seriousness, and the extent of the threat to public health.

4 *The accrued value of thorough evaluations.* In some circumstances, the careful, rigorous evaluation of certain categories of drug-associated events will facilitate more accurate evaluation of subsequent, related events. For example, consider a case where a drug under development is anticipated to cause hepatic events. Detailed evaluations of hepatic events induced by other similar drugs may allow more satisfactory causality evaluation of reports received on the new drug. In some cases this results from data collection being focused to a much greater degree, as has been initiated in France, where special reporting forms based on disease-specific criteria for events are being developed.

5 *Who will carry out the evaluation?* Although no specific studies have been carried out to evaluate the inter-rater differences among differently trained professionals, it is likely that the body of information held by each reviewer will have considerable impact on any of the methods used, including the Bayesian method.

## APPLICABILITY

Assessing the safety of drug products and their potential AE profile is a vital component in the life cycle of a product, from the discovery of a new molecular entity through postmarketing until the drug is no longer marketed. Thus, causality assessment is a continuous process, used by drug developers and manufacturers, as well as regulators and others.

## DRUG DEVELOPERS AND MANUFACTURERS

Pharmaceutical sponsors need to continually evaluate new and existing products for potential AEs. They must ensure that each product's AE profile is such that the product's benefits outweigh its risks for approved and new indications. The AEs must be assessed and evaluated using sound and acceptable methods that conform to the different regulatory requirements of countries worldwide. Identification of likely associated serious AEs can lead sponsors to halt the development, terminate clinical trials early, decide not to seek market approval, or lead to restricted marketing, risk evaluation and mitigation strategies, and even potential withdrawal of a product.

## REGULATORY AGENCIES

Drug regulators in different countries approach causality assessment somewhat differently. As stated, in France, a very specific "French Method" evaluation framework was developed in the late 1970s and has been in use since; all AEs are evaluated using this method (Begaud, 1984). Elsewhere in Europe, various assessment methods were formally considered, and a CPMP Working Party on

Pharmacovigilance reached general consensus on causality assessment. This consensus became a European Community Directive (EC Document III/3445/91-EN, July 1991). In 1994, Health Canada instituted a formal method of causality assessment for reports of vaccine-associated AEs. Other chapters discuss international regulatory efforts in greater detail.

## MEDICAL JOURNALS

Unfortunately, nearly all medical journals containing case reports of suspected adverse reactions to drug products require no formal assessment of causality claims. This is not a new problem. The absence of a structured approach to causality assessment in case reports was recognized in the early 1980s. At that time, a consensus conference published its recommendation that published case reports require *at minimum* the five elements of the criteria for causality: (1) details of timing; (2) the nature of the reaction; (3) de-challenge; (4) re-challenge; and (5) alternate causes based on prior history.

There was also a concerted effort on the part of the Associated Working Party for Imputolgy and others to rectify this failing in the medical literature. A symposium was convened in Switzerland in the early 1990s to which editors of notable medical journals and others involved in assessment of causality were invited. The organizers attempted to address the many AE causality methods, and also to solicit agreement from editors that, at the very least, key data elements for causality assessment (timing, challenge, re-challenge, and confounding) be addressed in any published versions of suspected adverse drug reactions (Venulet, 1991). Journal practices for the most part continued as before; no causality assessment was required prior to publication of a case report alleging a causal connection between an AE and a drug.

Similar publication guidelines were proposed in 2006 by a task force of the International Society of Pharmacoepidemiology. This effort was followed up later by publication in two journals on the data elements needed for publication of suspected AEs (Kelly *et al.*, 2007a,b). Only one journal, *The Annals of Pharmacotherapy*, follows this recommendation,

and it requires that the Naranjo method be applied and reported in all case reports published.

Owing to this lack of key information, there is a potential for implied causality that can lead to media bias and additional reporting of AEs that may or may not be causally related. Despite these efforts, the majority of single case reports, letters to the editor, or short publications do not provide an explicit judgment using any of the published algorithms. Further, many reports do not provide information on confounding drug therapy or medical conditions – data elements considered essential for considering causality.

The absence of an assessment suggests that published case reports are not likely to be very robust, and this further limits usability of published case reports. This fact was demonstrated by Haramburu *et al.* (1990), who compared 500 published reports with 500 spontaneous reports to determine whether they contained the information needed in most standard causality assessments. They found that, although the published reports contained significantly more information, data were sparse on alternate causes/other diseases and other drugs in *both* types of reports.

## OTHER APPLICATIONS

There are other settings where standard assessments of causality of serious events suspected to be linked to drug exposure could be useful. This includes early AEs in clinical trials of a new molecular entity, and formulary decisions by healthcare institutions where decisions to select one or another drug may not be well defined in the literature or the product labels.

## CONCLUSIONS

Some investigators, such as Louik *et al.* (1985), discount the value of causality assessment of individual reactions, deferring judgment to the results of formal epidemiologic studies or clinical trials. This philosophy effectively eliminates causality assessment of a large proportion of suspected drug-associated events that have not been subjected

to formal structured studies, such as randomized clinical trials or epidemiologic studies.

Others, however, have contended there is value in assessing case reports. The authors promulgating methods in the early 1980s, including Kramer *et al.* (1979), Jones (1982), and Naranjo *et al.* (1981), contend that the information in single reports can be evaluated to determine some degree of association, and that this can be useful – sometimes critical – when considering discontinuation of a clinical trial or development of a drug, or market withdrawal of a drug. This latter view has continued to stimulate further interest in the topic, resulting in the publication of further methods, or modifications of previously existing methods. Most attractive is the fact that evaluation can be *more consistent based upon structuring of evaluation to categories of data*, and terminology can be limited to relatively defined areas of uncertainty (e.g., possible, probably, not related, or unable to evaluate). In the absence of more definitive data such as is needed for proper Bayesian analysis, this state of affairs remains unresolved.

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# 20

## Quantitative Signal Detection and Analysis in Pharmacovigilance

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### BACKGROUND

The term “signal recognition” arises from electronic engineering, where with radio or radar waves there is a real signal that exists but it is accompanied by “noise” in the background, and there is a need to detect the signal, distinguishing it from the background. This terminology has been used in other contexts, notably in medical diagnosis, where similarities to the problems in electronics can also be seen. The terminology of electronics has been continued with “receiver operating characteristic” curves. These illustrate that with a given amount of

information there must always be a trade-off between the risk of the two different errors of classification: calling noise a signal (a false positive) and calling a true signal noise (a false negative). The sensitivity of a diagnostic test is high when there is a low false-negative rate; the specificity of a diagnostic test is high when there is a low false-positive rate.

With adverse drug reactions (ADRs) there are two levels of diagnosis of causality: first, diagnosis at a single case level; second, at a public health or epidemiological level. ADR causality in an individual patient is not the subject of this chapter, but

statistical approaches may help with single cases. The public health and epidemiological perspective is of greatest importance, and statistical methods can be of some help. The objective is to find those signals that are indicative of causal effects and to reject those signals of effects that are not caused by a particular drug. Where they are of public health significance they will either affect large numbers of individuals or have extremely serious effects in smaller numbers. In these circumstances, the public health view requires that true reactions caused by a medicine be recognized as early as possible. At the same time, those suspected reactions that are not caused by a medicine should be recognized as such and minimal resource should be spent on investigating them.

Signals of potential harmful effects may arise from literature reports, observational epidemiological studies, randomized trials, and spontaneous reports of suspected ADRs. In some countries the emphasis is on suspected reactions, but in others the emphasis is on adverse events. This chapter will primarily concentrate on the quantitative analysis of large volumes of spontaneous reports of suspected ADRs, although this will be put into perspective by comparison with qualitative approaches plus increased exploration of the use of other forms of real-world data for signal detection, while their more traditional use for signal analysis continues. The source of spontaneous reports will usually be health professionals, but may also include patients or others. The early evidence from spontaneous reports can be regarded as finding a "signal." A signal is "Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify confirmatory action," (CIOMS, 2010), a definition adapted from that proposed by Hauben and Aronson (2009).

The signal can initiate from the intrinsic characteristics of an individual case report or a case series, or from the identification of statistical relations between case reports in large amounts of data, the latter being referred to as quantitative signal detec-

tion (QSD). The object is to try to distinguish the real signals from "noise" with the maximum possible precision.

QSD has been referred to in the pharmacovigilance literature more or less synonymously with the term "data mining." Data mining is a term that germinated originally in the computational science literature and has been used to describe any computational method used to automatically and continuously extract useful information from large amounts of data. Data mining is a form of exploratory data analysis (Hand *et al.*, 2001) and a key component of the knowledge discovery process (Fayyad *et al.*, 1996). Data mining can clearly be used on any data set, but the approach seems particularly valuable when the amount of data is large and the possible relationships within the data set numerous and complex.

## QUALITATIVE SIGNAL DETECTION

QSD (e.g. an "abnormal" number, proportion, odds or rate of reporting of cases) implies a prior statistical analysis attesting that the observed value is outside of what would be expected. This is the most common sense of signal detection in pharmacovigilance and will be discussed in the third part of this chapter.

Notwithstanding, in some cases, a signal may ensue from the qualitatively "abnormal" nature of what is observed, either at the subject or the population level. Here, the term signal refers to the type of the event and/or its conditions of occurrence. For example, some drugs may induce symptoms not usually or seldom observed on other occasions. Their baseline incidence (i.e., in the absence of treatment or exposure) is so low that a single case, or at least some of them, observed in a treated population can trigger a robust signal. Paragons are clinical or biological symptoms specifically associated with a given drug (e.g., yellow-green dyschromatopsia with digoxin, cinchonism with quinine) or never observed in the absence of a drug treatment (e.g., fixed eruptions). Among others, historical examples are: (i) vaginal adenocarcinomas observed in 10–14-year-old girls, where the highly unexpected nature of this lesion led to dis-

covering the causal role of *in utero* exposure to diethylstilboestrol; (ii) the unprecedented syndrome consisting of myoclonias and encephalopathy, which led, in the late 1970s, to discovering the neurotoxicity of bismuth salts, which until then were not thought to be absorbable from the intestinal tract (Buge *et al.*, 1977).

A signal can also be generated not from the clinical or biological pattern of the event observed but from its unexpected severity or seriousness. This would be the case if three cases of fulminant hepatitis were observed during the first year of marketing of a given drug while only mild increases in plasma aminotransferase levels had been previously reported with this class of drug. The term “designated medical events” has been used to describe this type of adverse event in recent years; that is, events that may trigger an alert on the basis of only one to three cases since they are rare, medically serious, have a high drug-attributable risk, and may occur with drugs from diverse pharmacological/therapeutic classes (Hauben, 2004). The WHO Programme for International Drug Monitoring has a list of “critical terms” that are adverse event terms based on a similar concept and have been subject to more intense analyses, since the 1970s (Lindquist *et al.*, 1999). “Targeted medical events” are similar but refer to events based on clinical/pharmacological characteristics specific to a drug, its treatment indication(s), and to such factors as may be monitored in a similar fashion for specific products.

Evocative temporal associations between exposure and outcome are another possibility for qualitative signal detection. Caricatured illustrations are seizures or cardiac arrhythmias occurring during the first minutes of drug administration or during an intravenous drip. A more debatable example was the reports of first episodes of multiple sclerosis (Herroelen *et al.*, 1991) observed in France within days or weeks following injection of a dose of anti-hepatitis B vaccine. Whatever the reality of its causal nature, this temporal association assessed as suspect by several neurologists generated a strong enough signal to justify the funding of an ad-hoc pharmacoepidemiologic program (Touzé *et al.*, 2002). Comprehensive in-depth reviews of events whose clinical nature can make even spontaneous

reports dispositive for establishing causality have been published (Hauben and Aronson, 2007).

## **GENERAL PRINCIPLES OF STATISTICAL ANALYSIS OF SPONTANEOUS REPORTS: RATE COMPUTATIONS, DRUG–DRUG COMPARISONS, COMPARISON WITH A GIVEN THRESHOLD**

In this section we will focus on signal detection based upon spontaneous reports, apart from disproportionality approaches, which will be extensively discussed later. Sadly, because not all adverse reactions are recognized or reported in the framework of spontaneous reporting, the researcher has available only a limited number  $k$  of cases of a given event presented as associated with current or past exposure to a given drug and reported during a given timeframe. These reports come from a sort of “black box”; that is, the territory considered, not directly providing crucial information for signal strengthening and causality assessment, such as the background conditions of exposure and characteristics of subjects with and without adverse outcomes.

In some cases, as described above, these reports can trigger a signal by themselves. However, in most situations, one is interested in attempting to derive a reporting “risk” from this number of reports  $k$  and in knowing whether this “risk” remains acceptable when compared with a relevant reference. That is trickier than meets the eye. The quotation marks are to stress that, in real-world scenarios, it should not be expected that risk can be calculated or estimated from spontaneous reports data. Herein, we discuss the relevant concepts under idealized assumptions related to the control or adjustment of the numerous recorded and unrecorded confounders, effect modifiers, and other reporting artifacts that limit spontaneous reports data.

### **“RISK” ESTIMATES FROM SPONTANEOUS REPORTS**

First,  $k$  is likely to underestimate the actual number  $a$  of cases of this event having occurred during the

period in patients treated with the drug considered since:

$$k = \frac{a}{U} \quad (20.1)$$

$U$  being the underreporting coefficient, the magnitude of which is never actually known but may usually be expected to be large, even for serious adverse events and countries with efficient pharmacovigilance systems. Several studies have found that the proportion of adverse events actually reported to a pharmacovigilance system is in the order of 5–10%, which would correspond to an underreporting coefficient of 10 to 20 (Moride *et al.*, 1997; Bégaud *et al.*, 2002; Hazell and Shakir, 2006). To complicate matters, this coefficient is prone to be modified by many factors. If  $U$  were precisely known, the actual number of cases having occurred in the source population during the same period of time would be

$$a = kU \quad (20.2)$$

As this is scarcely ever the case, one may test several theoretical values of  $U$  in a sort of sensitivity analysis in order to assess the safety margin before  $k$  exceeds an acceptance threshold.

For risk estimates,<sup>1</sup> the number  $k$  should be paired with a relevant denominator, most often derived from sales statistics or reimbursement databases, provided they satisfactorily superimpose with the source population of cases for the time-frame considered. Reimbursement databases can provide information such as the precise number and characteristics of patients, exposure patterns (dose, duration, concomitant medications, etc.) in the source population, making possible both a coarse/reasonable “risk” assessment and hypotheses about a putative mechanism for the adverse event. Sales statistics only allow rough and averaged estimates of the exposure density in the source

population, preferably expressed in person-time or more uncertainly in a presumed number of treatments or patients. In any case, computations from both sources should consider assumptions about compliance; that is, the proportion of drug units prescribed or reimbursed that have been actually taken by patients.

One always should bear in mind that “risk” estimates derived from spontaneous reports ensue from an underestimated numerator and a probably inflated denominator. Therefore, except in extremely rare examples, they are far from reflecting the actual risk that would have been measured in the source population with an ad-hoc approach. Underestimation by a factor of 20 or more has to be considered as a starting point. However, this depends much on reporting rates or underreporting, which can vary much even within the same therapeutic class or for the same events, depending on time on market, familiarity with the drug and event, and notoriety of the association, including media attention.

## EXPECTED NUMBER OF REPORTS

If  $n_1$  was the total number of exposure units (exposed person-time, number of treatments, number of patients),  $i_0$  the baseline incidence of the event (i.e., in the absence of exposure), and  $RR_1$  the factor by which  $i_0$  is multiplied on account of exposure to Drug 1, the expected number of reports for the period and territory considered is

$$k_1 = n_1 i_0 \frac{RR_1}{U_1} \quad (20.3)$$

We use here the term of *exposure* and not *treatment*, since these two temporal sequences are not always superimposed: treatment refers to the time interval between actual start and discontinuation of drug administration, and exposure to the hazard function of the considered effect after beginning the treatment. For example, for anaphylaxis, patients will be exposed (i.e., “at risk”) during the first hours or days of treatment and not for the following time units. On the other hand, for pulmonary fibrosis or peripheral neuropathy, patients

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<sup>1</sup>The use of the term “estimate” in this chapter is a convenient expository device. From a purely scientific perspective, interpreting a disproportionality metric calculated using spontaneous reporting data as an “estimate” should be avoided.

become at risk (i.e., exposed for this event) only after several months of treatment. In more extreme cases, the “at-risk” period can be long after treatment discontinuation.

### HOW MANY REPORTS SHOULD TRIGGER A SIGNAL?

Equation 20.3 conveys one of the secrets of the indisputable value of spontaneous reporting for signal generation, at least for effects with a low baseline incidence in the population. Let us take the example of agranulocytosis, the baseline incidence of which in the general population is of the order of seven per million inhabitants per year (Kaufman *et al.*, 1996; Théophile *et al.*, 2004). For a drug with an average duration of treatment of 1.4 months, the baseline risk for this time interval is  $7 \times 1.4/12 = 0.82$  per million. While it would be unrealistic to put forward an estimate for the value of  $U_1$ , in reality it is unlikely that more than 20% of cases would be reported (Moride *et al.*, 1997; Bégaud *et al.*, 2002; Hazell and Shakir, 2006) (six to eight; i.e.,  $U_1 = 5$ ). In Equation 20.3, one sees that with  $i_0/U_1$  being  $(0.82 \times 10^{-4})/5 = 0.164$  per million,  $k_1$  is expected to remain markedly under one except if RR was  $>1$  or/and  $n$  extremely large. Therefore, in the absence of an association (causal or not) between exposure and event (RR<sub>1</sub> being one), it is most unlikely to expect one or more report(s). In our example, receiving two reports of a coincidental association would require  $n_1$  to be 12.2 million. Therefore, at least for events for which the baseline incidence in the population is very low (i.e., below 20 per million per year – agranulocytosis, toxic epidermal necrolysis, pulmonary hypertension, Guillain–Barré syndrome, etc.), receiving two or *a fortiori* three case reports is usually sufficient to trigger a signal (Tubert *et al.*, 1991). Obviously, this would not be the case for diseases and symptoms occurring commonly in the general population, even if in this case underreporting is expected to be even larger.

Statisticians know that when  $k$  outcomes are expected, the probability of actually observing  $k$  outcomes is never 100%. In that sense, cumulative Poisson probability tables provide several interesting figures:

- In order to be sure to receive one case report, with at least 95% probability, the expected number ( $k_1$  in Equation 20.3) should be at least three. When  $k_1 = 1$ , the probability of receiving one report or more is only 63%.
- On the other hand, if one report was received, the expected number has 95% probability of being 0.051 or greater, the value being 0.355 for two reports and 0.817 for three. Let us consider a drug for which the total time of exposure derived from sales statistics is 1.8 million months (i.e., 0.15 million years). Three cases of Guillain–Barré syndrome have been received during the period. The baseline incidence of this disease is about 12 per million per year (Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. 1997). The expected number of coincidental associations (RR being one) is thus  $0.15 \times 12 = 18$ . In view of the inevitable underreporting that will make their expected number lower, these three reports constitute a valuable signal. Indeed, assuming (an already good performance) that 20% of cases were reported ( $U = 5$ ), the expected number  $k_1$  becomes  $1.8/5 = 0.36$ , and Poisson tables show that there is only 0.6% probability to observe three or more cases when 0.36 were expected.

### MIGHT DRUG 1 CAUSE AN ADVERSE EVENT MORE OFTEN THAN DRUG 2?

The concern here is that the biases discussed above can differently alter each individual risk estimates, the worst being underreporting. For a given event, the risk ratio comparing Drug 1 and Drug 2 is

$$\text{RR} = \frac{U_1 k_1 n_2}{U_2 k_2 n_1} \quad \text{or} \quad \text{RR} = \frac{U_1}{U_2} \frac{k_1 n_2}{k_2 / n_1} \quad (20.4)$$

$k_1$  and  $k_2$  being the number of reports for Drug 1 and Drug 2 respectively and  $n_1$  and  $n_2$  the respective estimates for exposure levels in the source population. A differential underreporting ( $U_1 > U_2$  or  $U_1 < U_2$ ) would lead to aberrant estimates for RR. Since the individual values of  $U_1$  and  $U_2$  remain unknown, Tubert-Bitter *et al.* (1996) proposed

expressing the confidence interval (CI) for RR (Equation 20.4) as a function of  $U = U_1/U_2$ :

$$\text{CI}_{\text{RR}} = \left[ U \frac{N_2}{N_1} \frac{k_1 - Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}}{k_2 + Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}}, U \frac{N_2}{N_1} \frac{k_1 + Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}}{k_2 - Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}} \right]$$

Although daunting in appearance, this formula is straightforward to use. For example, 12 and 19 cases of a given event were reported for Drug 1 and Drug 2 when the respective total treatment durations were 2.5 million months and 34 million months. The apparent risk ratio is

$$\text{RR} = \frac{12 \times 34}{19 \times 2.5} = 8.6$$

The 95% two-tailed CI for RR is

$$\text{CI}_{\text{RR}} = \left[ U \frac{34}{2.5} \frac{12 - 1.96 \sqrt{\frac{12 \times 19}{31}}}{19 + 1.96 \sqrt{\frac{12 \times 19}{31}}}, U \frac{34}{2.5} \frac{12 + 1.96 \sqrt{\frac{12 \times 19}{31}}}{19 - 1.96 \sqrt{\frac{12 \times 19}{31}}} \right] = [3.7U; 17.2U]$$

One can safely conclude that Drug 1 is significantly more toxic than Drug 2, provided its reporting rate was not 3.7-fold higher than for Drug 2. In this case, the 95% CI for RR would include one, precluding statistical significance.

On the other hand, the risk with Drug 1 might be as much as 17.2 times higher than that for Drug 2. This might be relevant from a public health or regulatory point of view, following a precautionary principle. The reasoning might then be based on the maximal acceptable risk ratio at the upper limit of the 95% CI rather than on purely statistical significance of the lower limit.

Strength of inference of the type described in this section is realistically only potentially possible in a clearly defined region such as regional settings (e.g., the regional pharmacovigilance centers in France; Moore *et al.*, 2007), where drug use and occurrence rates of reporting as well as underlying population characteristics can be established. Caution is required when these attributes cannot be captured with accuracy, as would be the case on a wider macro level, particularly globally. The principles in this section can be applied in such settings, but the outputs should be interpreted with caution and in such situations solely used for hypothesis generation. Even on a national or international level, reporting rates can be useful for signal detection as long as appropriate caveats are emphasized. Other work on quantitative analysis of spontaneous reports on a global level includes estimation of reporting rates using IMS international sales data as a denominator (Lindquist and Edwards, 1997; Lindquist *et al.*, 1999). Several quantitative approaches to look for trends in reporting rates have been proposed, such as by Norwood and Sampson (1988) and Praus *et al.* (1993). When there is great variability and uncertainty around under- (and over-)reporting, drug utilization, confounding factors, at risk populations, and so on, other approaches, such as measures of disproportionality, can be a more robust quantitative initial screening tool for signal detection than reporting rates (Bate and Evans, 2009).

Another approach to examining the magnitude of underreporting is the use of the capture-recapture method to estimate the actual number of cases, or the degree of underreporting, when several separate and near-independent systems of case collection are available to the same population, such as in the UK spontaneous reporting and prescription-event monitoring (e.g., see Moore *et al.* (2003)), or potentially spontaneous reports to national systems and to industry, if duplicate reports can be identified.

## PRINCIPLES OF MEASURES OF DISPROPORTIONALITY

Measures of disproportionality compare the number of reports in a spontaneous report data-

Table 20.1 A  $2 \times 2$  contingency table for a specified drug and adverse event.

	+ Drug	- Drug	Total
+ Adverse event	$a$	$b$	$a + b$
- Adverse event	$c$	$d$	
Total	$a + c$		

base for a specific ADR reported for a particular drug with the number expected based solely on other reporting in the same database (Bate and Evans, 2009). This contrasts with other statistical analyses of spontaneous reports using sales or reimbursement data as discussed in the preceding section. The principles are not new, but were set out in a similar way by Patwary (1969), Finney (1974), and Mandel *et al.* (1976) for ADR reporting with World Health Organization (WHO) data. A physical implementation, a so-called “pigeon-hole system” has also been proposed (Napke and Bishop, 1966). Specific examples using disproportionality analyses (DAs) include an investigation of serum sickness like reactions and cefaclor (Stricker and Tijssen, 1992), and ACE inhibitors and hypoglycemia (Moore *et al.*, 1997). Such methods were effectively reinvented for safety surveillance, screening simultaneously huge numbers of combinations of drug–outcome pairs in the search for signals, and have now been in routine use in many organizations for more than a decade (Hauben and Norén, 2010).

One commonly used example of a measure of disproportionality is the PRR; the calculation of the PRR is

$$\text{PRR} = \frac{a/(a+b)}{c/(c+d)}$$

Using the cells  $a$ ,  $b$ ,  $c$ , and  $d$  as defined in a  $2 \times 2$  contingency table (see Table 20.1).

This is analogous to a relative risk, but applied to spontaneous report data, and therefore with associated weaker inferential capability (see next section, “Biases affecting disproportionality analyses from spontaneous reporting data”). An obvious alternative is to use an odds ratio ( $ad/bc$ ), sometimes referred to as a “reporting odds ratio,” or ROR. This has slightly more desirable statistical

properties than a PRR (van der Heijden *et al.*, 2002; Rothman *et al.*, 2004), but will be very similar in magnitude since in most circumstances  $b \gg a$  and  $d \gg c$ , and it is questionable whether this has any practical impact on routine pharmacovigilance (Waller *et al.*, 2004). Please note, a similar approach to the PRR and classical measures of disproportionality is used in classical epidemiology with death data – the “proportional mortality ratio” (e.g., Rothman and Greenland, 1998).

When a reaction is new and rare, then  $a$  (in the  $2 \times 2$  table, Table 20.1) can be one or a very small number, and it is possible that there are no other drugs with that exact reaction. This means that  $b$  is zero and the PRR or ROR is not calculable. However, the second row can refer to *all* drugs rather than “all other drugs.” This means that  $c$  is never zero and the estimate can always be calculated, and the estimated values are less than they would be otherwise; this conservatism applies when the numbers are small. When the PRR formula of PRR is taken and the second row refers to all drugs, this gives rise to a measure that underpins the two Bayesian methods in common use that are discussed below, namely the information component (IC) (Bate *et al.*, 1998) and the empirical Bayes gamma mixture (EBGM) identifier (DuMouchel, 1999).

On the other hand, if there is only a single report of a very specific reaction to the drug of interest, and none to any other drug, we are probably leaving the realm of disproportionality to return to the individual case assessment approach.

A more general approach than the above is to ask “What is the expected number of reports for this ADR and this drug?” and then to compare the observed number with the expected number. A first attempt to obtain the expected number is to assume that the proportion of reports for this ADR with this drug will be the same as the proportion for this ADR in the database as a whole,  $P_{\text{ADR}}$ . The expected number can then be obtained using the total reports for this drug,  $N_{\text{drug}}$ :

$$E_{\text{ADR,drug}} = P_{\text{ADR}} N_{\text{drug}}$$

The deviation of the observed number from the expected number can be expressed as a ratio; that is:

Table 20.2 Disproportionality measures for reports of hyperkalemia.

	+ Sulfamethoxazole and trimethoprim	- Sulfamethoxazole and trimethoprim	Total
+ Hyperkalemia	423	11 258	11 681
- Hyperkalemia	15 657	4 609 940	
Total	16 080		

In all reports between 1968 and 2011 (based on WHO database counts).

Selected estimates based on this table and in the case of the EBGM and EB05 based also on a prior distribution from all drug–event combinations in the database) are PRR = 9.5, EBGM = 9.1, EB05 = 8.3, and ROR = 9.9.

$$\frac{O_{ADR,drug}}{E_{ADR,drug}}$$

The expected count can be modified to allow for age and sex to be taken into account. This is equivalent to having a set of  $2 \times 2$  tables stratified by age and sex, where an estimate can be derived using a general Mantel–Haenszel estimator from several  $2 \times 2$  tables. It is also possible to use logistic regression to obtain such an estimate. These measures have allowed for the *magnitude* of the effect to be assessed; they have not made any allowance for chance variation. The usual chi-square test (corrected using the Yates method to be conservative), or for stratified tables using the Mantel–Haenszel method, can be calculated. This chi-square value indicates the probability that the play of chance could have resulted in a PRR of at least that magnitude.

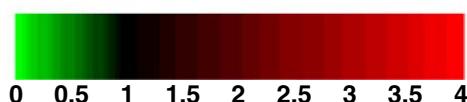
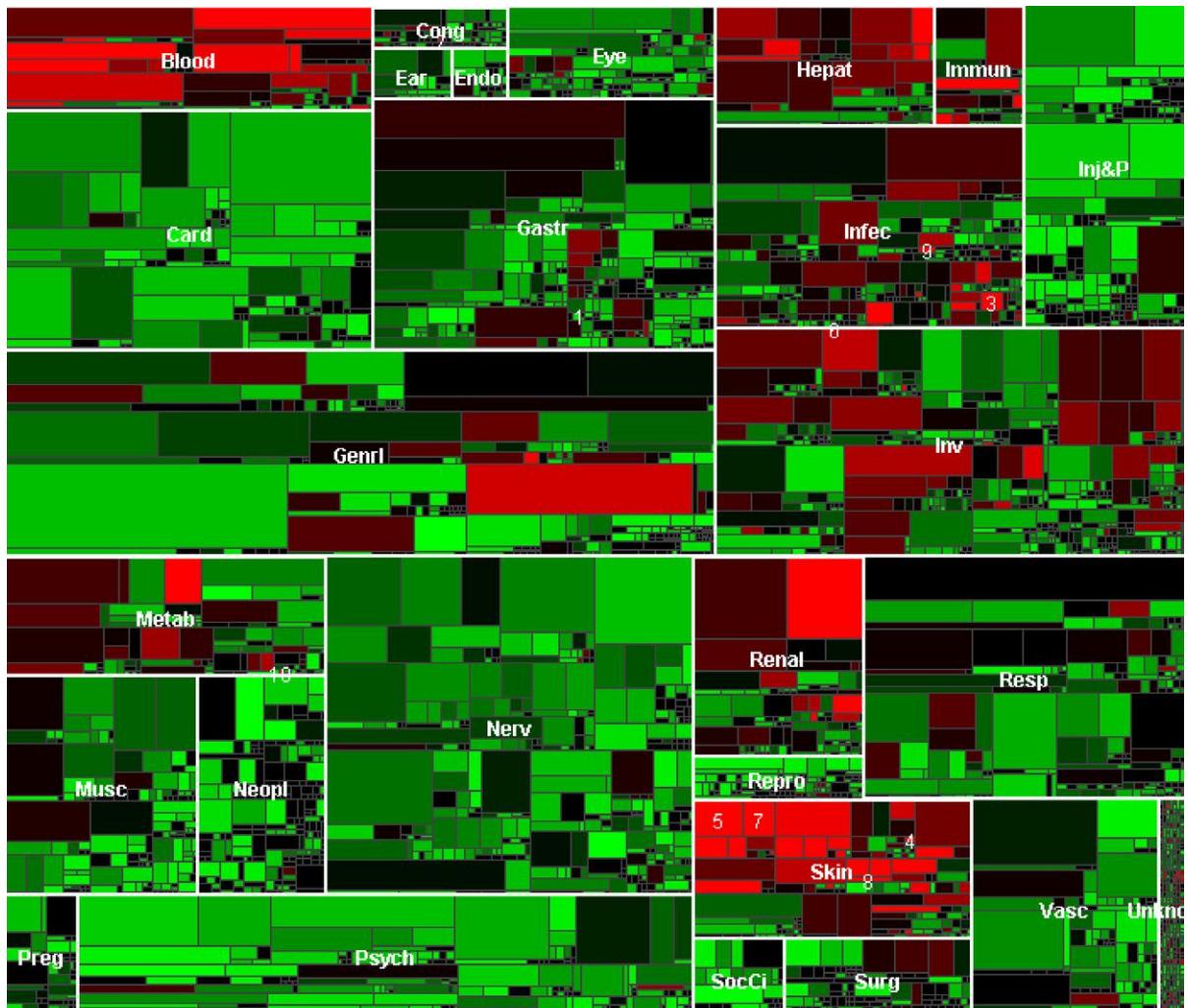
Table 20.2 gives an example of measures of disproportionality for reports of hyperkalemia with the drug combination sulfamethoxazole and trimethoprim. Consider the PRR estimate. The proportion of reports of hyperkalemia with the drug combination sulfamethoxazole and trimethoprim is  $[423/(423 + 11258)] = 0.0004$ , while the proportion for all drugs is  $15567/(15567 + 4609940) = 0.0004$ : PRR = 9.5. The scores for this drug combination with all adverse event terms are visualized in a heat map in Figure 20.1. The change over time for the association is shown in Figure 20.2.

It should be realized that all of this process should be used for the purpose of signal detection, and even more importantly for prioritization of the detected signals, which depends both on the magnitude of the disproportionality and the absolute number of observed cases for the combination

reported as a proxy of the population risk, to help decide which ones require most urgent further investigation.

The basic data are still subject to biases; they are at very best observational data, and to use a high value of a PRR or odds ratio as the sole convincing evidence of causation is unwarranted, and it is now well established that all have less than perfect performance characteristics (Lindquist *et al.*, 2000; Hauben and Reich, 2004; Roux *et al.*, 2005), meaning both false negatives and false positives are produced. They raise a question that merits further consideration. Commonly, the value of the lower limit of the CI of a score, or the score itself, triggers a clinical review when passing a predefined value (Bate and Evans, 2009). This mitigates the burden of false-positive results.

As mentioned above, Bayesian approaches have also been proposed as measures of disproportionality, in particular the IC and EBGM, and are in routine use. The WHO's approach (Bate *et al.*, 1998), originally based on a Bayesian confidence propagation neural network, although this is no longer the case, uses the log (to the base 2) of the observed/expected ratio based on the same  $2 \times 2$  table as that above, but it shrinks the estimate based on a “prior” assumption of no association between drug and event in the absence of data to the contrary. This weighting damps the observed/expected ratio towards the null value, and this dampening effect is increasingly inconsequential as data accumulate. The objective of this is to reduce false positives with limited data support and an inflated crude observed-to-expected ratio. The cut-off for a signal is based on the CI around the IC for other measures of disproportionality.



Rank	SOC	Term (PT)	EB05
1	Gastr	Tooth decalcification	31.932
2	Cong	Spine malformation	23.117
3	Infec	Pneumocystis jiroveci pneumonia	14.939
4	Skin	Acute febrile neutrophilic dermatosis	14.759
5	Skin	Stevens-Johnson syndrome	14.660
6	Infec	Nocardiosis	13.854
7	Skin	Toxic epidermal necrolysis	13.038
8	Skin	Drug rash with eosinophilia and systemic symptoms	12.678
9	Infec	Meningitis aseptic	10.935
10	Metab	Folate deficiency	8.627

Figure 20.1 Heat map representation of scores for the sulfamethoxazole and trimethoprim drug combination (subset: 1968–2011) with all adverse event terms. Adapted from Pariente 2009.

AERS 2011Q3-Sulfamethoxazole And Trimethoprim-Hyperkalaemia

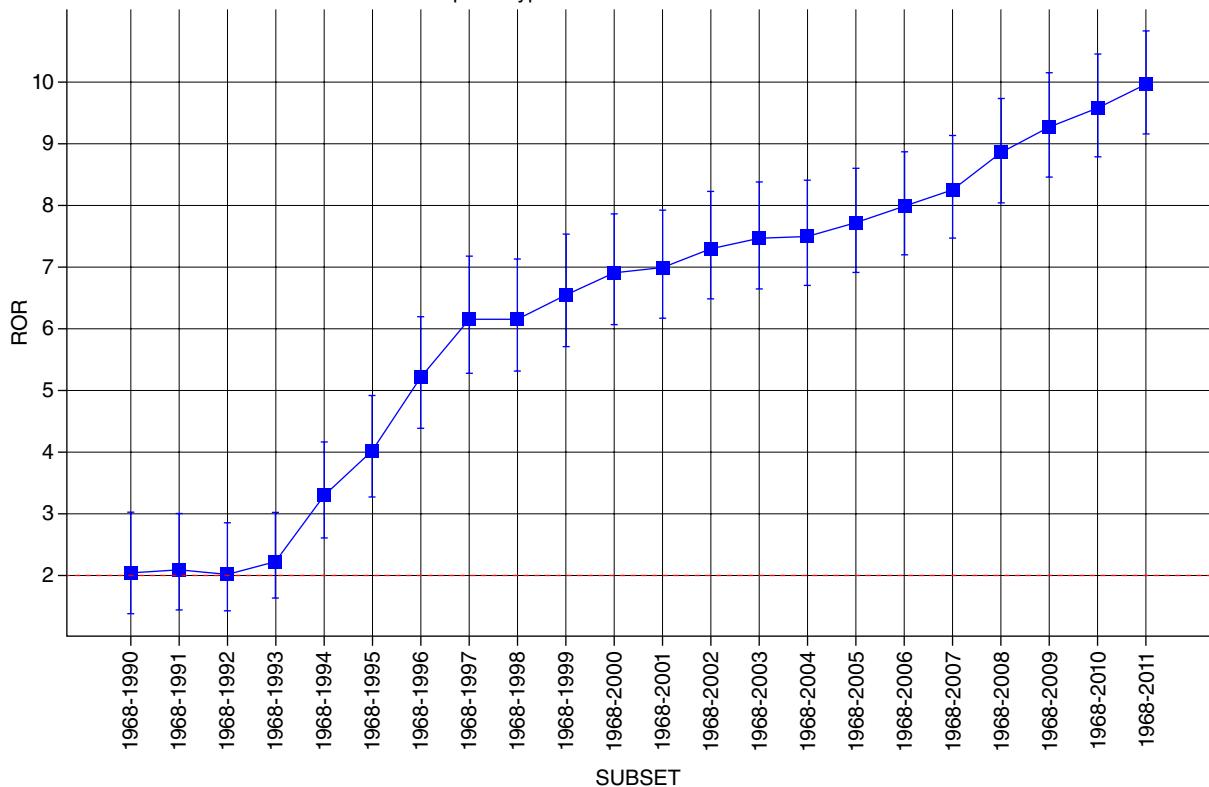


Figure 20.2 Cumulative change over time in ROR value for the combination of sulfamethoxazole and trimethoprim with hyperkalemia.

The IC can be defined as (Norén *et al.*, 2013)

$$\text{IC} = \log_2 \left( \frac{O + \alpha_1}{E + \alpha_2} \right)$$

The IC lower 95% credibility interval can be defined as (Norén *et al.*, 2013)

$$\log_2 \left\{ \frac{a + \alpha_1}{[(a + b + c + d)/(a + b)(a + c)] + \alpha_2} \right\} - 3.3(a + \alpha_1)^{-1/2} - 2(a + \alpha_1)^{3/2}$$

And the IC upper 95% credibility interval can be defined as (Norén *et al.*, 2013)

$$\log_2 \left\{ \frac{a + \alpha_1}{[(a + b + c + d)/(a + b)(a + c)] + \alpha_2} \right\} - 3.3(a + \alpha_1)^{-1/2} - 2(a + \alpha_1)^{3/2}$$

where  $a$ ,  $b$ ,  $c$ , and  $d$  are the counts in the  $2 \times 2$  contingency table, and  $\alpha_1$  and  $\alpha_2$  are both set equal to 1/2 in the routine implementation of the IC used at the Uppsala Monitoring Centre.

The above formulas were derived after empirical testing and represent a simplification of earlier proposed formulations of the credibility interval (Orre *et al.*, 2000; Norén *et al.*, 2006, 2008).

An alternative Bayesian approach is used by the FDA (DuMouchel, 1999; Szarfman *et al.*, 2002). It is very similar to other methods of disproportionality, but, as with the IC, offers better properties when very small numbers of observed and expected cases for a combination occur, as compared with non-Bayesian approaches. It uses an “empirical Bayes” method, which shrinks  $\log(O/E)$  towards zero, and, as for the IC, the shrinkage is important if  $E$  is small, but gives very similar

results when observed or expected numbers of reactions are reasonably large. Shrinkage is affected by modeling a prior based on the observed/expected ratios of all drug–adverse event combinations in the database under consideration, which in practice contains many nonsignals and has the effect of a prior similar to that of the IC, but is “data driven” in shape rather than defined by external judgment. It is slightly more complex in the calculations than the IC and non-Bayesian approaches, and consequently less transparent than other approaches. The more sophisticated empirical shrinkage employed by the EBGM means that the shrinkage varies depending on the nature of the data set to which the algorithm is applied to, and this is demonstrated in Almenoff *et al.* (2006), who showed that with an artificial data set with no injected signals (neither false nor true) that the EBGM algorithm could avoid false positives. In practice, on the spontaneous report data sets on which disproportionality methods are routinely applied, the difference in performance is often limited (scores are very similar when three or more cases are observed (van Puijenbroek *et al.*, 2002)) and no algorithm clearly outperforms the other. There are some that considers the Bayesian approaches (IC and EBGM) to be superior because of their capability in reducing false positives, which outweighs this decreased transparency with the added complexity of their approaches. While the overall intent of the Bayesian approaches is that overall false positives should be reduced with a limited practical impact on false-negative rate, on an individual combination level there is naturally the possibility that this shrinkage can lead to a false negative; and there has been some research suggesting this to be the case overall for EB05 – the lower 95% confidence limit of the EBGM; for example, see Chen *et al.* (2008) and Hauben *et al.* (2007a) – although there are to our knowledge no studies showing that this is a problem in practice for the IC. Recent variations of frequentist methodology have appeared (Huang *et al.*, 2012; Johnson *et al.*, 2012), some of which have been reported to produce results similar to empirical Bayesian approaches in initial investigations (Johnson *et al.*, 2012). For a summary of different measures of disproportionality see Table 20.3.

## **BIASES AFFECTING DISPROPORTIONALITY ANALYSES FROM SPONTANEOUS REPORTING DATA**

DAs in spontaneous reporting databases, testing whether an ADR is reported more often than expected and resulting in signals of disproportionate reporting (SDRs) (Hauben and Aronson, 2009), constitute the basis of most signal detection methods (van Puijenbroek, Bate *et al.*, 2002). These SDRs must be differentiated from safety signals, as a safety signal does not always imply a corresponding SDR, and the existence of an SDR is not always sufficient to constitute a safety signal (Hauben *et al.*, 2007c). SDRs are only statistical associations, very far from confirmed causal relationships. The potential causality underlying SDRs can be examined by (i) eliminating potential biases and (ii) assessing the quality and clinical relevance of the cases supporting the SDR, biological plausibility, dose-dependence, and other indicators of causality. This section will focus on these potential biases.

The DAs application to the particular context of spontaneous reporting does not protect them from the classical biases encountered in epidemiology (Moore *et al.*, 1997, 2003). To better understand how these might occur, it is important to know the content of a suspected ADR report, of a spontaneous reporting database, and the mechanism by which a report happens to be recorded in a spontaneous reporting database. Below, we discuss potential biases affecting signal detection from DAs according to their relation with these structures or these mechanisms.

## **BIASES RELATED TO THE DRUG-EVENT PAIR REPORTING**

A spontaneous report of adverse reaction is a notification in which one or more adverse events are associated with one or more drugs. The drugs mentioned are usually mostly those suspected to be responsible for the event(s). However, a drug will not be suspected only on the basis of its pharmacological properties or safety profile. The time sequence between drug exposure and event occurrence will also be crucial. For this reason, many

Table 20.3 Conditions, advantages, and disadvantages of different measures of disproportionality.

Measure of disproportionality	Type	Expected 'null value'	Conditions	Advantage	Disadvantage
Information component	Point estimate	0	None	Always applicable Large numbers of calculations can be made efficiently Adapted for Three-way associations	Relatively non-transparent for people not familiar with Bayesian statistics
Reporting odds ratio	Point estimate	1	Cells <i>b</i> and <i>c</i> have to contain reports	Easy applicable Different adjustments possible in logistic regression analysis In logistic regression analysis, is the actual metric, so these interaction terms can be used for the analysis of drug interactions and syndromes Easy interpretation	Odds ratio cannot be calculated if denominator is zero (specific ADRs) Interpretation difficult Results not always reliable in the event of small numbers in cells <i>a</i> , <i>b</i> , <i>c</i> , and <i>d</i> of the contingency table
Proportional reporting ratio	Point estimate	1	Cell <i>c</i> has to contain reports	Easy interpretation	Cannot be calculated for all drug-ADR combinations (see conditions of use)
Empirical Bayes Geometric Mean	Point Estimate	Varies with data set but approximately equal to 1	None	Reflects on structure of data (varying shrinkage) Adapted for three-way association	Nontransparent computationally intensive Risk of skewed/asymmetric prior in data sets with unusual properties leading to seemingly capricious shrinkage
Poisson	Test		Only for rare events	Correction for different covariates can be easily established in Poisson regression Always applicable	Only <i>p</i> -value provided
Chi square (Yates correction) ROR-1.96SE	Test		Cells <i>a</i> , <i>b</i> , <i>c</i> and <i>d</i> have to contain reports	Correction for different covariates can easily be established (see ROR strength)	Standard deviation cannot always be calculated
IC-2SD 5th percentile of posterior Empirical Bayes Geometric Mean (EB <sub>05</sub> ) PRR - 1.96SE	Test		None None	Always applicable As for EBGM	As for EBGM
			Cells <i>a</i> , <i>b</i> , <i>c</i> , and <i>d</i> have to contain reports		Standard deviation cannot always be calculated

drugs are often cited in spontaneous reports. A non-negligible amount may indeed be drugs traditionally used to prevent the reported event or to treat a disease predisposing to this event, and consequently used by the patient at the time the event occurred. This leads to numerous SDRs in which a drug is found associated with an event because it is indicated in patients with comorbidities that increase the risk of that event. This *indication bias* is related to the preferential prescription of drugs in patients at higher risk of an event. It has been demonstrated for several SDRs in the past, as for instance for those associating angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists to the occurrence of hypoglycemia (Moore *et al.*, 1997; Grégoire *et al.*, 2008). In fact, these antihypertensive drugs are of particular interest in diabetic patients. When restraining the analyses to reports referring only to diabetic or to nondiabetic patients, the association disappeared and the authors concluded that the bias was eliminated. On the other hand, if a drug is contraindicated in an at-risk population, then other drugs without the contraindication may be found associated with a higher rate of such events at risk (which would constitute a contraindication bias).

Similarly, the *co-prescription bias* may generate spurious SDRs, associating an event with drugs that do not intrinsically increase the risk of the event, but are frequently co-prescribed with drugs that really do. For instance, the co-prescription bias can result in an SDR associating acetaminophen with constipation, a well-known adverse effect of the opioids commonly prescribed with acetaminophen.

## BIASES RELATED TO THE SPONTANEOUS REPORTING DATABASE STRUCTURE

In epidemiology, a traditional  $2 \times 2$  contingency table opposes exposed to nonexposed, and cases to controls. In spontaneous reporting databases, all information concerns patients receiving drugs and having suspected adverse reactions. Thus, all patients are both exposed and cases. The  $2 \times 2$  contingency tables that underlie DAs thus oppose patients exposed to a drug to patients exposed to

other drugs, and patients with a specific event to patients with another event. This is why this approach is sometimes also called “case–non-case” (Moore *et al.*, 1997).

DAs will thus compare the proportion of one event among others for a given drug with that proportion for all other drugs. In doing this, they put in competition the different events: the greater the weight of an event in the global reporting of a drug, the less the other events can weight. If, for instance, bleeding accidents accounted for 60% of reports for an anticoagulant, other events could account at best for 40% of reports for that drug. If bleeding accidents accounted for 5% of reports for all other drugs in this database, any other event could represent up to 95% of reports for these drugs. The ability to detect SDRs not involving bleedings would thus be limited for anticoagulant agents by the important weight of bleed reports. This bias is called the “masking effect” or the “event competition bias,” and may mask SDRs for any drugs with a specific and highly reported event, which has an important weight in the drug’s overall reporting (Gould, 2003; Almenoff *et al.*, 2005; Wang *et al.*, 2010; Pariente *et al.*, 2012).

Conversely, when studying the potential signals associated with a given event, DAs will compare the relative importance of one drug among others for this given event with that observed for all other events, inverting the masking effect previously mentioned. Compared to the hypothetical anticoagulant, another drug would need to have at least 60% bleed reports for an SDR. The ability to detect SDRs for a drug will be constrained by the importance of the reporting involving other drugs for the event of interest. This masking effect as also been designated as the “(drug) competition bias” (Gould, 2003; Pariente *et al.*, 2010; Wang *et al.*, 2010); see Figure 20.3.

## BIASES RELATED TO REPORTING RATES VARIABILITY

The reporting of an event is conditioned by many variables, and spontaneous reporting is characterized by very important underreporting. This would not result in bias if it were constant over time and

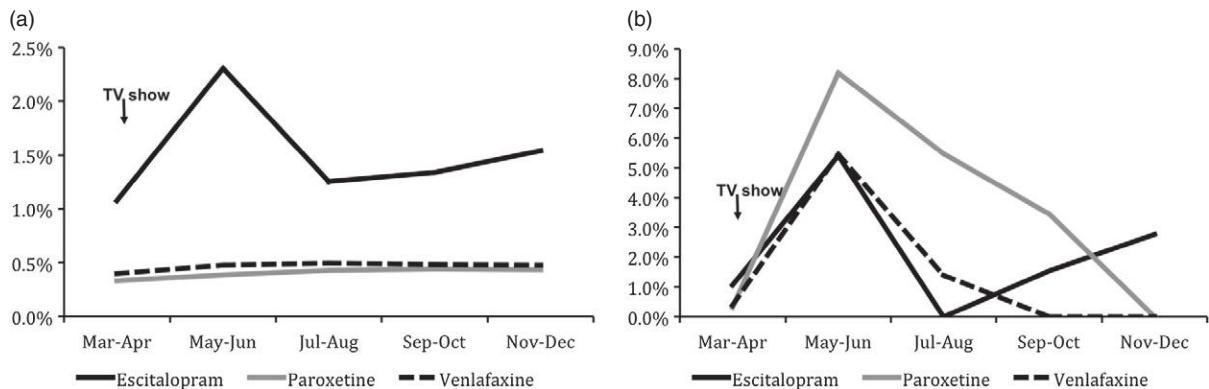


Figure 20.3 Competition bias and masking effect. Background rates of reporting for seven different events as estimated from the French pharmacovigilance database (2006) with or without considering reports mentioning drugs at risk for the event (e.g., anticoagulants for bleeding). Adapted from Pariente *et al.* (2010). Reproduced with permission of John Wiley.

nondifferential between drugs and between events. However, underreporting varies, especially in the case of media attention for a given drug–event association. This can lead to trends in reporting: an event can be more reported (or less underreported) with a given drug, though its occurrence remains constant. This increased reporting can result in an SDR for that drug if the reporting does not vary for other drugs. If this is related to an increased recognition of the effect with the drug incriminated and not with an increased incidence, this SDR will be spurious. This has been designated as the “notoriety bias” (Pariente *et al.*, 2007; Raschi *et al.*, 2011), and is related to the classical detection bias encountered in epidemiology. In the same way, media attention can result in the reporting of older cases (in a kind of dredging bias): analysis has to consider date of occurrence, not of reporting, although analysis by date of reporting may give valuable insight on reporter attitudes.

To result in an SDR, this increased reporting needs to be found significant; that is, to have a weight in the drug reporting that would be significantly higher than the corresponding weight for other drugs. This significance is easy to reach when the total number of reports for a drug is low before the media focus on an event. It will be difficult if the pre-existing number of reports is important. When all drugs in a class are similarly influenced by media interest in an event, this can result in dif-

ferences in SDRs detected *a posteriori* between drugs. Indeed, drugs with a long history of marketing, and thus larger numbers of pre-existing reports, will be less likely to generate an SDR after the mediatization of an ADR than newer drugs from the same class. This bias is called the “dilution bias” (Pariente *et al.*, 2009); see Figure 20.4.

Similarly, well-known adverse reactions may not be reported for old drugs. This could result in relative overreporting of the reaction with a new drug, related to an inverse notoriety effect.

Significant report duplication can escape the duplicate detection screening algorithms that are routinely applied in this domain. This may introduce a bias and impact data mining outputs because report duplication may be nonrandom. For example, reports involving multiple drugs or equivalently reports involving sicker patients may be more susceptible to duplicate reporting (Hauben *et al.*, 2007b). Also, clusters of very similar reports can also be received from the same reporter or institution that have unexpected characteristics on a more global level (Norén *et al.*, 2007), and it would seem overly simplistic to ignore such apparent “overreporting,” in the way that measures of disproportionality do. Further work is needed to determine how frequently such reporting patterns occur, and therefore the importance of such reporting patterns in impacting performance characteristics of measures of disproportionality.

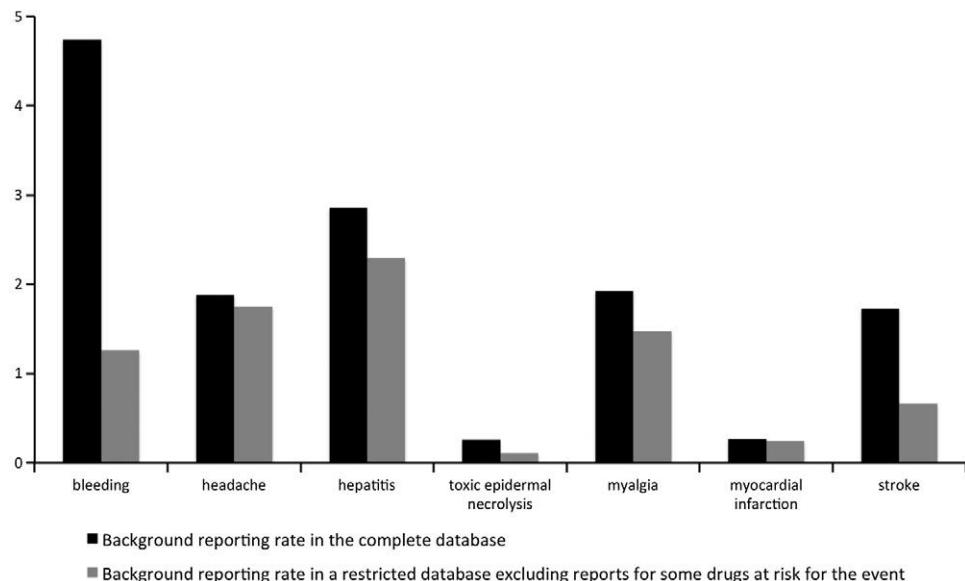


Figure 20.4 Dilution bias. Cumulated (a) and instantaneous (b) rates of reporting for death by suicides among all reports for three antidepressants in the UK. After a TV show discussed this possible issue, a signal of disproportionate reporting (cumulated) was found for the newest, escitalopram, but not the older drugs. Adapted from Pariente *et al.* (2009).

Many biases can affect the results of DA methods used for signal detection in spontaneous reporting databases, because of the very nature of spontaneous reporting. The results of these analyses, taken in isolation, should not be overinterpreted as stronger evidence than they are: they remain statistical associations based on occurrence of reports, and can only be translated into safety signals once the above biases have been eliminated and the cases they rely on have been clinically assessed by pharmacovigilance experts. Nevertheless, there is now increasingly a robust body of evidence that suggests the value of such approaches when used appropriately as a core component of overall signal detection strategy for many organizations. While initially performance characteristics were investigated using retrospective evaluation approaches, such as by Lindquist *et al.* (2000), there are published examples of now labeled adverse events that were highlighted when still unlabeled by QSD (Bate *et al.*, 2008) as well as prospective evaluation of signals detected (e.g., Alvarez *et al.*, 2010) showing the value of DAs in routine signal detection operations with large repositories of spontaneous reports.

## NOVEL APPROACHES FOR QUANTITATIVE ANALYSIS ON SPONTANEOUS REPORTS

The field of QSD has matured in recent years, and QSD is now routinely performed by many organizations as a component of a signal detection and analysis strategy. Measures of disproportionality and other metrics are used for screening large spontaneous reporting system (SRS) databases; monitoring for changes over time is important, and it is well recognized that, given the nature of the data, measures of disproportionality are hypothesis-generating tools rather than hypothesis testing and that clinical review of outputs is a crucial step in their routine application. The limitations discussed in the previous section are well understood and their implications appreciated; so, given that no method is perfect, there is a relentless pursuit to produce ever more effective methods. Efforts include use of different priors in Bayesian false discovery rates (Gould, 2003) and false discovery rates in a frequentist context (Ahmed *et al.*, 2010); and many other measures have been proposed, such

as Yules'  $Q$  (Egberts *et al.*, 2002). Subjective priors based on other data, such as clinical trial results, are also possible (Norén *et al.*, 2013) and might be a fruitful field of discovery to pursue. The theoretical basis for the similarity in methods of disproportionality was emphasized by Gipson (2012) as well, providing a framework for further methods comparison.

There are others areas of active productive research in the analysis of SRS data for signal detection and signal analysis. Some examples are given below.

A clear focus of much of the QSD literature has been on the development and testing of methods for the effective identification of single drug–signal–adverse event combinations; drugs and adverse events are defined in a strict hierarchical terminology in a given SRS database. Clearly, confounding influences the capability to effectively highlight drug–adverse events combinations effectively, and efforts to adjust for potential confounders have been investigated (DuMouchel, 1999; Woo *et al.*, 2008), though adjustment for potential confounders in practice is more complex (Bate *et al.*, 2003; Hopstadius *et al.*, 2008a,b; Hauben and Hung 2013). Adjustment for perceived potential confounding factors that are either effect modifiers or may hide stratum-specific effects is erroneous; instead of adjusting for, efforts should and are being made to detect such potential subgroup signals (Bate *et al.*, 2003; Evans, 2008; Hopstadius *et al.*, 2008b; Bate and Evans, 2009), and scalable systematic approaches to specifically search for stratum-specific signals are now being proposed (Hopstadius and Norén, 2012).

Performance of QSD algorithms is clearly limited by considering adverse event terms independently of one another and not considering clinical similarity (Bate *et al.*, 2012). Ontological reasoning approaches are being considered to take a more sophisticated approach to the use of the terminology itself (Bousquet *et al.*, 2005), and also empirical Bayesian approaches, where similarity of clinical terms is considered to set up the prior probability distribution for group-related events means that shrinkage varies between groups of adverse events and in practice is weaker when several related adverse events all exhibit disproportionality, and

thus are easier to highlight than a single isolated disproportionality score (Bate and Evans, 2009). Another approach, applicable either to drugs or adverse event terms, is to consider reporting in a regression model – see Caster *et al.* (2010) and An *et al.* (2010). Bayesian shrinkage regression is well suited to signal detection because of its capability of handling large numbers of exploratory variables; clearly, more work is needed to determine whether the increased complexity of such approaches is outweighed by the increase in performance capability. Quantitative analysis of temporality in spontaneous reporting data is another aspect of variability across adverse events terms that is being investigated, although experience with it is currently limited (Maignen *et al.*, 2010; Karimi *et al.*, 2013).

More sophisticated approaches for duplicate detection can also be effective in adapting the SRS data set to which the algorithms are run by determination and grading of estimated similarity between reports (Norén *et al.*, 2007). Such a weighting approach can also provide a mechanism for justifying down-weighting sets of similar reports to potentially improve performance in DAs (Norén *et al.*, 2008).

Approaches of linking spontaneous reports to other information or data sets is another fertile area of research; for example, linking of chemical structure properties to spontaneous reports (Vanderwall *et al.*, 2011), or linking established molecular properties to spontaneous report data (De Bruin *et al.*, 2005), or even looking at how similar side-effect profiles might be used to identify new drug targets (Campillos *et al.*, 2008). More work is needed to investigate the value of such approaches if used in a routine framework as the field moves forward. Another example is the work by Liu *et al.* (2012), where they did signal detection in spontaneous reports considering also the phenotypic characteristics of a drug, including indications and other known ADRs, with the drug's chemical structures and biological properties, including protein targets and pathway information.

There is ongoing research on drug–drug interaction signal detection (van Puijenbroek *et al.*, 2000; Almenoff *et al.*, 2003; Thakrar *et al.*, 2007; Norén *et al.*, 2008; Strandell *et al.*, 2011), but further work is needed to demonstrate its role as a routine tool

as done for single drug–event combinations. There remains limited use of cluster analyses, although some work has been done to look for clusters of adverse events terms for drugs (Orre *et al.*, 2005; Tatonetti *et al.*, 2012).

A crucial part of the analysis of spontaneous reporting databases is the underlying dataset and the way the information is coded and structured. The use of a common dictionary (MedDRA) may improve the way the data are analyzed. The granularity of the coding is important. Larger granularity (e.g., system-organ classes) reduces the sensitivity of QSD. Intermediate levels of granularity may improve performance in some aspects (Pearson *et al.*, 2009). In the other direction, excessive precision, as is found in the low-level terms, may also mask messages by dispersing similar reports over many different terms. Any analysis should, therefore, take this into account and include sensitivity analyses at various granularity levels. This might be true also for class effects of drugs, which might become apparent only when pharmacological or chemical classes are studied as a whole.

### **SIGNAL ANALYSIS AND DETECTION IN ELECTRONIC MEDICAL RECORDS/ TRANSACTIONAL CLAIMS DATA/ OTHER LONGITUDINAL OBSERVATIONAL DATABASES**

A signal represents a possible causal association that requires further investigation. Multiple aspects need to be considered in the next step of signal analysis; as well as further analysis of routinely collected healthcare data, other alternatives include testing of animal models and pharmacokinetic/pharmacodynamic investigations and, on occasion, clinical studies, all with the intent of refining or testing a specific hypothesis. A common approach is determining whether the secondary use of existing healthcare data like electronic medical records or databases of transactions of insurance claims can shed light on the signal through a formal hypothesis-testing study; if not, clinical studies or studies in purpose-built observational databases might also be considered. All study designs and data sources have limitations, and careful study

design and judicious interpretation of outputs are needed.

If a pharmacoepidemiological study is used, a range of methods and existing databases might be employed and their suitability will depend upon the question of interest. Study designs include cohort, case–control, self-controlled case series, and case crossover studies. For more details, see a standard text on pharmacoepidemiology; for example, Strom *et al.* (2012) or Hartzema *et al.* (2008). There exist multiple databases that can be used, but no database alone provides a panacea, and on occasion primary noninterventional data capture will be required to conduct research on some specific research questions.

Clearly, while considering next steps on detection, analysis, or attempted confirmation of a signal, aspects such as risk management, dissemination, and risk–benefit quantification need to be considered; while essential, these are considered out of scope of this chapter.

While formal observational studies in observational databases have been done for many years, there is a renewed focus on research into the use of such data sets for signal detection and also as sources for rapid signal analysis, referred to by some as “rapid search queries,” with a focus on transparent fast refinement of a signal without necessarily producing the same compelling evidence level as a full hypothesis-testing approach. Prospective monitoring of associations over time in secondary observational databases is also increasingly being proposed.

Similarly, while routine QSD has focused primarily on the analysis of spontaneous report data sets, with some exceptions (e.g., case–control surveillance (Shapiro, 1994)), increasingly there is exploration into whether exploratory data analysis can and should be usefully employed on other types of observational data that have traditionally been primarily the preserve of formal hypothesis-testing studies for signal analysis, as discussed above.

There remain considerable doubts about performance characteristics of the approaches, methodological challenges such as whether such data should be used for both signal detection and analysis, how to operationalize such approaches in overall signal detection and analysis strategies, and

the role as compared with other data streams and even lack of clarity in the use of terminology (Aronson *et al.*, 2012). Several different types of approach have been proposed, often originating from different research fields. Methods derived or adapted from spontaneous reports have been proposed, near mimicking its application in spontaneous reports (Zorych *et al.*, 2013) or more extensively adapted to consider the longitudinal nature of such data (Norén *et al.*, 2010, 2011, 2012; Svanström *et al.*, 2010; Schuemie, 2011). Also, approaches from the wider data mining literature have been applied to such data (Jin *et al.*, 2008; Walker, 2010), traditional pharmacoepidemiological methods implemented with a hypothesis-generation focus (Shapiro, 1994; Gagne *et al.*, 2012; Rassen and Schneeweiss, 2012), and even the use of sequential statistical approaches more commonly applied to monitoring of clinical trials (Musonda *et al.*, 2008; Cook *et al.*, 2012) and other novel approaches. Much elucidating research is anticipated in this fertile research area in the coming years. There are also several initiatives researching this field, including the Observational Medical Outcomes Partnership (Stang *et al.*, 2010), the FDA's Sentinel Initiative (Behrman *et al.*, 2011), EU-ADR (Coloma *et al.*, 2011), and IMI's PROTECT project (Arlett and Kurz, 2011). A particularly interesting aspect of the EU-ADR initiative is the integration of knowledge mining of biological mechanistic information with data mining to assess adverse event rates/frequencies. Some performance testing in observational data has begun to enter the literature (Ryan *et al.*, 2012), though prospective testing in particular is very limited, one example being work from the Vaccine Safety Data Link that reported low predictive performance (Yih *et al.*, 2011).

## OPERATIONALIZATION ASPECTS

Once a decision is made to utilize data mining, practical implementation entails multiple decisions and actions related to the selection and operation of the data mining algorithm (DMA) itself, as well as its overall integration into a comprehensive pharmacovigilance system. Herein, we touch on some key points that are based on real-world

unpublished experience and the published literature. The focus is on DA in  $2 \times 2$  contingency tables, as these are the most common approach to quantitative global database screening at the present time. Many of these questions/issues have no clear preferred answer or prescription. Choices will often and necessarily be situation dependent, and therefore guided by the relative premium on sensitivity versus specificity that makes sense for a given organization.

One of the most important issues pertains to the choice of DA variant; specifically frequentist versus Bayesian versus empirical Bayesian. Although published validation exercises and theoretical considerations point to Bayesian or other related shrinkage-based methods reducing the number of associations highlighted and with a reduced overall error/misclassification rate, there are real-world caveats. First, reducing overall error rates is desirable, this reduction in overall error may come at the cost of increased error for individual combinations, and it is not yet established that reducing overall error rates is the optimum goal. Second, most published validation exercises report performance gradients in terms of the number of SDRs returned (usually at the preferred term (PT) level rather than the associated report review burden). Additionally, the same exercises generally do not take into account how the method of signal evaluation impacts performance. Specifically, if signal evaluation involves formulating a case definition comprised of all clinically related PTs, whether statistically highlighted or not, the performance gradients are currently less clear (Hauben *et al.*, 2006) Nonetheless, shrinkage-based methods will generally provide a more manageable volume of statistically highlighted associations for subsequent processing.

One of the practical implications of the above, which is borne out by real-world experience, is that no matter which DMA is chosen, to a greater or lesser degree depending on selected algorithm and thresholds, the analyst is likely to be confronted with an overabundance of SDRs that will present a difficult-to-manage review burden if no other filters are applied. In some cases these filters consists of having multiple quantitative criteria (e.g., a threshold  $O/E$  plus a case count threshold). However, even the latter approach will probably not

Table 20.4 Data mining in pharmacovigilance: some operational considerations.

Analytical choice	Comments
Algorithm	No single algorithm demonstrated to be universally superior. Shrinkage-based methods can improve signal-to-noise ratio/reduce overall misclassifications and thereby achieve overall greater accuracy, but may make misclassifications for individual associations, emphasizing the need for clinical review of outputs. Calculus of costs and utilities not fully established.
Use as anchor method for signal detection versus use in series or parallel with other methods	Best to use data mining as one element of a comprehensive suite of signal detection programs using multiple methods and data streams. Organizations may maintain a so-called “worst first list” of designated medical events (DMEs) that are rare, serious, and have in general a high drug-attributable risk and for which a relative premium is placed on sensitivity over specificity. Primary focus on such a list of events for which a small number of reports triggers a close look allows somewhat more latitude for data mining performance since their initial detection is heuristically based.
Database: proprietary versus public versus both	Proprietary company databases may have skewed distributions of drugs and events compared with larger and more diverse health authority databases, making them more prone to phenomena such as masking. But they may be more current than publically available formats of some health authority databases.
Full database of all medicinal products versus restriction to subsets of drugs/products	Most systematic published validation exercises have used the full generality of the database. Use of specific subsets of the database to mitigate confounding factors (e.g., diabetes drugs, oncology drugs have been used to address specific safety issues rather than global database screening).
Inclusion criteria by reporting source	Many safety databases contain reports from various sources, including consumer, clinical trial, and solicited reports. Generally, users limit analysis to spontaneous reports, possibly supplemented by solicited reports.
Level of dictionary hierarchy	Most published validation exercises have analyzed at preferred term level (Bate <i>et al.</i> , 2012). Some limited published data indicate that mining at higher levels may offer some advantages, and borrowing strength across hierarchy is beginning to be explored in this setting (Pearson <i>et al.</i> , 2009).
Stratification	Commonly performed on basic covariates age, gender, and year of report. Age bands vary. Basic covariate stratification has little impact overall, primarily affecting peri-threshold combinations. Overstratification may reduce sensitivity. Consideration should be given to how to detect stratum-specific effects.
Frequency of analysis	Frequency of monitoring and threshold may change as the drug safety profile becomes firmly established, with a shift to focusing on selected issues (e.g., interactions of established drugs with new drugs).
Thresholds	Different metric/threshold combinations are commonly cited. Choice determined by relative premium placed on sensitivity versus specificity and corresponding predictive powers.
Suspect versus suspect+concomitant	Suspect-only views reported insight as valuable whereas suspect+concomitant approach is based on reporter knowledge/judgment as potential source of bias. Limited research evaluating the two alternatives (Sundström and Hallberg, 2009), but it is generally accepted that consideration of reporter suspicion is beneficial, and most routine quantitative signal detection focuses on suspect-only.

avoid the necessity of having a front-end triage step, based on scientific knowledge, judgment, and experience, that, in keeping with contemporary definitions of what constitutes a credible safety signal (Hauben and Norén, 2010), focuses evalua-

tion efforts on a subset of SDRs that are elevated to the status of a signal of suspected causality (Hauben and Aronson, 2009). A common scenario is the rational discounting of an association with an SDR due to likely confounding by indication.

However, this should be a thoughtful assessment so as not to discount so-called “paradoxical reactions” (Smith *et al.*, 2012). This front-end triage, which is to extract bona fide signals from a set of quantitatively highlighted associations, is distinct from the subsequent step of signal prioritization, in which a bona fide signal is triaged by public-health-related criteria to determine urgency of evaluation.

Because of the large amount of additional data that will be generated by data mining, it is highly desirable to establish a computer-system-based platform for the signal management system that not only facilitates data retrieval and review, but also memorializes front-end triage decisions, time of signal identification, signal prioritization, evaluation strategies and results, follow-up procedures, course of action/risk management interventions, and the real-time status of the signal (e.g., verified, refuted, indeterminate) and provides filters to reduce duplicative work (e.g., filtering out combinations that are under evaluation or that have been evaluated). Currently, there do not seem to be signal management systems that automatically incorporate labeling status of highlighted associations as filters. Multiple vendor-based systems are available for which there is no basis to recommend one over the others. Table 20.4 summarizes selected operational considerations on the deployment of data mining in pharmacovigilance, including those discussed above.

## CONCLUSIONS

The validity of QSD methods for use on spontaneous reports has been clearly demonstrated. They can detect many existing problems, find new signals, and help prioritize them for the benefit of assessors; the approaches are simple, transparent, and objective, and they have been automated into signal management tools. The major issues are the potential for misinterpretation of the quantitative outputs and overreliance on automation. The statistical methods are a first stage of assessment, and careful evaluation using medical scientific knowledge is still required. That is not to say that research cannot improve signal detection in spontaneous reports

still further: and has a main future in the detection of complex patterns in the data. QSD and analysis tools should allow for much easier and useful handling of large amounts of information; one would anticipate even greater improvements here as the field matures.

Quantitative signal analysis in observational data sets is now a core component of pharmacovigilance. As secondary sources of healthcare data become ever more prevalent, their judicious and effective analysis will become ever more important. Further research is needed into the use of QSD on such data, and the integration of signal detection and analysis into approaches for looking at risk–benefit research across multiple data streams is challenging and likely to be a rich area of research as pharmacovigilance continues to evolve.

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# 21

## Self-Controlled Case Series Analysis

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### INTRODUCTION

The self-controlled case series (SCCS) method was originally developed to investigate the safety of vaccines (Weldeselassie *et al.*, 2011). Its key feature is that all time-invariant confounding variables that act multiplicatively on the baseline risk are implicitly adjusted, without the need to specify them. For this reason, the method is well suited for use with data from computerized databases, in which confounder information may be absent or limited. A second key feature of the method is that only cases – that is, individuals who have experienced the adverse event of interest – are required. This obviates the need to select independent controls, and makes the method particularly well suited to the investigation of uncommon events.

These benefits come at the cost of additional assumptions, of which the investigator needs to be aware. These assumptions will be considered later;

they relate to the fact that, unlike other epidemiological designs, post-event time is included in the analysis; individual histories are not – and must not be – censored at the event. This stems from the statistical conditioning required to define the SCCS model, described in the next section. Note that all technicalities have been eschewed; readers requiring their fix of equations are directed to the technical material referenced in “Further details”.

### BASIC PRINCIPLES

Although the SCCS method requires only cases, it is derived from a cohort study, and it is sometimes helpful to keep this underlying cohort in mind. This cohort is (perhaps notionally) observed over a prespecified period, the “observation period,” which may be determined by calendar time and age constraints. In practice, the whole cohort need

not be observed, as only the cases from it will be needed.

Individuals in the cohort experience time-varying exposures (determined, for example, by times on medication), which may be of several types. They also experience adverse events, which in the SCCS framework are either independently recurrent, or nonrecurrent and uncommon, this meaning “with a frequency of less than 10% over the observation period.” Each individual within this cohort experiences some number of events within the observation period: typically zero, perhaps one, or more if the event is recurrent.

In a cohort study setting, this number is treated as a random variable. In the SCCS framework, it is regarded as fixed. Also regarded as fixed is each individual’s history of exposure over the entire observation period – including post-event exposures (if an event occurred). In statistical terms, the following quantities are being conditioned upon for each individual (i.e., regarded as fixed): (a) the observation period, (b) the exposures within it, and (c) the number of events experienced within the observation period.

The quantity that is *not* regarded as fixed in an SCCS analysis is the actual time of the event, for individuals who had one (or more). Since individuals in the cohort who did not have an event have no such time, they drop out of the analysis, and thus need not be sampled in the first place (which is why the cohort could be entirely notional – cases being picked up by some suitable ascertainment mechanism such as hospital admissions). This is why a valid model can be obtained involving only cases.

Second, the only variation considered is *within-individual*. The estimation rests on expressing in terms of a model the following probability,  $p_i$  say, for case  $i$ : given that case  $i$  had  $n_i$  events with the observed exposure history,  $p_i$  is the probability that these events occurred when they actually did, rather than at other times within the observation period. The probability  $p_i$  is the likelihood contribution of that case. Note that it is not correct, in general, to treat the cases as if they were themselves a cohort, and conduct a person-time analysis on them, as this loses the key “within individual” element.

A consequence is that factors that multiply the risk by a constant amount drop out of the expres-

sion for the probability  $p_i$  – which is why fixed multiplicative confounders are implicitly controlled. Measured time-varying confounders (such as age), on the other hand, can be accommodated explicitly. The model is conveniently specified as a log-linear conditional Poisson model, with a factor comprising a separate level for each case.

## AN EXAMPLE

The method is illustrated with a study by Douglas *et al.* (2009). This study was undertaken to test a signal from clinical trials that thiazolidinedione antidiabetic agents may be associated with an increased risk of fracture in women. Owing to concerns over possible confounding, an SCCS design was chosen. The study was undertaken in the General Practice Research Database (GPRD).

The cases included in the study were all individuals with both a diagnosis of fracture and a first recorded thiazolidinedione prescription at least 12 months after initial registration with the GPRD. (Note that it is not a requirement of the method to include only individuals that have been exposed; including unexposed individuals can improve estimation of age effects in some circumstances, though often it makes little difference.) Where more than one fracture was recorded for a patient, it was assumed that the fracture was incident if it occurred at a different site from the previous fracture, or was recorded more than 6 months after a fracture at the same site. Only incident fractures defined in this way were included in the analysis.

The duration of exposure (i.e., time on drug) following each individual prescription was calculated using information recorded in the GPRD about pack size and dosing frequency. Where such information was not recorded, the median time was used. The exposure was regarded as continuous when any treatment break was less than 60 days. However, the investigators were unsure as to how long after treatment cessation an exposure effect, if any, might persist. To circumvent this problem, follow-up was curtailed at the first treatment break of more than 60 days. (In other studies, a washout period is sometimes included after treatment ends, after which the risk is assumed to return to the baseline level.)

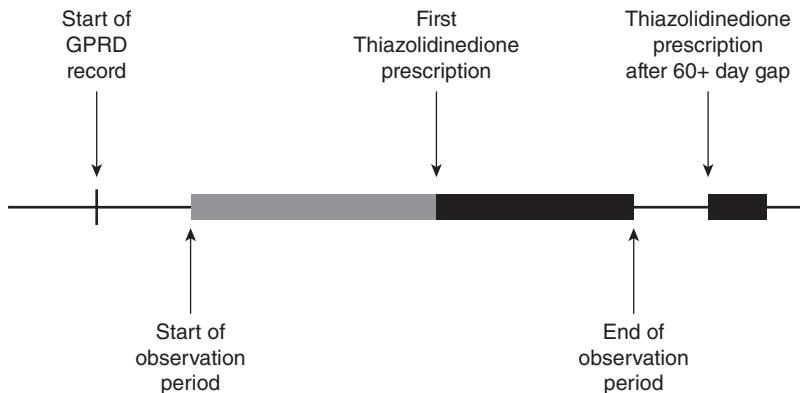


Figure 21.1 Observation period for a typical case. The thick gray band within the observation period represents unexposed time. The thick black band within the observation period represents exposed time.

For each case in the study, the start of the observation period was taken as the time of registration in the GPRD plus 12 months, and the earliest of end of registration in the GPRD and first extended treatment break. In this study, therefore, the time from start of observation to first prescription is regarded as unexposed, and the time from first prescription to end of observation is regarded as exposed. (More typically, unexposed time may also occur after exposure has ceased.) Figure 21.1 shows the time course of an individual in this study.

Because risk of fracture and risk of exposure both increase with age, age may be a confounder and so must be controlled explicitly. This was done by assuming an age effect varying in 1-year bands.

Thus, the observation period for each case was subdivided into adjacent intervals classified according to age and exposure status. The number of events for each individual in each interval was then modeled using conditional Poisson regression. The basic SCCS model has factors for individual, exposure and age, and offsets equal to the logarithm of the interval duration. Fixed confounders are, of course, controlled in the SCCS design, but the effect of fixed covariates on the relative risk (i.e., interactions with the exposure) can be estimated. This was done for sex, drug type, duration of exposure, and fracture site.

There were 1819 cases with 2266 incident fractures. The age-adjusted rate ratio was 1.43, 95% confidence interval (1.25, 1.62). There was no sig-

nificant difference in the rate ratio between men and women. The rate ratio increased with duration of exposure.

The authors undertook a series of sensitivity analyses to check the robustness of their results. For example, they reanalyzed the data after excluding the 155 patients who died, and after restricting follow-up in various ways to avoid possible notoriety biases. They also tested association with sulfonylureas as a “control therapy” (for which there was no reason to suspect an association with fracture), and found no association. Such a “control analysis” provides evidence of robustness of the design as a whole.

## KEY ASSUMPTIONS OF THE SELF-CONTROLLED CASE SERIES METHOD

The key assumptions of the SCCS method derive from the basic principles by which it is obtained: it must be possible to condition for each individual on (a) the observation period, (b) the exposures within it, and (c) the number of events experienced within the observation period, without this biasing the association between exposure and outcome.

Conditioning (a) is invalidated if the observation period is influenced by the event time. This arises if the event is associated with substantial increased mortality, as in the case of stroke. Conditioning (b) is invalidated if occurrence of the event alters

subsequent exposures. This arises if prior occurrence of an event is a contraindication to treatment, as in the case of intussusception and anti-rotavirus vaccination. Conditioning (c) is invalidated if occurrence of one event changes the risk of further events, as is the case with myocardial infarctions.

Thankfully, adjustments to the basic SCCS method are available in all three settings. In some cases the adjustment required can be very simple. Here are some such examples relating to the three types of conditioning. For (a), it might be possible to undertake a sensitivity analysis, excluding patients who died, as was done in the study of fractures and thiazolidinediones described above. For (b), if occurrence of an event affects subsequent exposure only for a defined period, then this can be accommodated within the basic SCCS model by including a pre-exposure "risk" period. And if the exposure is unique and time limited (as is the case with exposures associated with treatment initiation) then the basic SCCS model can be used, with observation period starting at exposure. For (c), if a first event precipitates another, then the analysis can be restricted to first events (provided these arise with frequency less than 10% over the observation period).

In other circumstances, simple adjustments may not be sufficient, in which case more elaborate adjustments to the method are required, and available. References are provided in "Further details". The only circumstance in which *no* adjustment is possible is when events affect subsequent exposures, and exposures are very long lasting or indefinite. In this case, methods other than SCCS must be used.

## FURTHER DETAILS

Methodological details of the basic SCCS method may be found in Farrington (1995; Farrington and

Whitaker, 2006). Detailed implementation is discussed in Whitaker *et al.* (2006, 2009). Further elaborations of the method are described in Farrington *et al.* (2011) for event-dependent observation periods, in Farrington *et al.* (2009) for event-dependent exposures, and in Farrington and Hocine (2010) and Simpson (2011) for dependent recurrent events.

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# Prescription–Event Monitoring (PEM): The Evolution to the New Modified PEM and its Support of Risk Management

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## BACKGROUND

The recognition that not all hazards could be known before a drug was marketed and that spontaneous adverse drug reaction (ADR) reporting systems have limitations to identify all hazards led to several proposals for schemes based on the identification of patients by means of prescription data. These schemes were largely intended to provide information on populations of known size so that the incidence of adverse reactions could be estimated with reasonable accuracy. This led to the founding of a prescription-based monitoring system to monitor events regardless of relatedness to drug exposure (Prescription-Event Monitoring (PEM)) by W. H. W Inman and the establishment of the Drug Safety Research Unit (DSRU). The DSRU is an independent registered medical non-

profit organization that operates in association with the University of Portsmouth.

The system's key objective at inception in the 1980s was to recruit the first 10 000 patients who received a new drug of interest so that any adverse event that occurred in more than one in 1000 patients would be reliably identified. Based on the success of these standard PEM studies over a period of 30 years, this methodology has subsequently evolved in response to the requirements for risk management of medicines to facilitate more targeted safety surveillance. This has been achieved through the technique known as modified (M)-PEM, which retains all the strengths of the standard method with the same underlying process but also tries to overcome some of its limitations (further details in following sections).

## GENERAL PRINCIPLES

### STUDY DESIGN

The general methodology common to both standard and modified approaches uses a retrospective noninterventional observational cohort design to provide active surveillance of targeted medicines on a national scale in England. Data analysis utilizes several approaches that combine the application of epidemiological methods with medical evaluation to provide estimates of prevalence of selected drug utilization characteristics, incidence rates for events reported in the exposed cohort, exploration of risk profiles within different subpopulations, and also provides the opportunity for further clinical evaluation of selected events of interest. Details of the methodology of standard PEM, including the methods of data coding, computerization, and analysis, have been provided in a number of publications, and thus are not covered in detail in this chapter (Freemantle *et al.*, 1997; Layton and Shakir, 2011). The majority of all new studies are now constructed using the M-PEM approach, and examples of bespoke analytical requirements necessary to achieve an M-PEM's study aims and objectives are provided later.

The eligible cohort is identified based on a single common exposure identifier (a prescription for the new medication under surveillance). The method is noninterventional because the decision to prescribe has already been taken and there are no additional constraints on care imposed by subsequent participation in the study. Confirmation of exposure status and outcome are ascertained retrospectively to assemble the evaluable cohort (i.e., the cohort available for analysis). The design is also longitudinal because health outcomes can be examined over a span of time. Furthermore, since prescription data collection begins immediately after the new drug has been launched (and covers the national population in England), evaluable patient cohorts can be accrued rapidly, which provides the opportunity to detect safety issues as early as possible after market launch, a fundamental principle in pharmacovigilance. Furthermore, the study design is highly dynamic, such that newly emerging safety issues can be investigated while a study is in progress.

The evaluable cohort is also regarded as an inception cohort (where study drug is a new entity) or a new user cohort (e.g., where the drug under study might be a new formulation or new indication). Here, the observation period begins as soon as the patient starts the medication, which is particularly important if the risk of an event is higher in the early period after starting therapy. An advantage of an inception cohort is that potential confounding factors can be measured before treatment starts and adjusted for in subsequent statistical analysis. Unlike standard PEM, the M-PEM methodology offers greater scope to collect this baseline data.

A wide range of drugs have been studied using one of the two approaches, including agents to treat hypertension, angina, asthma and chronic obstructive pulmonary disease (COPD), diabetes, epilepsy, depression, schizophrenia, erectile dysfunction, urinary incontinence, and a number of nonsteroidal anti-inflammatory drugs (including selective COX-2 inhibitors). Thus, the drugs included in the system are those intended for widespread, long-term use, special emphasis being given to drugs for which treatment is likely to be both initiated and continued by the general practitioner (GP) (Anon., 1986; BMA, 2006). In addition to drugs that are taken regularly, it has also been possible to study products that are not used daily, such as sildenafil for erectile dysfunction (Shakir *et al.* 2001).

Of the 119 studies listed in Table 22.1, an average of 55.5% of the 108 standard PEM questionnaires sent out have been returned by the GPs to the DSRU with an average evaluable cohort size of 10947. For the 11 M-PEM studies given in Table 22.1, an average of 58.8% of M-PEM questionnaires sent have been returned, with a smaller average final evaluable cohort size of 6876 patients.

### DATA SOURCE

Within the British National Health Service (NHS) structure, all individuals are registered with a primary-care GP. Medical records held by the GP are generally lifelong, transferable when a patient relocates, and include information on healthcare consultations and interventions provided by both primary and secondary care. The sampling frame is

hierarchical, comprising of two levels: all GPs in England who prescribe the study drug and their patients. This wide coverage aims to provide an evaluable cohort that is representative of the whole population of patients who are registered with an NHS GP in England who take the study drug during the study period.

### DATA COLLECTION PROCESS

This occurs through a two-phased approach, which is summarized in Figure 22.1. The first phase is the collection of prescription data to capture patient and prescriber details, and the second is the collection of exposure and outcome data.

The first phase of the identification of prescribers and patients relies on data from dispensed NHS prescriptions. Prescription data are provided to the DSRU under long-standing arrangements and through secure transmission, by a central NHS prescription processing center, known as the NHS

Business Services Authority (NHSBSA). This operates for a length of time necessary for the DSRU to collect a sufficient number of prescriptions to identify the required study sample size. The NHSBSA receives remuneration from the DSRU for this service. These data are reconciled with GP identifier records available from the NHS Organisation Data Services (ODS), to obtain prescriber contact details and, with existing records on the DSRU customized PEM database, to ascertain whether the data pertain to an existing eligible patient already within the DSRU PEM database. It should be noted that all relevant prescriptions are collected, irrespective of whether they are a new or repeat course.

The second phase involves secondary use of medical records data that have been entered into medical records as part of routine clinical care (EMA, 2012). For each eligible patient identified, a questionnaire is sent by post (according to chronological order of prescription issue date) to the

Table 22.1 List of 119 completed studies, by type (standard, modified).

Generic name	Drug name	Group	Response (%)	Final cohort
<i>Standard PEM studies</i>				
Enalapril	Innovace	ACE-inhibitor	68.3	15 361
Lisinopril	Zestril+Carace	ACE-inhibitor	63.5	12 438
Perindopril	Coversyl	ACE-inhibitor	53.4	9 089
Ramipril	Tritace	ACE-inhibitor	47.3	1 371
Doxazosin	Cardura	Alpha-blocker	60.1	8 482
Tamsulosin	Flomax mr	Alpha-blocker	57.4	12 484
Donepezil	Aricept	Alzheimer's treatment	58.9	1 762
Tramadol	Zydol	Analgesic	55.8	10 532
Bupropion	Zyban	Antismoking aid	51.5	11 735
Fosfomycin	Monuril	Antibacterial	45.6	3 363
Terodilime	Terolin	Anticholinergic	69.6	12 444
Tolterodine	Detrusitol	Anticholinergic	59.0	14 526
Mirtazapine	Zispin	Antidepressant	56.0	13 554
Nefazodone	Dutonin	Antidepressant	54.9	11 834
Venlafaxine	Efexor	Antidepressant	54.6	12 642
Acarbose	Glucobay	Antidiabetic	62.8	13 655
Repaglinide	Novonorm	Antidiabetic	42.6	5 729
Troglitazone	Romozin	Antidiabetic	60.3	1 344
Rosiglitazone	Avandia	Antidiabetic	54.2	14 418
Pioglitazone	Actos	Antidiabetic	54.7	12 772
Nateglinide	Starlix	Antidiabetic	50.2	4 557

(Continued)

Table 22.1 (Continued)

Generic name	Drug name	Group	Response (%)	Final cohort
Vildagliptin	Galvus	Antidiabetic	47.3	4 828
Lamotrigine	Lamictal	Anti-epileptic	67.9	11 316
Vigabatrin	Sabril	Anti-epileptic	69.2	10 178
Gabapentin	Neurontin	Anti-epileptic	66.4	3 100
Oxcarbazepine	Trileptal	Anti-epileptic	60.7	2 243
Fluconazole	Diflucan	Antifungal	68.6	15 015
Itraconazole	Sporanox	Antifungal	63.5	13 645
Acrivastine	Semprex	Antihistamine	56.5	7 863
Cetirizine	Zirtek	Antihistamine	57.4	9 554
Fexofenadine	Telfast	Antihistamine	50.9	16 638
Loratadine	Clarityn	Antihistamine	50.7	9 308
Desloratadine	Neoclarityn	Antihistamine	44.7	11 828
Levocetirizine	Xyzal	Antihistamine	49.2	12 876
Irbesartan	Aprovel	Antihypertensive	59.4	14 398
Losartan	Cozaar	Antihypertensive	59.9	14 522
Valsartan	Diovan	Antihypertensive	54.7	12 881
Sildenafil	Viagra	Anti-impotence	54.7	22 473
Apomorphine	Uprima	Anti-impotence	57.1	11 185
Tadalafil – Cohort 1	Cialis	Anti-impotence	47.0	6 266
Tadalafil – Cohort 2	Cialis	Anti-impotence	39.5	16 129
Vardenafil	Levitra	Anti-impotence	46.1	15 656
Sumatriptan	Imigran	Antimigraine	70.8	14 928
Tiotropium	Spiriva	Antimuscarinic bronchodilator	54.0	13 892
Iatropium Bromide	Atrovent	Antimuscarinic bronchodilator	63.0	13 211
Orlistat	Xenical	Anti-obesity	50.1	16 022
Sibutramine	Reductil	Anti-obesity	56.3	12 336
Olanzapine	Zyprexa	Antipsychotic	68.9	8 858
Risperidone	Risperdal	Antipsychotic	64.7	7 684
Sertindole	Serdolect	Antipsychotic	78.2	436
Quetiapine	Seroquel	Antipsychotic	59.1	1 728
Cisapride	Prepulsid	Antispasmodic	62.4	13 234
Aciclovir	Zovirax	Antiviral	74.1	11 051
Famciclovir	Famvir	Antiviral	65.4	14 169
Valaciclovir	Valtrex	Antiviral	64.1	12 804
Buspirone	Buspar	Anxiolytic	54.1	11 113
Nedocromil	Tilade	Asthma prophylaxis	68.1	12 294
Bambuterol	Bambec	Beta2 agonist	50.8	8 098
Eformoterol	Foradil	Beta2 agonist	52.9	5 777
Salmeterol	Serevent	Beta2 agonist	61.9	15 407
Betaxolol	Kerlone	Beta-blocker	54.7	1 531
Alendronate	Fosamax	Bone disease	59.4	11 916
Strontium Ranelate	Protelos	Bone disease	52.7	10 865
Amlodipine	Istin	Ca-antagonist	58.7	12 969
Diltiazem	Tildiem	Ca-antagonist	67.3	10 112
Isradipine	Prescal	Ca-antagonist	51.3	3 679
Mibefradil	Posicor	Ca-antagonist	54.1	3 085
Nicardipine	Cardene	Ca-antagonist	62.6	10 910
Cefixime	Suprax	Cephalosporin	39.6	11 250
Famotidine	Pepcid	H2-antagonist	51.8	9 500
Nizatidine	Axid	H2-antagonist	44.7	7 782
Zolpidem	Stilnoct	Hypnotic	49.0	13 460
Zopiclone	Zimovane	Hypnotic	54.8	11 543

Table 22.1 (Continued)

Generic name	Drug name	Group	Response (%)	Final cohort
Xamoterol	Corwin	Inotropic	68.7	5 373
Nicorandil	Ikorel	K-channel activator	58.3	13 620
Montelukast	Singulair	Leukotriene antagonist	53.6	15 612
Zafirlukast	Accolate	Leukotriene antagonist	42.3	7 976
Fluvastatin	Lescol	Lipid-lowering	63.2	7 542
Rosuvastatin	Crestor	Lipid-lowering	40.2	11 680
Azithromycin	Zithromax	Macrolide	52.4	11 275
Moclobemide	Manerix	MAOI	58.8	10 835
Celecoxib	Celebrex	NSAID	44.1	17 458
Etodolac	Lodine	NSAID	49.9	9 091
Etoricoxib	Arcoxia	NSAID	42.7	12 665
Meloxicam	Mobic	NSAID	52.0	19 087
Nabumetone	Relifex	NSAID	54.9	10 444
Rofecoxib	Vioxx	NSAID	38.9	15 268
Tenoxicam	Mobiflex	NSAID	44.5	10 882
Raloxifene	Evista	Osteoporosis	57.2	13 987
Risedronate	Actonel	Osteoporosis	58.6	13 643
Misoprostol	Cytotec	Prostaglandin analog	67.3	13 775
Finasteride	Proscar	Prostate treatment	63.0	14 772
Lansoprazole	Zoton	Proton pump inhibitor	51.0	17 329
Omeprazole	Losec	Proton pump inhibitor	62.4	16 204
Pantoprazole	Protium	Proton pump inhibitor	44.5	11 541
Esomeprazole	Nexium	Proton pump inhibitor	41.8	11 595
Ciprofloxacin	Ciproxin	Quinolone	60.0	11 477
Enoxacin	Comprecin	Quinolone	44.5	2 790
Norfloxacin	Utinor	Quinolone	50.0	11 110
Ofloxacin	Tarivid	Quinolone	45.7	11 033
Aliskiren	Rasilex	Renin inhibitor	52.4	6 285
Duloxetine	Cymbalta+Yentreve	SNRI	49.4	19 485
Fluoxetine	Prozac	SSRI	58.4	12 692
Fluvoxamine	Faverin	SSRI	59.9	10 983
Paroxetine	Seroxat	SSRI	61.6	13 741
Sertraline	Lustral	SSRI	60.2	12 734
Tacrolimus	Protopic	Topical immunomodulator	52.8	12 895
Pimecrolimus	Elidel	Topical immunomodulator	45.1	10 660
<b>Mean</b>				10 974
<i>M-PEM studies</i>				
Modafinil	Provigil	ADHD treatment	60.1	2 092
Atomoxetine	Strattera	ADHD treatment	60.3	5 079
Quetiapine XL	Seroquel XL	Antipsychotic	55.9	14 616
Fluticasone	Flixotide Evohaler	Corticosteroid	63.9	13 413
Fluticasone/ Salmeterol	Seretide Evohaler	Corticosteroid	62.0	13 464
Pulmicort	Budesonide	Corticosteroid	55.4	10 408
Varenicline	Champix	Nicotinic receptor partial agonist	54.5	12 135
Lumiracoxib	Prexige	NSAID	42.9	285
Fentanyl buccal	Effentora	Opioid analgesic	56.2	556
Fentanyl citrate	PecFent	Opioid analgesic	53.0	63
Travoprost	Travatan	Prostaglandin analog	82.7	3 528
<b>Mean</b>				6 876

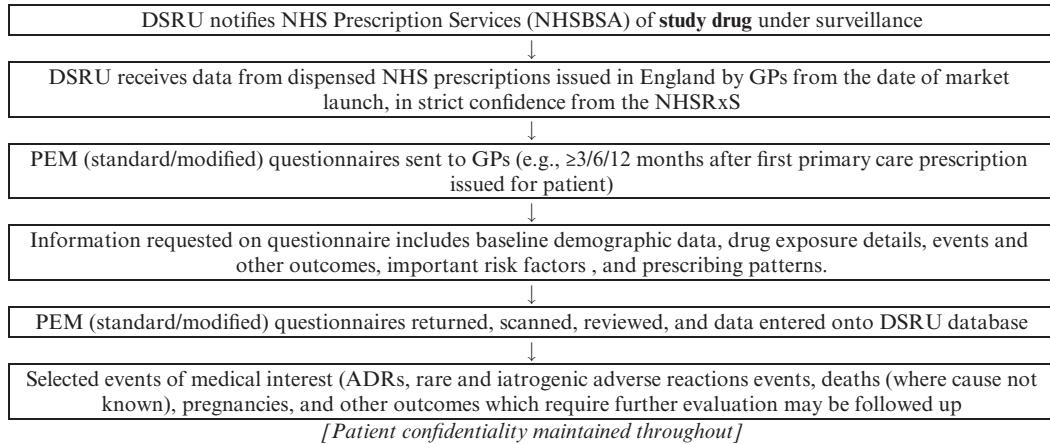


Figure 22.1 Common process of a standard PEM or M-PEM study.

prescribing GP until the target sample size (usually many thousands of patients) is achieved. In order to avoid placing an unreasonable demand on the prescribers, no more than four questionnaires for each M-PEM study are sent to each doctor in any one month for any one study. Data collected include patient demographics (age, sex), prescribing information, and details of all significant events that have been recorded in the patient's medical records during a specific time period after starting the study drug. Early modifications to the standard methodology involved adding a small number of additional questions (with yes, no, don't know answers) on the questionnaire. These focused on issues specific to the drug under study; for example, the standard questionnaire for the standard PEM study on the NSAID meloxicam included questions about previous history of gastrointestinal conditions and intolerance to NSAIDs to identify possible confounding by indication (Martin *et al.*, 2000). The customized M-PEM format questionnaires were developed to collect relevant supplementary information in order to perform more detailed exploration of specific safety issues. An example is shown in Figure 22.2. The M-PEM questionnaire collects more detailed information on outcomes (including specific events that comply with prespecified case definitions), drug exposure, and other relevant disease risk factors at the start of treatment. This improves data accuracy and quality, reducing the possibility of

information bias through misclassification. GPs are offered a modest reimbursement to cover administrative costs in recognition of the time spent completing the more detailed M-PEM data collection forms.

Within the DSRU, each questionnaire is scanned into the system and the image is reviewed by a scientific member of the DSRU staff. This initial review aims to identify possible serious ADRs or events requiring action (e.g., external communications or expedited follow-up). An aggregate assessment of drug-relatedness, clinical features/manifestations, clinical course, and prognosis of clinical conditions may be performed (see later). Supplemental information may be sought from GPs using targeted questionnaires, where such information is not obtained in the initial survey. Such questionnaires are sent within weeks of the initial review; but in some cases, where an objective of a study might be to monitor events with longer time to possible onset, a lag period may be introduced (e.g., 12 months from the date of first occurrence of the event of interest), such as for androgenic manifestations with testosterone use in women using a testosterone patch for reduced sexual drive. A list of medically serious events (ICH, 2003) that have been associated with the use of medicines (e.g. aplastic anemia) has been compiled by the DSRU; such events routinely undergo further evaluation. All pregnancies reported during treatment or within

DSRU Reference: «srefCode»  
 Patient Year of Birth: «sYOB»  
 Patient Sex: «sSexDescription»  
 Start Date «startdate»

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## LUMIRACOXIB (PREXIGE®) MODIFIED PEM STUDY MEDICAL IN CONFIDENCE

### PATIENT IDENTIFICATION CODE

Please provide an identification code that is only recognisable by you and can be used in the case of future correspondence about your patient if necessary.

Your Patent ID:

### PRESCRIBING DATA

#### 1. According to PPD data, this patient was first prescribed lumiracoxib on the date given above. Please confirm below:

- a) Start date: \_\_\_\_ / \_\_\_\_ / \_\_\_\_      b) Dose at start: .....mg/day  
 c) Sex: M  F       d) YOB.....

#### 2. Please confirm this patient is still registered with your practice

<input type="checkbox"/> Yes  Go to Question 3 <i>and continue to complete questionnaire</i>	<input type="checkbox"/> No  Left practice? <input type="checkbox"/> Yes  Or Died? <input type="checkbox"/> <i>Please return the questionnaire in the FREEPOST envelope</i>
---	--

#### 3. Please specify the clinical prescribing Indication(s) for lumiracoxib (tick all that apply)

- Osteoarthritis (OA): OA Knee  OA Hip  OA Other   
 Acute pain relief from surgery: Orthopaedic  Dental   
 Primary Dysmenorrhoea

Other: please specify.....

#### 4. Please indicate the reason for prescribing lumiracoxib for the above indications: (tick all that apply)

- Prescriber decision  Patient preference   
 Initiated in secondary care  Prescribing formulary

#### Non-response to previous NSAID:

COX-2 selective inhibitor  Other NSAID

#### Intolerance to previous NSAID:

COX-2 selective inhibitor  Other NSAID

Other: please specify.....

#### 5. Please provide the following data regarding stopping treatment with lumiracoxib

Has treatment stopped? Yes  No  DK

If Yes please provide:

a) Stop date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ and/or last prescription date \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Reason for stopping:.....

### PATIENT DATA

#### 6. Please specify your patient's ethnicity, if known:

- Caucasian  Asian (Indian sub-cont)  Hispanic   
 Black  Asian (China/Japan)

Other.....

#### 7. At the time of starting lumiracoxib, please specify this patient's status regarding general health:

Body Mass Index.....kg/m<sup>2</sup> DK

Smoking status: Current  Past (ex)  Never  DK

Alcohol consumption: Occasional  Excessive\*  Never  DK

\*Male > 21 units/week; Female > 14 units/week

#### 8. Prior to starting lumiracoxib did the patient have a history of the following: (tick all that apply)

- |  | Yes                      | No                       | DK                       |
|--|--------------------------|--------------------------|--------------------------|
| Hypersensitivity reactions (e.g. angio-oedema/urticaria) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Serious skin reactions (e.g. erythema multiforme)        | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Excessive* alcohol use                                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

\*Male > 21 units/week; Female > 14 units/week

#### 9. At the time of starting lumiracoxib did the patient have any of the following: (tick all that apply)

- |  | Yes                      | No                       | DK                       |
|--|--------------------------|--------------------------|--------------------------|
| Dyspeptic or other upper gastrointestinal conditions       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Cardiovascular disease (e.g. hypertension)                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Coronary disease (e.g. arrhythmia/infarct/cardiac failure) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Cerebrovascular disease (e.g. CVA/TIA)                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Abnormal renal function/renal disease                      | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Diabetes   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Rheumatoid arthritis                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Abnormal liver function/hepatic disease*                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

\*Because of recent prescribing restrictions for lumiracoxib, we are collecting additional information on liver function tests and relevant risk factors (see q14 and 15)

#### 10. Was this patient taking any of the following medications in the periods indicated: (tick all that apply)

	In 3 months prior to starting			During treatment		
	Yes	No	DK	Yes	No	DK
Antacids	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Histamine <sub>2</sub> Antagonists / PPIs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Misoprostol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Aspirin (analgesia >300mg od)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Aspirin (cardioprotection <300mg od)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Anticoagulants / Antiplatelet agents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Non-selective NSAIDs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
COX-2 selective NSAIDs (inc meloxicam)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Corticosteroids (oral/systemic)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Antidepressants (SSRIs and similar)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Antihypertensives	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Statins or Fibrates	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sex Hormones (HRT/OC)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Figure 22.2 Example of M-PEM questionnaire.

DSRU Reference: «srefCode»

## EVENT DATA

An **EVENT** is any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter in the patient's notes. Example: a broken leg is an **EVENT**.

**IMPORTANT:** please indicate any events reported to Commission on Human Medicines (CHM) [previously known as Committee on Safety of Medicines (CSM)] or manufacturer

**11. Please list any events after starting treatment with lumiracoxib?**

None

**12. Please list any events within 3 months after stopping lumiracoxib?**

None

Event date	Event

**13. If your patient has died please provide:**

Date of death:
Cause of death as recorded on death certificate:
1a
1b
2

#### LIVER FUNCTION

**14. On starting lumiracoxib, please specify if this patient had any specific risk factors for abnormal liver function/hepatic abnormality?**

M. B. A. S. S.

Yes No DK

- Malignancy
- Autoimmune Disease
- Chronic Viral Infection (e.g Hepatitis B/C, EBV)
- Iron or copper overload
- Other conditions:

If Yes to Other conditions, please specify:.....

.....

#### **Concomitant medications**

Paracetamol DMARDs (e.g methotrexate) Biologics (e.g beta-interferon) Other medications (prescribed, OTC, herbal products):	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
--	--

If Yes to Other medications, please specify:.....

**15. Please provide liver function lab test values in the table below / send copies of reports as applicable on starting lumiracoxib and during treatment.**

**NB** Please include **normal ranges** as they are vital for interpretation.

	At start*	During treatment			After stopping	Normal range (Units)
		(1)	(2)	(3)**		
Date						
Bilirubin						
AST						
ALT						
GGT						
Alk Phos						
Albumin						

*Percent to the luminescent start date*

**\*\* If test results reported on more than three occasions during treatment please provide on a separate**

**Thank you for your co-operation.  
Your time and effort is greatly appreciated**

**Please return in the FREEPOST envelope provided.**

Figure 22.2 (Continued)

3 months of stopping the drug are followed up using a supplementary questionnaire to determine the outcome of the pregnancy. All reported deaths for which no cause is specified are also followed up to try to establish the cause of death, provided the reporting GP has supplied a practice identification code for the patient.

For each report, trained coding staff prepare a computerized, longitudinal, chronological record of demographic, exposure, and outcome data associated with starting the study drug. All events reported on questionnaires are now coded onto a DSRU database using Medical Dictionary for Regulatory Activities (MedDRA) terminology (this replaced the DSRU bespoke dictionary in 2012). Selected attributes are linked to selected data. For example, an event is coded as an ADR if the GP specified that the event is attributable to a drug (either the study drug, or another drug taken during the study observation period), if the event had a fatal outcome, or if the event was a reason for stopping. Data quality are assured through a number of methods based on error prevention, data monitoring, data cleaning, and documentation.

## SAMPLE SIZE

In standard PEM, the sample size of 10 000 exposed patients has been driven by the methodology's original objective to bridge the gap between randomized trials and spontaneous reporting regarding sensitivity to rare and uncommon events that can be achieved by including a larger sample size than premarketing studies. Based on the general "rule of 3",<sup>1</sup> it follows that the larger the sample size, the rarer the event that can be detected (Strom, 1994). Thus, a sample size of 10 000 within a standard PEM should allow for the detection of at least three cases of an adverse event, with 85% power, if the event occurs at a rate of at least 1 in 2000 patients (assuming the background rate is zero) (Machin *et al.*, 1997: Table 7.1). If the background rate is

known and there is an *a priori* hypothesis of the effect size, then it is possible to analyze the statistical power of a study given a fixed sample size. For example, assuming 5% (two-sided test) significance, the power of a study based on 10 000 subjects to detect as statistically significant an increase in incidence from 0.1% to 0.2% would be 80% (Machin *et al.*, 1997: Table 7.2). Because of the customized nature of M-PEM studies, a specific sample size is calculated depending on the research question of interest, for which the outcomes are chosen and defined through internal DSRU scientific discussion as those which best reflect the research question. For the majority of M-PEM studies that have been undertaken to date, the sample size has been smaller than the 10 000 required for standard PEM studies.

Importantly, the final evaluable cohort sizes and the duration of a study are dependent on the level of prescribing of the study drug in England by GPs. However, cohort accrual is likely to be faster and larger than in postmarketing clinical trials or existing longitudinal medical records databases that sample from a subset of the population.

## PRINCIPLES OF GOOD PHARMACOVIGILANCE PRACTICE

M-PEM studies are conducted according to national and international guidelines for ethical conduct of research involving human subjects (RCP, 1996; DOH, 2000; CIOMS and WHO, 2002; GMC, 2013). Following the principles of good pharmacovigilance practice (EMA, n.d.), a full protocol is written for each study to monitor and research the safety of medicines. In addition, under Section 251 of the NHS Act 2006, the DSRU has received support from the Ethics and Confidentiality Committee of the National Information Governance Board<sup>2</sup> to gain access to and process patient identifiable information without consent for the purposes of medical research (October 2009) (Health Research Authority, n.d.). Patient information security is assured through strict measures guided by DSRU policies. Highly confidential

<sup>1</sup>The rule for safety data is commonly referred to as the "rule of 3." In many situations involving rare reactions it is assumed that the frequency of the event is small, so that the occurrence of the event follows a Poisson distribution, and the 95% confidence interval is calculated based on the number of events. If no events are observed in a study of  $X$  individuals, then one can be 95% certain that the event occurs no more often than  $3/X$ .

<sup>2</sup>The responsibility for Section 251 was transferred to the Health Service Authority and the Confidentiality Advisory Group (CAG) in April 2013.

patient data (name and address) supplied by the NHSBSA used to identify the patient to the prescriber are then made anonymous through use of a unique study identifier code assigned by the DSRU and separately one supplied by the GP on the questionnaire at the point of return. The practice code or number is used for subsequent correspondence if additional information is sought from the doctor.

At least one interim report is written to summarize the data for each study based on per-protocol predefined milestones (e.g., annually, or number of evaluable patients). These reports may include a listing, by month since the beginning of treatment, of all events reported, and evaluation of factors that may affect cohort accrual and impact on the ability to meet study objectives. They are, if possible, discussed with the marketing authorization holder (MAH) so that reporting obligations to the regulatory bodies can be fulfilled and any remedial action undertaken. Wherever possible each study is undertaken in a collaborative, but always independent relationship with the MAH.

## **CONTRIBUTION OF STANDARD AND MODIFIED PRESCRIPTION-EVENT MONITORING TO PHARMACOVIGILANCE**

The methodology is recognized as a tool for pharmacovigilance and risk management contributing to the monitoring of overall safety of newly marketed medicines as used in real-life clinical practice. It is included within EU regulatory guidelines as a pharmacoepidemiological method that can be used in post-authorization safety studies (PASS) (EMA, 2012).

As describe earlier, a number of M-PEM studies have been completed and several are ongoing. The results of these studies have been published separately elsewhere or the studies are in process; however, Tables 22.2 and 22.3 provide an overview of the methods used to illustrate the potential applications of M-PEM in the context of pharmacovigilance and risk management. These studies were designed to address specific research questions, including characterization of real-life drug use, adherence to prescribing recommendations or guidelines, and targeted surveillance or analysis of

specific events, including those considered to require special monitoring by regulatory authorities. Through M-PEM it is possible to evaluate the safety of a medicine in particular subpopulations defined by particular prognostic characteristics or risk factors at various points in time (pre exposure and/or at treatment index date and/or concurrent) during treatment which are considered important for the events of interest. In such studies, patients may be identified according to prespecified criteria (age, sex, indication) through use of an eligibility questionnaire. This may be necessary to define the inception cohort to exclude, for example, those who received the product prior to the approval of an extension to license subgroups (Davies *et al.*, 2007; Aurich-Barrera *et al.*, 2009) or following important changes in the product's lifecycle (e.g., a licensing or formulation change) (ENCEPP n.d.e).

Examples of modifications to provide targeted safety surveillance for a specific ADR (and sequelae) are, for example, idiopathic bronchospasm in new users of chlorofluorocarbon (CFC)-free formulations of inhaled corticosteroids or anticholinergics (Perrio *et al.*, 2007), misuse and diversion in new users of opioid products (Layton *et al.*, 2011; Osborne *et al.*, 2013), and psychiatric events in new users of rimonabant (Buggy *et al.*, 2011). Examples of exploration of drug utilization and compliance with recommended prescribing regimens include the use of ivabradine in patients with conditions that are contraindicated or for whom special warnings apply (Doe *et al.*, 2010), or use of selected medicines which, for example, affect cytochrome P450 metabolism and hence drug response, such as CYP3A4 moderate and strong inhibitors, which are contraindicated for use within 14 days prior to starting a novel formulation of fentanyl (Osborne *et al.*, 2013).

## **SIGNAL DETECTION AND HYPOTHESIS TESTING**

Signal detection and evaluation are the primary concerns of pharmacovigilance. Common to both standard and M-PEM study designs, several methods are applied for signal detection, both qualitative and quantitative, not only to look for new unexpected adverse reactions, but also for further

Table 22.2 Examples of applications of M-PEM methodology: completed studies.

Drug ( <i>n</i> )	Background	Data collection	Targeted population or event surveillance	Applications
Carvedilol (Eucardix™) (Aurich-Barrera <i>et al.</i> , 2009) [Roche Products Ltd] ( <i>n</i> = 1666)	UK license extended to treat mild to moderate chronic heart failure subject to supervision of hospital specialist	Patient demographics, treatment initiation and supervision, dose titration, severity of heart failure, pretreatment tests, past medical history, concomitant medication	Heart failure subgroup identified by initial eligibility questionnaire	Assessment of compliance with prescribing recommendations and clinical management guidelines post-license extension
Flixotide™ Evohalers™ (Perrio <i>et al.</i> , 2007) [Allen & Hanburys Ltd, Uxbridge, Middlesex, UK] ( <i>n</i> = 13413)	Regulatory requirement to monitor introduction of CFC-free inhalers in Europe	Patient demographics, severity of indication, use of oral corticosteroids, spacer devices, and other respiratory treatments	Event rates compared for specific respiratory event rates (paradoxical bronchospasm) before and after starting CFC-free inhalers	Active surveillance post-formulation change from metered dose inhaler to CFC-free Evohalers™ Identification of off-label use in COPD
Travoprost eye drops (Travatan™) (Davies <i>et al.</i> , 2007) [Alcon Labs. UK Ltd] ( <i>n</i> = 1441)	License extension to first-line use in the treatment of ocular hypertension in open-angle glaucoma granted in 2003	Patient demographics, hospital initiation and specific questions on the occurrence of abnormal eyelash growth, abnormal eyelid hair growth, and iris or periocular skin discolouration	Eligibility questionnaire used to identify population of patients who started treatment post-license extension Incidence of specific ocular events reported in premarketing trials assessed	Active surveillance post-licence extension Quantification and better understanding of specific events of interest
Modafinil (Provigil™) (Davies <i>et al.</i> , 2013) [Cephalon (UK) Ltd.] (post-licence extension cohort; <i>n</i> = 1096)	License extended to include the treatment of "excessive sleepiness associated with chronic pathological conditions" in 2004. Low projected use	Prescribing patterns, plus selected aspects of patient management in terms of contraception. Data also collected on risk factors for cardiovascular and psychiatric adverse events and serious skin reactions	Subcohort of users identified post-license extension. Analyses further stratified by indication	Enhanced characterization of real-life drug use Active surveillance post-license extension

(Continued)

Table 22.2 (Continued)

Drug ( <i>n</i> )	Background	Data collection	Targeted population or event surveillance	Applications
Rimonabant (Acomplia™) (Buggy <i>et al.</i> , 2011) [Sanofi- Aventis] ( <i>n</i> = 10 011)	Anti-obesity drug launched in the UK in 2006 (product withdrawn from market during course of this study)	Patient demographic data, health status (body mass index, weight, smoking), past medical and psychiatric history and specific questions on events of depression, anxiety, insomnia and seizures	Comparison of specific psychiatric event rates occurring in the 6 months prior to and after starting treatment	Assessment of risk of specific psychiatric/ nervous system events of regulatory concern
Varenicline (Champix™) (Kasliwal <i>et al.</i> , 2009) [Pfizer Ltd] ( <i>n</i> = 12 159)	Smoking cessation therapy. Regulatory concern over psychiatric events (suicidal ideation)	Demographic data, past and current smoking habit, past medical history, current morbidity and reason for stopping (if stopped)	Focused time-to- event analysis on prespecified events of interest: myocardial infarction, depression, anxiety, aggression, suicidal ideation, and nonfatal self-harm	Characterization of real-life drug use Hypothesis testing on pre-specified events of particular concern
Atomoxetine (Strattera™) (Davies <i>et al.</i> , 2010) [Eli Lilly and Co. Ltd] ( <i>n</i> = 5079)	Licensed for treatment of attention-deficit hyperactivity disorder. Regulatory concern over an increased risk of suicidal thinking (Layton <i>et al.</i> , 2011)	Demographic data, prescribing patterns, targeted capture of data (both prior to and during usage) on psychiatric events, convulsions, abnormal liver function, and selected cardiovascular events	Matched cohort analysis on events of interest	Hypothesis testing on prespecified events of particular concern
Fentanyl buccal tablets (Effentora™) (Layton <i>et al.</i> , 2011; Osborne <i>et al.</i> , 2013) [Cephalon (UK) Ltd] ( <i>n</i> = 556)	Launched in the UK in January 2009, licensed for the management of breakthrough pain in patients with cancer already receiving and tolerant to opioid therapy	Data collected on demographics, initiation of therapy (setting and titration) and past opioid use. Specific questions to identify potential misuse or inappropriate/ off-label use	Targeted capture of data (both prior to and during usage), including respiratory, renal and hepatic conditions, and concomitant medication	Enhanced characterization of drug use and misuse Specific evaluation of use of medicine in relation to concomitant medication or diseases that are contraindicated or where precautions are advised

Table 22.2 (Continued)

Drug ( <i>n</i> )	Background	Data collection	Targeted population or event surveillance	Applications
Fentanyl nasal spray tablets (PecFent™) (Osborne <i>et al.</i> , 2013) [Archimedes Pharma] ( <i>n</i> = 63)	Launched in the UK in 2010, licensed for the management of breakthrough pain in patients with cancer already receiving and tolerant to opioid therapy	Data collected on demographics, initiation of therapy (setting and titration) and past opioid use. Specific questions to identify potential misuse or inappropriate/off-label use	Targeted capture of data (both prior to and during usage), including respiratory, renal and hepatic conditions, and concomitant medication	Enhanced characterization of drug use and misuse Specific evaluation of use of medicine in relation to concomitant medication or diseases that are contraindicated or where precautions are advised
Ivabradine (Procorean™) (Doe <i>et al.</i> , 2010) [Servier Lab. Ltd] ( <i>n</i> = 4624)	Licensed in the UK in 2006 for treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contraindication or intolerance for β-blockers	Demographic data, information on treatment initiation, past medical history, current morbidities, contraindications for use, baseline and ongoing results of tests of heart rate and concomitant medications	Targeted data capture and analysis for selected ocular and cardiovascular events	Specific evaluation of use of ivabradine in relation to diseases/conditions that are contraindicated or where precaution is advised Quantification and characterization of specific ocular and cardiovascular events of interest observed in premarketing clinical trials
Quetiapine extended release (Seroquel XL™) (ENCEPP n.d.e) [AstraZeneca UK Ltd] ( <i>n</i> = 13 276)	Extended-release formulation licensed for the treatment of schizophrenia, manic episodes associated with bipolar disorder, or as add-on therapy for major depressive disorder	Data collected on demographics, use of medication that may cause somnolence or EPS and other risk factors for these events	Nested matched case-control study to explore relationship between dose and events of somnolence and EPS Targeted data capture and analysis of pattern of events related to diabetes mellitus/metabolic syndrome over time	Hypothesis testing on prespecified events of particular concern in risk management plan

EPS: extrapyramidal symptoms; XL: extended release.

Table 22.3 Examples of applications of M-PEM methodology: ongoing studies.

Drug (target number for cohort)	Background	Data collection	Targeted population/event surveillance	Applications
Exenatide (Bydureon™) (ENCePP, n.d.a) [Eli Lilly and Co. Ltd] (n = 5000)	Once weekly injection launched in UK in April 2011 for treatment of diabetes mellitus	Data collected on demographics, initiation of therapy (setting and titration) and current/past antidiabetic medication use and adherence. Specific questions to identify risk factors for pancreatitis and gallstones	Targeted data capture and analysis of pattern of events related to diabetes and pancreatitis	Quantification and characterization of specific gastrointestinal events of interest observed in premarketing clinical trials
Asenapine (Sycrest™) (ENCePP, n.d.b) [N.V. Organon] (n = 5000)	A novel atypical antipsychotic developed for treatment of moderate to severe manic episodes associated with bipolar disorder and schizophrenia	Data collected on demographics, initiation of therapy (setting and titration), and past antipsychotic use. Primary focus on somnolence and sedation, weight gain, oral hypoesthesia, swelling of the tongue and throat, and allergic reactions	Self-controlled case series study to explore temporal relationship between starting treatment and oral events  Targeted data capture and analysis time to event	Enhanced characterization of drug use and misuse  Specific evaluation of use of medicine in relation to concomitant medication or diseases that are contraindicated or where precautions are advised  Quantification and characterization of specific oral events of interest observed in premarketing clinical trials
Rivaroxaban (Xarelto™) (ENCePP, n.d.c) [Bayer Pharma A.G.] (n = 10000)	A highly selective direct factor Xa indicated for the prevention of venous thromboembolism (VTE) in patients undergoing elective hip or knee replacements, prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF) and the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)*	Data collected on patient demographics, medical history/ medication use, adherence, prescribing decisions. Primary focus on haemorrhagic events. Secondary foci on drug utilisation, off-label use and quantifying incidence of other events.	Specific evaluation of use in special populations  Targeted data capture and analysis time to event.	Quantification and characterization of haemorrhagic events and VTE events indicating failure of anticoagulation

\*Also indicated for secondary prevention following an acute coronary syndrome in combination with aspirin alone or aspirin plus clopidogrel or ticlopidine.

information regarding expected drug–adverse events associations of interest that might affect the benefit–risk balance of a drug. The M-PEM study design offers greater opportunity to systematically collect supplementary information at the patient level for the whole cohort, facilitating the investigation and exploration of a range of additional research questions beyond that originally explored by the standard PEM approach.

### INCIDENCE RISK AND INCIDENCE RATES (DENSITIES)

Both standard and M-PEM approaches enable analysis of longitudinal data and examination of temporal relationships of outcomes to new exposures. The methodological approach provides a numerator (the number of reports of an event), denominators not only in terms of the number of patients, but also number of patient-months of exposure to the drug, and a known time frame. This allows for event profiles over time to be examined through application of various statistical methods. In standard PEM, the scope for this analysis is limited to crude estimates, since information cannot be collected on all important risk factors that may be confounding factors for all outcomes because of the nature of the simple questionnaire design balanced with no remuneration to respondents. In M-PEM, additional information is collected for all patients within the cohort regarding relevant co-morbidities and other potential confounding factors, which can, through statistical modeling techniques, provide adjusted estimates for selected outcomes.

For both approaches, initial simple crude analysis of the incidence (risk) of events for an evaluable cohort by month by system organ class is an effective descriptive method in which one may observe disproportionately higher counts than expected from summary of product characteristics or other drugs within the database. Examples of signals as seen in a standard PEM are gynaecomastia with finasteride (Wilton *et al.*, 1996) and hallucinations with tramadol (Dunn *et al.*, 1997). An example seen in an M-PEM study is that of psychiatric events with varenicline (Buggy *et al.*, 2013).

However, the principle statistic of interest ID<sub>t</sub> is the crude incidence density (ID) (or rate) that can be calculated for a given fixed time period *t* for all events reported in patients for a given time period, and expressed usually in units of first event reports per 1000 patient-months of treatment (or observation). Since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID does not initially include censoring. These rates can be used to give estimates of the “real-world” frequency of reported events by estimating the cumulative incidence rate over fixed time periods. In standard PEM studies, these estimates are crude (unadjusted). For example, consider the standard PEM study of drospirenone/ethinyl estradiol (Yasmin®), which identified 13 cases (five of deep vein thrombosis and eight of pulmonary embolism) in 15 645 females, each with possible risk factor(s). Applying complete case analysis, the crude incidence rate was 13.7 cases per 10 000 woman-years (95% confidence interval (CI): 7.3, 23.4) (Pearce *et al.*, 2005). In the PEM study of strontium, which was an early example of modification collecting information on prior history of a targeted outcome (venous thromboembolism (VTE)), the crude annualized incidence of VTE was (95% Poisson exact CI) 6.24 (4.60–8.27) per 1000 patient-years strontium treatment (Osborne *et al.*, 2010).

Compared with the “classic” cohort design with multiple exposure groups, the methodology is more efficient in terms of resources. However, the absence of data on a contextual comparator can, in some cases, be a limitation. To attempt to address this, it is possible to undertake calculations of measures of effect (risk or rate ratios) for internal comparisons within cohort according to time periods and/or between subgroups according to different defined particular characteristics, or external comparisons to carefully selected data sources. Again, common to both standard and M-PEM approaches, within-cohort estimates of crude ID rate differences or ratios can identify events that occur significantly more frequently soon after starting the study drug. The null hypothesis is that the incidence rates are constant between the two groups being compared; the alternative hypothesis is that the incidence rates

are different. In rejecting the null hypothesis where substantial differences are observed, this could be explained by a number of factors, including drug treatment.

Most frequently, for signal generation purposes for general surveillance, for each reported event, the difference or ratio between time periods is calculated to allow the examination of the null hypothesis; that is, the IDs in the first month after starting treatment and the IDs for months 2 to 6 ( $ID_1 - ID_{2-6}$ ). A 95% CI is applied to the rate difference or ratio (based on the normal approximation). Thus, where the  $ID_1 - ID_{2-6}$  value for an event is positive, or  $ID_1/ID_{2-6}$  is above one and the confidence limits around the point estimate exclude the null value (zero or one respectively), the null hypothesis is rejected. This result can be considered to be a signal for an event associated with starting treatment with the study drug. If the rate of events in months 2 to 6 combined is considered to be significantly greater than during month 1, this result is considered to be a signal for a delayed-onset event. In comparing these two time periods, the assumption is made that, given an event, its reporting is equivalent in both periods in a fixed cohort. These signals then require confirmation or refutation by further study. An example of a signal as seen in standard PEM is the association of skin reactions with lamotrigine (Mackay *et al.*, 1997). For drugs where pattern of use is intermittent and/or short term, such summaries are also produced, but there are several differences. First, the numerator is based on total incident counts irrespective of treatment status (whether recorded during/post treatment or whether "unknown") and the denominator takes into account the observation period (between start date and end of survey date). Second, the comparator (reference) period may be restricted. For example, in a standard PEM study of an antihistamine (desloratadine) (Layton *et al.*, 2009) intended for short term (<30 days) intermittent use, the second month was considered most appropriate as the reference period.

Other complementary quantitative analyses common to both standard and modified approaches include capturing information on and ranking by frequency the reasons for stopping and comparing with ranked IDs. In general, there appears to be a

high degree of correlation between these two sets of values. The values are presented for the standard PEM study of desloratadine in Table 22.4. These values can be used to compare and contrast drugs within one therapeutic class; for example, with anti-histamine drugs it shows that drowsiness and sedation are the most frequently reported events likely to be a drug side effect with levocetirizine, whereas this is far less common with desloratadine; similarly, lower respiratory tract infection (which occurs month in and month out in all cohorts and which is, with many drugs, unlikely to be related to either the drug or disease being treated) is fairly common among the ID values but virtually never appears among the common reasons for drug withdrawal. A more detailed exploration of associations between patient characteristics and reasons for stopping is possible within M-PEM. A recent example is the exploration of psychiatric events as reasons for treatment withdrawal for rimonabant (Willemen *et al.*, 2012).

#### FURTHER QUANTITATIVE ENHANCEMENTS WITHIN MODIFIED PRESCRIPTION-EVENT MONITORING

For signal strengthening and exploration of specific safety issues, a key characteristic and advantage of M-PEM is the possibility to conduct comparisons, such as pre- and post-exposure periods, that help control for within-subject change in disease severity as well as reducing between-group differences. The bespoke M-PEM design offers greater scope for analysis within the cohort using self-controlled methodology, because it allows lines of enquiry about possible fixed and time-variant confounders.

Consider the ID rate or difference statistic. A significant result may appear to be a safety signal arising for the product under study, but such events may be associated with the indication for treatment (confounding by indication), and/or channeling (preferential prescribing to subsets of patients defined by specific characteristics, such as having a condition that is resistant to previous therapy) (Petri and Urquhart, 1991) and/or switching (past experience with an alternative drug may modify the risk of adverse events associated with current use of the study drug) (Ray, 2003). Examples include

Table 22.4 Most frequently reported events during first 2 months of observation with the two antihistamine drugs desloratadine and levocetirizine, ranked in order of counts in first month  $N_1$ .

Desloratadine				Levocetirizine			
DSRU dictionary higher term	$N_1$	$N_2$	RFS	DSRU dictionary higher term	$N_1$	$N_2$	RFS
Condition improved	1384	606	1984	Condition improved	1470	434	1896
No further request	658	77	733	No further request	640	59	699
Not effective	537	238	772	Not effective	460	133	588
Course completed	177	24	201	Course completed	160	29	189
Upper respiratory tract infection	53	47	4	Other drug substituted	62	26	88
Patient request	40	16	56	Upper respiratory tract infection	56	25	4
Hospital referrals no admission	30	13	14	Drowsiness, sedation	46	4	43
Headache, migraine	28	7	9	Headache, migraine	22	9	6
Lower respiratory tract infection	24	17	1	Hospital referrals no admission	22	11	10
Other drug substituted	23	13	36	Noncompliance	21	2	18
Urinary tract infection	19	6	0	Rash	20	9	8
Effective	17	2	19	Pregnancy	11	2	5
Infection skin, unspecified <sup>a</sup> / local bacterial	17	9	0	Urinary tract infection	18	12	0
Rhinitis allergic	17	18	5	Anxiety	17	4	0
Asthma worse	16	12	2	Lower respiratory tract infection	17	21	0

$N_1$ : total number of first reports of each event during observation in month 1;  $N_2$ : total number of first reports of each event during observation in month 2. RFS: reasons for stopping.

Desloratadine: total no. reports 3969 during months 1 and 2 of observation out of 5559 reports for whole study period in 5502 patients (46.5% of cohort) for whole study period.

Levocetirizine: total no. reports 3732 during months 1 and 2 of observation out of 5509 reports for whole study period in 5453 patients (44.1% of cohort).

<sup>a</sup>Unspecified: no event term currently exists in DSRU dictionary.

paradoxical increase in rates of gastrointestinal adverse effects in users of COX-2-selective inhibitors at high baseline risk of gastrointestinal adverse effects. Selection bias introduced by these phenomena may affect the generalizability of the study results since the evaluable cohort may not be fully representative of the postmarketing users of the product. Other factors that may introduce selection bias are external influences on prescribing (such as expert committee guidelines and/or decisions for reimbursement). In M-PEM, whilst prescribing patterns of a new drug cannot be predicted or controlled for, the issues of prescribing governance, channeling, and influence of previous therapy can be examined through careful data capture and a variety of analytical methods to provide a better understanding of the cohort characteristics and

health outcomes and the population to whom the results may be applicable. Examples of particular design and analytical applications nested within M-PEM studies are provided below.

### Drug Utilization

Drug utilization research describes the extent, nature, and determinants of drug exposure at the patient level. Data from M-PEM studies can inform about prescriber adoption of new drugs. The demographic and clinical characteristics of new users can be described and examined in relation to signals of off-label use; for example, indications, dose, and conditions or other factors that are contraindicated or special warnings for use. An example is the M-PEM study of ivabradine (which is licensed for

chronic stable angina) and its utilization in patients under 40 years of age, in which use for other indications was observed since the prevalence of angina (which is the indication for this product) is low in this age group (Doe *et al.*, 2010). In addition, M-PEM studies can examine aspects of adherence to prescribing guidelines. One M-PEM study is underway to explore the impact of expert guidelines on adoption within clinical practice of a novel anticoagulant (ENCePP, n.d.c; Layton *et al.*, 2013).

### Before and After Studies

“Before and after” studies compare the rate of particular outcomes during a defined period of exposure (or observation) after starting the study drug with those rates in the same individuals during a defined period of observation before starting, using a repeated-measures matched-pair analysis. The null hypothesis is that event rates are the same prior and post starting treatment. One example within an M-PEM study was the examination of rates of respiratory events with the introduction a CFC-free formulation of an anticholinergic (ipratropium) metered dose inhaler (MDI) in populations who were “switchers” from the original MDI and those naive to ipratropium treatment (Osborne *et al.*, 2011). The analyses suggested that characteristics of these two subpopulations differed such that naive patients were more likely to be children, have an indication of asthma, and have milder disease severity, while switchers were more likely to be adults, have an indication of COPD, and have more severe disease. Such differences have an important impact on ongoing evaluation of risk–benefit balance of the new formulation. The matched analysis in each subset revealed that, in naive patients, dyspnea was shown to be significantly lower in the “before” reference period (relative risk (RR) 0.6 (95% CI 0.40, 0.88) for post- versus pre-treatment), while dyspnea for switchers was shown to be significantly higher in the “after” high-risk period (RR 1.46 (95% CI 1.02, 1.81)).

### Predictors of Risk

The nested case–control design is particularly advantageous for examining predictors of disease.

The method itself overcomes some of the disadvantages associated with non-nested case–control studies while incorporating some of the advantages of a cohort study (Flanders and Louv, 1986). As a pharmacoepidemiologic tool for risk management plans, the design potentially offers reductions in costs and efforts of data collection and analysis compared with the full cohort approach, with relatively minor loss in statistical efficiency. M-PEM cohorts provide opportunities to conduct such nested case–control studies, for example, for patients who develop selected ADRs and matched patients who receive the same drug without developing ADRs. Two prospectively designed nested case–control studies are underway to investigate the association between dose and the occurrence of two outcomes (extrapyramidal symptoms; somnolence and sedation) in users of a new formulation of an atypical antipsychotic (ENCEPP, n.d.e).

### Self-Controlled Case Series Analysis

Other methodologic developments that are being introduced to M-PEM studies to examine temporal associations between specific events of interest and starting treatment with a new drug include the application of the method of self-controlled case series studies proposed by Farrington *et al.* (1996). The method was originally developed to study adverse reactions to vaccines. The method uses only cases; no separate controls are required as the cases act as their own controls, thus minimizing the effect of confounding by factors that do not vary with time, such as genetics and gender. Each case’s given observation time is divided into control and risk periods. Time-varying confounding factors such as age can be allowed for by dividing up the observation period further into age categories. Because the method requires time-varying covariate data on cases only and not for the whole cohort, it is efficient in terms of sample size and resource. The method requires that specific criteria are met (for example, occurrence of the event of interest should not affect subsequent exposure history or increase mortality) and thus is not applicable to all outcomes. Using this approach, measures of effect (risk or rate ratio estimates) are automatically adjusted for all fixed confounders. Non-cases can

be ignored without bias, while cases are self-matched. Conditional regression modeling will provide the adjusted estimate of relative incidence (with 95% CIs) of the outcome for the high-risk observation period of interest relative to the remaining observation time. M-PEM studies provide an ideal platform to enable the relative incidence of newly diagnosed outcomes of interest to be studied between predefined high- and low-risk periods in new users, thus enabling time-to-occurrence of selected events to be explored and reviewed for evidence of temporal patterns (ENCePP, n.d.b).

### Time to Event Analysis

It is acknowledged in signal detection that the generalized approach to segregation of time periods may not be appropriate for all events with respect to their most relevant time periods of excess. However, it is possible to explore the time of occurrence of an event by using statistical methods, termed “time to event” analysis, based on survival methodology. Using these methods, a hazard function can be estimated using an appropriate distribution (e.g., Weibull) that shows the instantaneous risk of an event over time. The use of this technique is now incorporated within M-PEM studies to explore temporal relationships for targeted events of interest as an additional tool for signal generation purposes. Examples include calculation of smoothed hazard functions in examining rates of hypoglycemia in thiazolidinedione antidiabetic drugs (Vlckova *et al.*, 2009) and neuropsychiatric outcomes associated with varenicline (Buggy *et al.*, 2013).

### Modeling

Multiple regression modeling allows the simultaneous testing and modeling of multiple independent variables on an outcome of interest. An example of a conditional logistic regression modeling was a within-PEM study comparison to examine the risk of pioglitazone treatment combinations (with insulin or other antidiabetic agents) on risk of edema, weight gain, cardiac failure, and anemia (Kasliwal *et al.*, 2008). This was a standard PEM with modification to include history of use of

important antidiabetic drugs. The null hypothesis was that the risk of these outcomes was the same regardless of treatment. Pioglitazone may be used alone or in combination with a sulfonylurea, metformin, or insulin as an adjunct to diet and exercise for the management of type 2 (noninsulin-dependent) diabetes mellitus. Though the combination of pioglitazone and insulin is licensed and allows improvement of glycemic control, this combination is associated with increased risk of edema and may cause weight gain. The adjusted hazard ratios for each of the separate models based on PEM study data for patients taking pioglitazone–insulin combination compared with those taking pioglitazone monotherapy and/or pioglitazone with another antidiabetic (sulfonylurea or metformin) were: edema 2.28 (95% CI: 1.37, 3.78); weight gain 2.03 (95% CI: 1.15, 3.58), and cardiac failure 1.73 (95% CI: 0.63, 4.74). This suggests that patients taking the pioglitazone–insulin combination had higher risks than pioglitazone monotherapy or pioglitazone combined with another antidiabetic drug.

### ASSESSMENT OF THE EFFECTIVENESS OF RISK MANAGEMENT (RISK MINIMIZATION) PROGRAMS

Risk management is attracting immense interest in pharmacovigilance. M-PEM methodology contributes not only to the identification and measurement of risks of medicines, but, with some additions, can also examine how the risks of medicines are being managed in real-world clinical settings. An example is the M-PEM study that was conducted to monitor the introduction of carvedilol for the treatment of cardiac failure (Aurich-Barrera *et al.*, 2009). The product (combined alpha- and beta-adrenergic blockers) has been used for the treatment of angina and hypertension for some time, but there was concern about its appropriate use for cardiac failure in the community. The aim of the study was to monitor how the product is being managed in the community; for example: What investigations were undertaken prior to starting the drug? Who supervised the dose titration (GP or specialist)? Was the drug given to patients with the appropriate severity of heart failure? The design

included sending an eligibility questionnaire followed by up to three detailed questionnaires for a period of up to 2 years.

## **EXPLORATION OF SIGNALS AND FOLLOW-UP OF IMPORTANT EVENTS**

Analysis and evaluation of pharmacoepidemiological data should include medical assessment, both to improve the understanding of signals raised by epidemiological techniques and to raise (and evaluate) new signals or hypotheses by using medical judgment with appropriate systems for causal inference. Once a signal has been recognized through either the standard or M-PEM approach, supplementary analysis is required to further characterize important attributes. Medical evaluation of reports is an important component. Further information on events of interest and/or signals may be obtained from the prescriber and a case series constructed. As highlighted previously, M-PEM design provides the opportunity for the collection of detailed information on targeted events of interest from the initial survey for the evaluable cohort, as opposed to case-only information for standard PEM studies.

Important safety signals have been generated and events of interest explored in this way. In the standard PEM study of the anti-epileptic drug vigabatrin, following published case reports of visual field defects associated with the use of the product, four cases of visual field defects were identified initially in the PEM cohort. In view of the importance of the signal, 7228 patients who were reported to be taking the product by the end of the study were followed up by sending a simple questionnaire to the GP to ask whether any serious adverse events or changes in vision had been reported since the initial study form had been returned. In addition, if the patient has been seen by an ophthalmologist for visual problems, the ophthalmologist was asked to complete a questionnaire giving details of visual field testing before and during treatment with vigabatrin. In addition to the initial four reports, the follow-up information revealed 29 cases of visual field defects that were considered by the ophthalmologist to be probably or possibly related to vigabatrin, giving an inci-

dence of risk of 7.00 per 1000 patients (Wilton *et al.*, 1999). Other events that routinely undergo evaluation include pregnancies and deaths. Data collected from reported pregnancies include the proportion and nature of congenital anomalies in babies born to women exposed to newly marketed drugs during pregnancy, in particular in the first trimester (Wilton *et al.*, 1997). All deaths are followed up to ascertain cause of death where cause has not been reported.

## **SIGNAL STRENGTHENING**

Signal strengthening can also be conducted through a variety of comparisons using selections of the PEM database (within therapeutic class, specific patient groups) (Layton *et al.*, 2001, 2004, 2006; Acharya *et al.*, 2005). Such comparisons are appropriate because the database is comprised of new drug-user populations assembled at the same stage in time in the immediate postmarketing period since introduction of each product. As described previously, it is also possible to conduct external comparisons using demographic data of the population as a whole (Boshier *et al.*, 2004).

The DS RU also receives requests from regulatory authorities and manufacturers to investigate drug safety signals in the PEM database. Whenever possible the DS RU conducts retrospective analyses (which usually include follow up of reports for the drug in question and comparator drugs). Such analyses contribute to the debates on these signals and to regulatory and public health decisions. One example used data from a standard PEM study on sertindole (Wilton *et al.*, 2001). Sertindole is an atypical antipsychotic known to be associated with prolongation of the QTc interval. The product was withdrawn from markets in the EU following reports of sudden death and serious cardiac arrhythmias. The comparative analyses of the PEM studies of sertindole and two other atypical antipsychotics, risperidone and olanzapine, studied cardiovascular events, deaths from cardiovascular events, and deaths from other causes (such as suicide) and were considered to be a very important source of information for the regulatory decision on the matter. Other M-PEM studies where results informed regulatory decisions regarding ongoing

benefit-risk evaluations included those examining cardiovascular and gastrointestinal safety of COX-2 selective inhibitors (Kasliwal *et al.*, 2005).

Where appropriate, comparisons are made between patients identified within an evaluable cohort and an external reference group, if a suitable internal reference cohort cannot be found within the DSRU database and the research question requires the result to be contextual. An example is the analysis of cardiovascular events of the PEM study on sildenafil (a phosphodiesterase type 5 inhibitor used for erectile dysfunction) (Boshier *et al.*, 2004). Reported deaths from myocardial infarction and ischemic heart disease in users of sildenafil in the PEM study were found to be no higher than expected according to national mortality statistics. Similarly, death from ischemic heart disease in the bupropion PEM (when used for smoking cessation) was compared with external data and showed no difference in the standardized mortality ratio (Boshier *et al.*, 2003). The precautions with regard to possible sources of bias and confounding also apply to external comparisons, principally due to differences in study design and data collection methods. Therefore, results of external comparisons must be interpreted very carefully.

While such comparisons produce valuable additions to the understanding of the safety of medicines, it is important to emphasize that comparisons of independent cohorts are subject to bias and confounding that must be taken into consideration in the analysis and evaluation process. However, the paucity of postmarketing safety studies in large populations makes the information provided by these comparative studies very useful. Real benefit can only be achieved when not only the limitations of any postmarketing safety study are taken into consideration, but also when its results are considered in relation to other studies that had been conducted on the same product.

## DISCUSSION

PEM, and its modern replacement M-PEM, is a well-established postmarketing surveillance technique in England, and internationally recognized as a tool for pharmacovigilance and risk management

contributing to the monitoring of overall safety of newly marketed medicines as used in real-life clinical practice. M-PEM studies combine the advantages of standard PEM studies (in monitoring general safety and identification of unexpected risks of a medicine) with that of a more targeted safety study that addresses specific questions (to better understand known or partially known risks with a medicine).

The disadvantages and limitations of the methodology, like those of most of the available techniques of pharmacovigilance, are however real. They include the following:

- 1 Selection bias is possible, in that there is the potential that the PEM cohort is not representative of the general population using NHS services. This cannot be assessed because PEM does not monitor an unexposed cohort concurrently. Non-response bias is another form of selection bias that is possible, since not all questionnaires sent are returned. The mean returns of the standard PEM and M-PEM questionnaires sent out are 56% and 60%, respectively. These are significantly higher than the reporting rate in the yellow card and similar schemes (Heeley *et al.*, 2001; Hazell and Shakir, 2006), but it cannot be established in each PEM study whether the patients whose doctors return the questionnaires are in any way different from those whose doctors fail to complete and return the questionnaire. We already know that the responding and nonresponding GPs differ very little in the distribution of ages in which they became principals or in their geographical distribution (Mackay, 1998; Key *et al.*, 2002).
- 2 Until recently, the methodology did not involve monitoring within the secondary care setting. Thus, a "survivor bias" can operate whereby patients who both started and stopped a drug under hospital care may never receive a GP prescription and may, therefore, be undetected by PEM. None of the current methods of pharmacovigilance is ideal in respect of this problem – hence the importance of extending PEM methodology into hospital practice. The DSRU has adapted the principle method to examine drug initiations by specialists in the secondary

care setting (DSRU, 2013). An example of the specialist cohort event monitoring (SCEM) design is the Observational Assessment of Safety in Seroquel (OASIS) study (ENCEPP n.d.f). This was designed to examine the short-term (up to 12 weeks) safety and use of quetiapine fumarate in a prolonged-release formulation (Seroquel XL™), along with a comparator group started on the quetiapine immediate-release (IR) formulation. Any patient seen by a psychiatrist in England in the mental health care setting was considered eligible for inclusion where a clinical decision was made to prescribe either the XL or IR preparation of quetiapine as part of normal clinical practice for schizophrenia or mania associated with bipolar disorder. Other SCEM studies are underway as PASS that support RMP (ENCEPP, 2013; ENCEPP n.d.d.; Layton *et al.*, 2013). The SCEM methodology facilitates the systematic collection and reporting of safety and utilization data on patients newly initiated within the secondary care setting and, thus, is complementary to M-PEM PASS, which are based in primary care.

- 3 Like other observational studies, PEM has limited ability to collect information on confounding factors that might be important for all possible outcomes. The adoption of M-PEM methods has provided considerable opportunities to enhance collection of supplementary data on important risk factors. Furthermore, as described earlier, new techniques are being introduced to examine temporal associations, such as the application of the methods of self-controlled case series studies. However, even without analysis, lists of reported events are useful to prescribing doctors for they show which events are reported in everyday clinical practice and the relative frequency with which these events will be seen. They are perhaps more useful than the unquantified long lists of possible side effects given in the standard prescribing information.
- 4 Whilst efficient in terms of resources, the single-group cohort design where evaluable patients are included on the basis of a single common exposure has the limitation that there is absence of an unexposed comparator. Thus, comparisons need to be undertaken with great care. The “trade-off”

is between capturing the real-world and generalizable data through the observational design and randomization in clinical trials that in postmarketing settings have many logistical and even ethical difficulties, as well as limited external validity caused by exclusion criteria and other restrictions.

- 5 One of the strengths of the PEM/M-PEM technique is that it collects dispensed rather than prescribed data. This is in contrast to other data sources, such as data collected in the General Practice Research Database. However, while indeed compliance is not examined routinely in PEM/M-PEM, it is possible, if necessary, to monitor repeated dispensing for the same patient as an indicator of compliance and provide estimates of compliance with treatment regimen by calculating medication possession ratios.

The advantages of PEM and M-PEM are:

- 1 It is noninterventional, and thereby minimizes the selection biases that occur when the study design interferes with the doctor's choice of drug for the individual patient. This means that in PEM/M-PEM, data are collected on patients who have received the study drug because the doctor considered it the most appropriate treatment for that patient, as in everyday “real-world” clinical practice.
- 2 It is national in scale, and the cohort comprises all patients given the drug usually immediately after its launch into general practice. In Europe it is the only database that can regularly identify cohorts of thousands of patients for newly introduced medicines soon after launch. This is in contrast to some data sources that have limited data on newly marketed products in this immediate postmarketing period because of small size of because of population exposed in the subset of the population monitored within these systems. The methodology prompts all prescribers to provide information on safety and use because they automatically receive a questionnaire for each patient prescribed the drug being monitored. It is probably this prompting function that is responsible for the success of the methodology; it does not rely on the doctor

- taking the initiative to report happenings. These features ensure that the studies are population based and that they disclose the real-life clinical experience with the drug; there are no exclusions, and all patients prescribed the drug are recruited even if they are very old, very young, or receiving several drugs concurrently for multiple illnesses.
- 3 Exposure data are derived from dispensed prescriptions, with validation from prescribers through confirmation of such data on the questionnaires. Considering the large proportion of patients who do not get a prescription dispensed (Beardon *et al.*, 1993), this is an advantage in that exposure data are more accurate than that derived from records of physician-issued prescriptions (which are not always dispensed), as held in some databases.
  - 4 Because the data are concerned with events, the system could detect side effects that none of the doctors have suspected to be due to the drug. The information provided by event reporting does not require the doctor to decide whether or not an individual event in a single patient is drug related. It thereby avoids a very difficult clinical decision, since as most reactions resemble fairly common clinical events, avoiding the doctor having to decide on causation may well encourage reporting. The system allows direct contact between the doctors working in the DSRU and the GPs, so that follow-up surveillance of individual cases (including long-latency events) or deaths and all pregnancies is facilitated.
  - 5 Additional advantages accrue from the increasing size of the PEM database, which has been built up since 1984. The database now contains information on 120 completed PEM/M-PEM studies and over 1 million patients. This has started to provide opportunities for comparing products and patient groups in the database. As time passes and more studies are completed, the value of the database as a research tool increases progressively.
  - 6 A number of M-PEM studies have been undertaken to support the construction of risk management plans by providing opportunities for a number of additional research applications that can be used to generate signals of potential safety

hazards and to further evaluate safety concerns identified by other pharmacovigilance methods or arising from regulatory concerns. Their customized sample size is advantageous in terms of study conduct, limiting costs, and providing timely information to the dynamic risk management process. Thus, they should be considered a valuable tool when developing a risk management plan for the evaluation of the safety of a new medicine.

- 7 M-PEM contributes to risk management plans not only by the analysis and understanding of possible adverse events, including those considered to be potential and identified risks in risk management plans, but also by providing opportunities for studying drug utilization to answer questions regarding missing information and the characteristics of postmarketing users of medicines. Furthermore, M-PEM is being used to study the effectiveness of risk minimization methods.

## FUTURE PLANS

The mission of the DSRU is to continue to improve its research methods and foster the conduct of innovative national and international collaborative research.

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# Prescription–Event Monitoring in New Zealand

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## INTRODUCTION

In New Zealand (NZ), prescription–event monitoring (PEM) is the main tool of the Intensive Medicines Monitoring Programme (IMMP), a national unit that performs proactive postmarketing surveillance on selected medicines. PEM studies – which may also be referred to as cohort event monitoring studies – are prospective observational cohort studies, in which cohorts are established from prescription data and adverse events are solicited from prescribers primarily by using follow-up questionnaires. This chapter describes how the IMMP has developed, enhanced, and utilized PEM in NZ.

## HISTORY

In 1976, the NZ national Committee on Adverse Drug Reactions, advisory to the then Department of Health, recommended supplementing NZ's spontaneous reporting activities ("yellow card"

scheme) with an early postmarketing surveillance program. The purpose was to speed up the identification of previously unrecognized adverse drug reactions (ADRs) and to provide better information about risk (McQueen, 1977). The stimulus for this was the international recognition that spontaneous reporting had proved inadequate in recognizing the serious oculomucocutaneous syndrome with the new beta-blocker practolol, even though the early symptoms were quite common (Skegg and Doll, 1977).

The additional program, which commenced in 1977, was called the Intensified Adverse Drug Reaction Reporting Scheme and was aimed at selected new medicines. It was to function by establishing patient cohorts from prescription information provided by community and hospital pharmacies and by identifying adverse events from "intensified" spontaneous reporting. For the medicines selected for study, this intensified reporting was an attempt to change the nature of reporting from that of suspected adverse reactions of

recognizable clinical significance (where the patient's doctor is required to identify an association between the reported symptom and the medicine) to that of reporting *all* adverse events of any type or severity and without any judgment on causality. A high rate of reporting of all types of events was expected to provide greater opportunity for identifying signals of previously unrecognized adverse reactions.

The cohorts of identifiable patients would also allow the estimation of rates/frequencies of adverse events and thus provide a measure of risk.

The first drugs monitored in this way were metoprolol, atenolol, acebutolol, labetalol, perhexiline, sodium valproate, and cimetidine. Although the reporting rates for these drugs were much higher than rates in the standard spontaneous reporting program (Coulter and McQueen, 1982), it was decided to also send questionnaires to the prescribers – after the drugs had been marketed for at least 6 months – requesting information on any adverse events noted in the patients' records. These were called "event-recording surveys," and their use was aimed at enhancing the reporting rate still further. In addition, it was possible to identify when the monitored medicine was no longer dispensed and request information on why treatment had ceased.

The use of these questionnaires was the first endeavor at what was later called PEM (Inman, 1981b), and the first publication resulting from the use of this methodology was the investigation of a new signal with labetalol (Coulter, 1979). Other findings published in this very early period concerned perhexiline (Department of Health, 1979, 1980), reasons for the cessation of therapy with perhexiline, sodium valproate, and labetalol (Coulter, 1981), and sodium valproate (McQueen, 1982). The early stages of the programme were reviewed after 5 years' activity (Coulter and McQueen, 1982). In 1983, the scheme was given a more appropriate name, the IMMP.

## THE INTENSIVE MEDICINES MONITORING PROGRAMME AS PART OF NEW ZEALAND PHARMACOVIGILANCE

The organization and systems of pharmacovigilance in NZ are described in Chapter 16a. The

IMMP operates within the NZ Pharmacovigilance Centre (NZPhvC), which also incorporates the national spontaneous reporting program – the Centre for Adverse Reactions Monitoring (CARM). This arrangement is very beneficial because it enables all spontaneous reports for the monitored medicines to be entered into the IMMP databases, which enhances the identification of adverse events (see Identification of Adverse Events section).

The NZPhvC is located in the Department of Preventive and Social Medicine at the University of Otago in Dunedin. Most of the activities of the NZPhvC are performed under contract to the Ministry of Health's medicines regulatory body (Medsafe), which for many years has provided the majority of the funding for the center (see Chapter 16a). However, Medsafe funding of the IMMP has gradually decreased in recent years and ended in June 2012. The IMMP is currently operating on residual research funding, and its future is under discussion.

## SELECTION OF MEDICINES FOR MONITORING

For many years, new drug applications submitted for licensing in NZ were considered by the Medicines Assessment Advisory Committee (MAAC), which advised Medsafe and recommended which medicines should be monitored by the IMMP. For each medicine recommended, the IMMP Director would undertake a feasibility study that would then be considered by an expert panel, with a final recommendation then made to the Ministry of Health. The IMMP panel gave priority to monitoring those drugs where the conditions in Table 23.1 applied.

In recent years there have been changes in the systems by which new drugs are approved in NZ, and some applications are now approved by Medsafe without referral to the MAAC. For those medicines which are referred, the committee no longer makes recommendations for monitoring by the IMMP. Instead, Medsafe advises pharmaceutical companies to prepare a postmarketing risk management plan (RMP). The RMP for a new medicine is required to outline appropriate post-

Table 23.1 Conditions to support selection of medicines for monitoring.

Use is expected to be widespread and/or long term Safety issues have been raised from clinical trials or post-marketing experience, and further evaluation is needed	There are related medicines with significant problems The target disease is of low risk, and any increased risk arising from therapy would adversely affect the benefit-risk balance	Safe treatment options are already available and any increase in risk would be unacceptable Another drug of the same class is being monitored or considered
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marketing studies, but does not necessarily have to include an IMMP study in an NZ population.

Between 2008 and 2012 only one medicine was identified for IMMP in this new system. This may be because the number of applications for new medicines has been decreasing, because pharmaceutical companies are choosing to perform post-marketing studies in other countries, or because companies are performing different postmarketing surveillance.

Since cessation of funding from Medsafe in 2012, all new monitoring studies are outlined on the IMMP website (<https://nzphvc.otago.ac.nz/immp/>) and the monitored medicines continue to be listed in the *MIMS* catalogue. IMMP medicines are also identified in the recently developed NZ Formulary (<http://nzformulary.org/>).

## OVERVIEW OF INTENSIVE MEDICINES MONITORING PROGRAMME METHODS

The IMMP performs prospective observational cohort studies on selected medicines, and the core methods remain similar to those described in earlier reviews (Coulter, 1998, 2000; Clark and Harrison-Woolrych, 2006). Exposure data are obtained by establishing cohorts of patients prescribed and dispensed the monitored medicine, and outcome data are obtained by identifying clinical events at various time points after the medicine was prescribed.

Since its inception as the first PEM program in the world, the IMMP methods have been developed considerably. This chapter describes and illustrates the methodology, with reference to new developments and with emphasis on those features that are unique to the NZ IMMP.

## ESTABLISHING THE COHORTS

The IMMP patient cohorts are established directly from dispensing records supplied by community and hospital pharmacies throughout NZ. In NZ it has been necessary to use individual dispensing pharmacies as the source of prescription data for PEM. In the UK, the Drug Safety Research Unit obtains these data from a central source, the Prescription Pricing Division (see Chapter 22), but there is no equivalent database in NZ. Whilst there are centralized records of subsidized medicines, new medicines are not usually subsidized in the first year after licensing, and some medicines never become subsidized, even though they may be widely used. Therefore, the IMMP is the only national unit able to collect dispensing data for any prescribed medicine in NZ.

Pharmacists' provision of data to the IMMP is voluntary and unpaid, although the NZ Pharmaceutical Guild's Code of Ethics advises pharmacists to participate in the program. Compliance with returning IMMP dispensing data has always been extremely high (greater than 90%), and the relationships established with pharmacists are valuable in providing additional prescribing information and further reports of adverse events.

## METHODS OF DISPENSING DATA CAPTURE

Computer software programs in each pharmacy flag the IMMP medicines and these dispensing records are sent directly to the IMMP. For many years, dispensing data capture operated entirely as a hard-copy system: on request from the IMMP, all prescriptions dispensed for IMMP medicines were printed out by each pharmacist and sent by mail (Freepost) every 4 months. However, the system is now being converted to an electronic data capture system, as described below.

## DEVELOPMENT OF ELECTRONIC DATA CAPTURE

During 2008–2009 the IMMP undertook a feasibility study to develop an electronic system to capture dispensing data directly from pharmacists. Consultation with a randomly selected group of community and hospital pharmacists showed a high level of support for the proposed new “eIMMP” system (Harrison-Woolrych *et al.* 2011a). Following the feasibility study, the IMMP worked with the two companies supplying software to community pharmacies to modify their software in order to identify, extract and electronically send to the IMMP the pharmacy records for patients dispensed the monitored medicine.

Community pharmacists throughout NZ are now being invited to join the eIMMP scheme. Once each pharmacy has joined the scheme, there is an automated monthly procedure for electronic submission of dispensing data for the monitored medicines directly to the IMMP. At the time of writing, 75% of community pharmacies in NZ have joined the eIMMP scheme, with the remainder still sending IMMP dispensing records in hard copy. It is anticipated that at least 90% of pharmacies will ultimately send data electronically to the IMMP. This will allow patient cohorts to be established in a more timely manner.

## COMPONENTS OF PRESCRIPTION DATA

The data elements normally captured from the prescription dispensing information are summarized in Table 23.2. There may be variations on the type of data captured for particular medicines.

## PATIENT IDENTIFICATION

It is essential that the IMMP correctly identifies each patient in the cohorts to avoid errors in the data (e.g., duplications) and to accurately obtain follow-up information. The IMMP has always used patients' names, date of birth, and address for identification (Table 23.2). In recent years, the IMMP has also been able to identify the unique National Health Identification (NHI) number for over 98% of the patients in the monitored medicine cohorts.

Table 23.2 Data elements captured from prescription dispensing information.

Data element	Details recorded in IMMP databases
Patient details	First and last names, address, date of birth, gender, NHI number
Prescribing doctor	Name and specific worksite address, type of doctor (GP or specialist)
Dispensing pharmacy	Name and worksite address
Medicine name and formulation	Brand name, generic name, and specific formulation
Dose	Recorded as daily dose
Dispensing dates	Dates of all prescriptions dispensed in monitoring period
Quantity dispensed	For each prescription, number of days (if regular treatment) or number of tablets/injection (if prn)

This is valuable for checking each patient's identification and also allows record linkage to national morbidity and mortality databases (see Data Linkage section).

## VALUE OF CONTINUOUS PRESCRIPTION RECORDS

The continuous dispensing records obtained by the IMMP are very useful for studying how specific medicines are used (see Drug Utilization Studies section). Analyses of the duration of use of monitored medicines from the dispensing data records have provided some interesting results relevant to clinical practice. Investigation of use of the weight reduction medicine sibutramine showed that the majority of the cohort (59% of patients) had a treatment period of 90 days or less, suggesting mainly short-term use, although 11% were prescribed sibutramine for more than 1 year (Hill *et al.*, 2007).

For medicines not continually administered, it is possible to identify how many courses of treatment patients have and how long each course is. An IMMP study of the utilization of the smoking cessation medicine varenicline showed that only 4% of

patients were dispensed the recommended 12-week course (Harrison-Woolrych and Ashton, 2010).

## DURATION OF PRESCRIPTION DATA COLLECTION

All dispensings for the monitored medicine during the period of monitoring are recorded, providing a prescribing history for each patient for as long as treatment continues. This is different to PEM in the UK, where medicines are usually monitored for an average time of 6 months after first prescription (Chapter 22). The longer duration of monitoring in NZ provides greater opportunity for identifying (a) delayed effects, (b) use in pregnancy or lactation, (c) death rates and causes of death, (d) reasons for the cessation of therapy, (e) changed indications (these frequently broaden over time), (f) evidence of tolerance or dependence, (g) changes in prescribing practice, which for new medicines takes time to be established, and (h) changes in patient characteristics, which in the early postmarketing phase may differ from later use.

## COHORT SIZE

The desirable size for a PEM cohort has been estimated at around 10 000 patients (Inman, 1981a). For 22 completed IMMP monitoring studies, mean cohort size was 10 964 patients, and the mean duration of monitoring was 58 months. However, for some medicines (e.g. entacapone) it has been difficult to establish cohorts of sufficient size in a reasonable time frame. This is sometimes due to the small population of NZ (about 4 million) but may also be due to other factors, including which medicines are subsidized for use. This said, lack of government subsidization has not always limited use – none of the cyclo-oxygenase (COX) II inhibitor medicines were subsidized in NZ, and yet the cohorts for rofecoxib plus celecoxib grew to around 60 000 patients in 1 year (Harrison-Woolrych *et al.*, 2005).

It is sometimes necessary to establish cohorts larger than 10 000 patients. As outlined above, IMMP dispensing data for the obesity medicine sibutramine showed that the duration of treatment

for the majority of patients was less than 3 months, and thus greater numbers were needed to increase the patient-years of exposure to this medicine.

## COMPARATORS

For several medicines, it has been possible to monitor more than one of the same class, or those with a similar indication, although not always concurrently. Examples include beta-agonists, lipid-lowering medicines, COX II inhibitor, atypical antipsychotic medicines, and bisphosphonate medicines. Having comparators has obvious advantages, but unlike a clinical trial, there may be confounders that make interpretation of differences difficult (Beggs *et al.*, 1999). Concurrent (rather than sequential) monitoring of two or more similar medicines is valuable as it reduces the likelihood of potential confounding factors that may affect the analyses and interpretation of results.

Monitoring rofecoxib and celecoxib during the same time period allowed comparison of the incidence of thrombotic cardiovascular events with each medicine (Harrison-Woolrych *et al.*, 2005). During monitoring of the atypical antipsychotic medicines a comparative cohort study of nocturnal enuresis was performed, which showed adult patients taking clozapine experienced a higher rate of bedwetting than patients taking other atypical antipsychotic medicines (Harrison-Woolrych *et al.*, 2011b). However, for some medicines, it is not always possible to provide a suitable comparator, and it may not always be desirable from the point of view of cost and demands made of practitioners.

## IDENTIFICATION OF ADVERSE EVENTS

### DEFINITION

The IMMP definition of an adverse event is any new clinical experience since the patient started the medicine, whether or not the event is thought to be related to the medicine. This definition incorporates several possible clinical outcomes, which are summarized in Table 23.3.

Table 23.3 IMMP definition of an adverse event.

Any new clinical experience since the patient started the medicine, including:
• All new clinical events, including common and minor ones
• Worsening of a pre-existing condition
• Abnormally changed laboratory values
• Unexpected failure of therapeutic effect
• Any possible interactions
• Accidents
• Pregnancies
• All deaths

### INTENSIVE METHODOLOGY FOR IDENTIFYING EVENTS

The IMMP methodology is unique, in that adverse events in patients taking the monitored medicines are identified from *multiple* sources. The primary method is by follow-up questionnaires to patients' doctors (as in UK PEM), but the IMMP *also* identifies adverse events from spontaneous reporting, from duplicate prescriptions, from pharmacy data, and also from data linkage to national morbidity and mortality databases. This intensive methodology for identifying adverse events is described in the following.

### FOLLOW-UP QUESTIONNAIRES

IMMP questionnaires seeking information on adverse events are sent to patients' doctors at regular intervals. Most often this is the patient's general practitioner (GP), but it may be another prescribing doctor, including specialists. Doctors are asked to report all new clinical events (Table 23.3) recorded in the patient's notes from a specified date. For a new patient, this will usually be from the commencement of therapy, but if questionnaires have been sent previously, doctors are requested to record events from the date of the last received questionnaire (this date is provided to facilitate record searching).

The compliance rate for returning IMMP questionnaires was previously very high (greater than 80% for many medicines) but has decreased to around 45–50% for some medicines in recent years.

This may be because of generally increasing demands on GPs' time. However, the average response rate has been generally higher than that normally obtained in the UK PEM program, which may be related to several factors, including the high spontaneous reporting rate observed in NZ (Olsson, 1999).

Doctors are not paid for completing IMMP questionnaires, but are able to claim Maintenance of Professional Standards (MOPS) points from the Royal NZ College of General Practitioners program (for maintenance of registration, contribution to patient safety, and continuing medical education) for each questionnaire completed.

### SPECIFIC QUESTIONNAIRES

Whilst all IMMP follow-up questionnaires have similar core elements (e.g., patient, prescription, and doctor details) and are designed primarily to obtain information on adverse events, each questionnaire for a specific medicine is designed according to other outcomes of interest. Thus, questionnaires for intra-uterine devices (IUDs) included questions about pregnancies, sibutramine questionnaires included questions on body mass index, and varenicline questionnaires had questions on smoking cessation. Questionnaires may also seek information on indication for use of the medicine, past medical history, and concurrent medications. All questionnaires request information on the cessation of therapy and reasons for stopping treatment.

### SUPPLEMENTARY QUESTIONNAIRES

It has sometimes been necessary to obtain additional information to that gained from the standard questionnaires described above. Examples include:

- pregnancy questionnaires (sent for women of reproductive age) for varenicline;
- baseline and serial liver function tests for tolcapone;
- asthma severity questionnaire for salmeterol and eformoterol;
- questions about previous history of peptic ulcer disease for the COX II inhibitors.

For reported deaths, further information on the cause of death and possible relationship with the medicine is sought by further questionnaires or specific letters to doctors and also by linkage to mortality databases (see Data Linkage section).

### DUPLICATE PRESCRIPTIONS

During the 1980s, the IMMP developed duplicate prescription pads to enhance event reporting. In certain regions of NZ (covering about 25% of the population) personalized prescription pads were given to GPs, private specialists, and hospital doctors. Doctors gave the original and a copy of the prescription to the patient who took both to the pharmacist, and then the accumulated copies were sent to the IMMP. An early study showed that the event-reporting rate in the duplicate prescription region was 14 times greater than that in a non-duplicate region (Coulter, 1986). The IMMP prescription pads have now largely become supplanted by electronic prescribing. Computer software for practitioners flags the monitored medicine and prints out a duplicate prescription whenever a monitored medicine is prescribed. Events may still be reported on the duplicate prescriptions, which are returned to the IMMP at regular intervals. The duplicate prescription scheme appears to continue to maintain doctors' awareness of the IMMP.

### INTENSIFIED SPONTANEOUS REPORTING

Spontaneous reports ("yellow cards") sent to the NZPhvC for IMMP medicines may come from health professionals, patients/carers, or pharmaceutical companies. These reports are often of great value as they may highlight a specific clinical concern and form the index case for a series being considered as a signal.

Doctors and other health professionals in NZ are made aware which medicines are being monitored by the IMMP via listings in the *MIMS* catalogue, which is linked to most patient management systems and also from listings in the NZ Formulary (<http://nzformulary.org/>). In addition, drug companies have also been required to state that their medicine is monitored by IMMP in all product information. The inclusion of a medicine in the program should

thus increase the spontaneous reporting rate, and an early study of beta-blockers showed this to be the case (Coulter and McQueen, 1982).

The symbiotic relationship between the IMMP and the NZ spontaneous reporting program (CARM) is valued as both programs benefit from working together in the same national pharmacovigilance unit (see Chapter 16a). This is a key difference to the UK PEM scheme, which operates separately to the UK spontaneous reporting scheme.

### PATIENT REPORTING TO THE IMMP

In addition to the multiple "intensive" methods of patient follow-up described in this chapter, the IMMP conducted a pilot study of direct patient reporting (Harrison-Woolrych, 2011). During the monitoring of dapoxetine (a selective serotonin reuptake inhibitor for the treatment of premature ejaculation) it was noted that most of the follow-up questionnaires sent to doctors in the routine way were returned with insufficient information for assessment of adverse events, or not returned at all. This suggested that patients should be invited to report their experiences with dapoxetine directly to the IMMP.

Pharmacists were asked to distribute a flyer to patients when dapoxetine was dispensed. This flyer invited patients to report to the IMMP, either by completing a form available on the IMMP website, or by email, phone, or fax. Doctors were also sent reporting forms to be completed by the patient, in addition to the routine IMMP follow-up questionnaires that are usually completed by health professionals.

This initiative of inviting patients to report their experiences with a medicine directly to the NZPhvC was not in fact new. For many years patients in NZ have been able to report adverse reactions to any medicine to the CARM (see Chapter 16a). However, this pilot study demonstrated a more proactive method of encouraging patient reporting for a specific medicine.

### DATA LINKAGE

In NZ, there are national databases containing information on births, deaths, hospital admissions,

and other morbidity outcomes (e.g., cancer). Identification of patients in these databases is by their unique NHI number, which, as discussed earlier, is now available for the vast majority of patients. It is therefore possible to obtain mortality and morbidity data for patients in the IMMP cohorts by record linkage to these national databases.

The IMMP routinely uses a data-linkage approach to obtain more information about patients in the IMMP cohorts at various time-points in each study. At the time of entry of each new patient, national database records are checked for information, including NHI number, and other patient details, including ethnicity. Such information provides useful data on medicine utilization in NZ, as discussed earlier in this chapter.

As monitoring proceeds, IMMP follow-up questionnaires are routinely sent out to doctors, with the primary purpose of recording adverse events that have been reported to the patient's GP (see Follow-Up Questionnaires section). Limitations of this method include underreporting of events (including events that may not have been reported to the GP) and the declining response rate for return of IMMP questionnaires. Some of these limitations can be reduced by use of data linkage to national morbidity and mortality databases as a further method of following up patients in the IMMP cohorts. Therefore, at the time IMMP questionnaires are returned to the IMMP, each patient's NHI number is linked to the national datasets to identify deaths and any adverse events that have resulted in hospital admission since the time the patient started the monitored medicine.

In recent studies (e.g., varenicline), this linkage has also been undertaken for patients for whom a follow-up questionnaire has *not* been returned. This process means that virtually all (about 98%) patients in the IMMP cohorts can be followed up for deaths and serious adverse events (see Data Linkage Studies section).

## PROCESSING OF EVENTS

### CLINICAL REVIEW OF REPORTS

All events identified during the monitoring process are assessed by a physician at the IMMP, using the

same process as for reviewing ADR reports in the spontaneous reporting program (Kunac *et al.*, 2008). A “relationship” is established between the drug and the event following the protocol for causality assessment recommended by the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring (<http://www.who-umc.org/Graphics/24734.pdf>) (see Drug–Event Relationship Assessment section).

Adverse events are classified according to system/organ class using the IMMP events dictionary, which is a hierarchical terminology based on the WHO adverse reactions terminology (WHOART). Each event has a “print code” that allows events to be sorted into clinically related groups for further assessment as required.

## DRUG–EVENT RELATIONSHIP ASSESSMENT

Each drug–event relationship is coded as one of the following: definite, probable, possible, unlikely, or unclassified as defined by the WHO (<http://www.who-umc.org/Graphics/24734.pdf>). In line with this guidance, IMMP causality assessments consider: (i) the temporal relationship between the medicine and the adverse event (in particular the duration to onset of the event), (ii) response to withdrawal (dechallenge information) (iii) rechallenge information if available, (iv) possible confounders (including patient's medical history and condition being treated), (v) concomitant medicines, and (vi) biological plausibility (including possible mechanism). *These assessments are made without prejudice* at the time each report is received and may be reviewed later for specific events as the monitoring of a medicine progresses and more information becomes available.

Previously in the IMMP, assessed events were divided into two categories: those with a relationship of certain, probable, or possible were classified as “reactions” and those with a relationship of unlikely were called “incidents” (i.e., likely to represent the background noise of the condition in the population being treated). However, routine practice is now to include *all* events in evaluations to identify signals of previously unidentified adverse reactions (see Signal Identification section).

## PRIVACY AND ETHICAL CONSIDERATIONS

The processes and practices of the IMMP have been set up to comply with the NZ Health Information Privacy Code 1994, and the Privacy Commissioner has been advised of the purpose and methodology of the program (Coulter, 2001). In line with the Privacy Code, there are processes in place within the IMMP to protect patient privacy and maintain confidentiality. These include appointment of a privacy officer and training of staff in all aspects of confidentiality. All IMMP staff (and any other staff collaborating on IMMP studies where access to the data is required) are asked to sign the IMMP confidentiality agreement.

Regarding patient consent for involvement in the program, the IMMP operates on the “opt-out” principle, like other national epidemiological studies. Patients should be informed by their doctor that they have been prescribed a monitored medicine, the reasons why their medicine is monitored, and the type of information collected. The IMMP provides information leaflets that doctors may give to patients and there is additional information on the IMMP website (<https://nzphvc.otago.ac.nz/immp/>) if required. The patient then has the right to opt out of the monitoring study by requesting that the IMMP does not store their personal data. In practice, this happens very rarely and – although the reasons for this have not been evaluated formally – it is possible that patients view the monitoring of their medicine as a “safety net” in place to protect them rather than as an invasion of their privacy.

The ethical aspects of the IMMP were formally reviewed in late 2004 and Ethics Committee approval was granted for the ongoing work of the program. Therefore, Ethics Committee approval is not required for routine new monitoring studies. However, for particular studies that are not part of the routine monitoring, ethics approval is sought in the usual way and approval has invariably been given.

## OUTPUTS OF PRESCRIPTION-EVENT MONITORING IN NEW ZEALAND

### SIGNAL IDENTIFICATION

There are several key elements to successful identification of previously unrecognized adverse reac-

tions in the IMMP. These have been reviewed (Clark and Harrison-Woolrych, 2006) and include:

- the intensive methodology used to obtain events from multiple sources (see above);
- the high quality and completeness of clinical reports received by the IMMP;
- the evaluation of every event report by at least one clinical assessor;
- the ability to obtain further follow-up information in many cases.

The IMMP does not rely on automated processes for signal identification, preferring regular clinical assessment of event listings for each medicine from early in the monitoring study. Possible signals first identified by individual clinical assessment are further investigated by obtaining additional evidence from other sources. These might include the reporting doctor (or other health professional), other databases, including the WHO-UMC international spontaneous reporting database, pharmaceutical companies, overseas medicine regulatory bodies, and the published literature. Using these methods, the IMMP has had some success in signal identification, as outlined in the following.

### PUBLISHED SIGNALS BEFORE 1995

Early signals published in the wider medical literature include cough and angiotensin-converting enzyme (ACE) inhibitors (Coulter and Edwards, 1987), eye pain with nifedipine (Coulter, 1988), ACE inhibitors and anemia (Edwards and Coulter, 1989), mianserin and agranulocytosis (Coulter and Edwards, 1990), the intestinal effects of captopril (Edwards *et al.*, 1992), psoriasis with ACE inhibitors (Coulter and Pillans, 1993), and fluoxetine and hyponatremia (Pillans and Coulter, 1994).

### SIGNALS REPORTED TO THE NEW ZEALAND MEDICINES ADVERSE REACTIONS COMMITTEE

Signals generated in 11 drugs between 1985 and 1995 were searched from the agenda material and minutes of the MARC meetings and from publications. For the purposes of this evaluation, a signal was recorded as such if the MARC was alerted before the date of the second non-IMMP

publication. The date that the MARC was alerted to each signal was recorded, and this date was compared with the date of the first two publications (if any) found by Medline and AdisBase searches of the international literature (all languages with an English abstract). Medline was searched from 1985 and AdisBase from 1989. Case reports and clinical trials were included in the searches. AdisBase searches included publications from regulatory authorities internationally. Data sheets were not searched. The dates of any IMMP publications were also recorded. Any recommendations of the MARC because of considering the signals were noted. Events that are expected because of known pharmacological action (e.g., tremor with beta-agonists) were not recorded as signals.

This analysis identified 153 signals recorded in the 10-year period. Many of the early signals were published in the *NZ Family Physician* published by the Royal NZ College of General Practitioners or in *Prescriber Update*. Of the 153 signals identified, 132 (86%) were notified to the MARC before any publication found in the international literature. Eighty-six (56%) of the signals have since been strengthened or confirmed by at least one non-IMMP publication. In 72 (47%) instances, the IMMP publication was the first report of the signal identified, and in 23 (15%) it was the second. On 39 (25%) occasions, the MARC recommended action after considering the signals. These included articles in *Prescriber Update*, writing to pharmaceutical companies for further information, changes to data sheets, and further investigations.

Signals published in the international literature for the period 1995–2012 are listed in Box 23.1.

## VALIDATION OF SIGNALS

### Investigating Signals by Survey of Cohort Sample

The IMMP cohorts offer a great opportunity to further investigate signals identified early in the monitoring process. Such studies aim to estimate occurrence rates of specific adverse reactions and may also investigate risk factors for these reactions. Following a cluster of reports of nocturnal enuresis (bedwetting) associated with the atypical antipsy-

### Box 23.1 Signals Identified, 1995–2012

Signals published in the international literature during the period 1995–2012 include:

- hypertension with moclobemide (Coulter and Pillans, 1995b)
- fluoxetine and extrapyramidal effects (Coulter and Pillans, 1995a)
- acute psychiatric reactions with the COX II inhibitors (Coulter, 2002)
- acute visual impairment with rofecoxib and celecoxib (Coulter *et al.*, 2003a)
- psoriasis associated with rofecoxib use (Clark and Coulter, 2003)
- activation of pain by sumatriptan (Coulter *et al.*, 2003b)
- nose bleeds associated with risperidone (Harrison-Woolrych and Clark, 2004)
- amnesia associated with sibutramine (Clark and Harrison-Woolrych, 2004)
- cardiac dysrhythmias with COX II inhibitors (Savage *et al.*, 2005)
- QT interval prolongation associated with sibutramine (Harrison-Woolrych *et al.*, 2006a)
- bruising associated with sibutramine (Harrison-Woolrych *et al.*, 2006b)
- alopecia associated with quetiapine (McLean and Harrison-Woolrych, 2007)
- symptoms of depression in children prescribed risperidone (Harrison-Woolrych *et al.*, 2007)
- hair loss with use of the levonorgestrel intrauterine device (Paterson *et al.*, 2007)
- life-threatening clozapine-induced gastrointestinal hypomotility (Palmer *et al.*, 2008)
- withdrawal reactions to varenicline (Harrison-Woolrych and Ashton, 2011)
- epistaxis and other hemorrhagic events associated with varenicline (Harrison-Woolrych *et al.*, 2012)
- memory impairment with varenicline (Tan and Harrison-Woolrych, 2013)

chotic medicine clozapine, the IMMP further investigated this signal. Cohorts of patients taking clozapine, olanzapine, quetiapine, or risperidone during 2003 were identified and follow-up questionnaires with additional specific questions about bedwetting were sent to patients' doctors. It was considered necessary to add specific questions for doctors/mental health nurses to ask the patients directly, as enuresis is a problem that is unlikely to be spontaneously reported. This comparative cohort study showed that one in five patients taking clozapine experienced bedwetting (Harrison-Woolrych *et al.*, 2011b).

### Use of Prescription History

The evaluation of 50 reports coded as "tolerance" with sumatriptan was facilitated by having a longitudinal record of prescription data with the numbers of tablets or injections dispensed recorded for many patients over a period of several years. The reports described patients who claimed that over a period of months or years the drug did not work as well as it did initially and they required higher or more doses to relieve an attack of migraine, or the drug did not work at all. In the natural history of the disease, there are fluctuations in frequency and severity of attacks, and so these reports were difficult to interpret. It was considered that if there was any general trend to tolerance, then mean usage per patient over time would increase.

The prescription data were therefore analyzed, and the mean number of injections or tablets (100 mg equivalent) per patient per 6-month interval was calculated. The results for those patients who had used injections only are shown in Table 23.4 over a period of eight intervals, and an increase was demonstrated at each interval. The first interval was omitted because it would be a trial period of use and for many patients may not be typical of later use.

The latest interval was also excluded because it may not have been complete. The slope of the changes was statistically significant for both the injections and the tablets, but the changes were more marked for the injections. There were no identifiable confounders (Coulter, D.M., presentation at

Table 23.4 Sumatriptan: mean numbers of injections (0.6 mg) dispensed per patient per 6-month intervals.

Interval	Patients	Mean
2	1765	5.23
3	1372	5.87
4	1031	6.67
5	750	8.76
6	494	10.34
7	300	13.49
8	135	18.61
9	41	26.46

Table 23.5 Analyses performed from dispensing data.

Analyses performed	Comments
Age and gender distribution of cohort	Presented in tabular and graphical formats
Patient ethnicity	Obtained for each patient from national datasets
Regional distribution	Prescribing and dispensing of medicine by area of NZ
Dose distribution	Mean doses calculated for first, latest, and all prescriptions
Duration of exposure	Calculated as patient-years exposure of cohort Mean exposure per patient may also be calculated
Prescribing patterns	Courses and cycles of treatment examined with mean and median durations

the 18th Annual Meeting of National Centres Participating in the WHO International Drug Monitoring Programme, Portugal, 1996).

### ROUTINE ANALYSIS OF DATA

At various time points in each monitoring study, the IMMP performs routine analyses of both the exposure (prescription/dispensing) data and the outcome (events) data. The analyses performed on the dispensing data are summarized in Table 23.5.

## DRUG UTILIZATION STUDIES

The analyses summarized in Table 23.5 may contribute to studies of drug utilization in nationwide NZ patient cohorts. Such analyses have resulted in research papers on the utilization of specific monitored medicines in NZ. Examples of such studies include the utilization of sibutramine (Hill *et al.*, 2007) and the utilization of varenicline (Harrison-Woolrych and Ashton, 2010). Further information on how medicines are used in NZ – for example, indication for use or the place of administration/insertion of a medicine/device – can be obtained from IMMP follow-up questionnaires.

## ANALYSES OF OUTCOME DATA

The main outcome analyzed is adverse events whilst the patient is taking the medicine and for a feasible period after cessation of treatment. The main formats for presenting the events data are as follows:

- **Table of all events:** A listing of all the individual events is presented by system/organ class, and within the classes the events are sorted into clinically related groupings. This allows a clinically orientated assessment of the events reported and is useful in signal detection. It shows, for every event, the age and gender of the patient, the dose, the duration to onset, and the relationship that was established at the time of the review of the report. It also shows deaths and withdrawals. The individual events can be cross-referenced with the table of reports for each patient, which presents the events in the context of the whole reaction.
- **Table of reports:** This is a listing by report for each patient and shows all the events associated with each report; for example, one report describing eosinophilia, arthralgia, malaise, and rash with omeprazole, thus presenting the events in the context of the whole reaction. The age and gender for each patient is shown along with the dose, severity, relationship, and outcome of each event.
- **Profile of adverse events:** This provides a table and histogram showing numbers and rates by system/organ class of all events.

- **Frequency rates of adverse reactions:** This provides a listing of all events, showing the percentage of each within each system/organ class, the percentage of each reaction amongst all reports, and the rate of occurrence of each reaction. These are sorted into clinical groupings within each class.
- **Most frequent events:** These are shown (usually the “top 10”) with numbers and rates together with the numbers and rates of withdrawals and deaths for these events.

Other analyses of outcome data may include, but are not restricted to (i) time to onset of adverse events, (ii) risk factors for adverse events (e.g., age, gender, past medical history), and (iii) reasons for the cessation of therapy.

Whilst the primary outcomes of most IMMP studies are safety endpoints (i.e., adverse events) and utilization analyses as described earlier in this chapter, more recent studies have also attempted to obtain information on effectiveness of treatment. In the varenicline monitoring study, doctors were asked to report (on the follow-up questionnaires) if the patient had been successful in stopping smoking. During the monitoring of dapoxetine, patients were asked to report whether they had found the medicine to be effective in treating premature ejaculation (see Patient Reporting to the IMMP section). Whilst such assessments are subjective and only limited information may be obtained, inclusion of effectiveness questions in PEM studies can provide additional post-marketing data on the benefit–risk profile of a medicine.

## SPECIFIC STUDIES USING INTENSIVE MEDICINES MONITORING PROGRAMME DATA

In addition to the routine data analyses performed for every monitored medicine, the cohort and event databases of the IMMP are used for specific pharmacoepidemiology studies. Some examples of studies that have been performed are discussed next.

## STUDIES OF INTRA-UTERINE DEVICES

IUDs are important contraceptive products that may not be included in other monitoring programs. The IMMP has effectively adapted PEM methods for the purpose of monitoring IUDs in the post-marketing setting (Zhou *et al.*, 2003).

Both the copper IUD Multiload Cu375 and the levonorgestrel-releasing device Mirena® have been monitored by the IMMP. Cohorts were established with the use of registration forms supplied (by the manufacturer) with each IUD. Doctors completed the registration form at the time of IUD insertion and returned it to the IMMP. Follow-up questionnaires were then sent annually for each woman, usually to her GP, but often to family planning doctors or gynecologists if this was more appropriate.

For Multiload Cu375, two specific studies were conducted using a cohort of over 16 000 women who used this device in NZ during a 10-year period. The first study was an analysis of insertion problems and reported an overall incidence of approximately 2% for failed/difficult insertion and an incidence of about 1% for adverse reactions to insertion (Harrison-Woolrych *et al.*, 2002). This study also identified nulliparity and experience of the inserting doctor as risk factors for inserting problems.

The second IMMP Multiload Cu375 study investigated the incidence of uterine perforation with this device (Harrison-Woolrych *et al.*, 2003a). The rate of 1.6 per 1000 insertions was higher than previously reported, and one reason for this was thought to be the long period of intensive follow-up (10 years) in the IMMP study compared with other studies. Most uterine perforations (86%) were not diagnosed at the time of insertion, with some remaining undiagnosed for several years.

The IMMP also performed a comparative study of the Multiload Cu375 device and the levonorgestrel-releasing IUD Mirena (Harrison-Woolrych *et al.*, 2003b). This reported a significantly higher incidence of insertion problems with the Mirena device than with the copper IUD, although difficult insertions were reported in fewer than 4% of Mirena insertions. The levonorgestrel IUD is widely used in many countries for contra-

ception and treatment of menorrhagia, and comparative studies of this kind are useful in assisting women and their doctors to make appropriate choices (Harrison-Woolrych, 2003).

## STUDIES IN SPECIAL POPULATIONS INCLUDING CHILDREN AND PREGNANT WOMEN

The IMMP has studied specific issues in defined populations, including women of reproductive age for pregnancy exposure and children who have been prescribed a monitored medicine.

A study was conducted of pediatric use of atypical antipsychotic medicines (Harrison-Woolrych *et al.*, 2007). A population of children aged 15 years or under was identified from the IMMP cohorts, and specific follow-up questionnaires were sent to child/adolescent psychiatrists and/or the children's GPs. This study showed that over 90% of atypical antipsychotic prescriptions for this population were for risperidone, which was most commonly prescribed for disruptive disorders. Assessment of the targeted symptoms identified unexpected use for the treatment of sleep disorders. The most frequently reported adverse events included weight gain and somnolence, and symptoms of depression were identified as a potential new signal for risperidone in the pediatric population.

More recently, a study of pregnancy exposure to the smoking cessation medicine varenicline has been completed (Harrison-Woolrych *et al.*, 2013). Although varenicline is not indicated for use in pregnant women and the mean age of the cohort was 47 years, this study showed that about 1% of women of reproductive age became pregnant whilst taking this medicine. This could result in significant worldwide fetal exposure to varenicline and illustrates the need for global pregnancy registers.

## DATA-LINKAGE STUDIES

NZ is an ideal country in which to perform data linkage pharmacovigilance studies for serious outcomes. The linkage process used by the IMMP (see Data Linkage section) allowed calculation of the risk of completed suicide in patients prescribed

varenicline, which had not been possible in other countries using spontaneous reporting methods alone (Harrison-Woolrych, 2010). The vast majority of deaths in NZ are likely to be recorded in the national datasets, unless a patient has moved overseas and the death has not been reported back to NZ.

Adverse events resulting in admission to a public hospital (including day cases) are also recorded, but admissions to private hospitals may not be, so this is a limitation of the data linkage method. Another limitation is that less detailed information on adverse events is obtained from the national datasets compared with completed GP questionnaires. However, this can be overcome by medical assessors at the IMMP contacting the patient's GP for more information after the serious event has been identified. This has frequently resulted in identification of high-quality and detailed information on serious adverse events that have resulted in death or hospitalization.

The IMMP has now used data linkage methods in several monitoring studies, including antipsychotic medicines, sibutramine, and more recently varenicline. However, there is huge potential to perform further record-linkage studies using IMMP cohorts previously established. The IMMP has collected (in parallel) patient cohorts for four atypical antipsychotic medicines: clozapine, olanzapine, quetiapine, and risperidone. This could allow comparison of the incidence of particular adverse events resulting in hospitalization or death (e.g., myocarditis and cardiomyopathy) in patients taking these medicines. Such studies are important for further understanding the risks of the newer antipsychotic medicines in comparison with clozapine (Hill and Harrison-Woolrych, 2008).

#### PHARMACOGENETIC STUDIES

The ability to identify individuals who are susceptible to ADRs has the potential to reduce the personal and population costs of medicine-related morbidity. Data from the IMMP cohorts and events databases have been used to initiate pharmacogenetic studies, and it is hoped that this will be another area of future development.

A pilot study was conducted to investigate the methodology of linking PEM studies with pharmacogenetics in the IMMP (Clark *et al.*, 2004). This study used a nested case-control design to investigate whether patients with genetic variants in P-glycoprotein and CYP2C9 are more susceptible to psychiatric or visual disturbances following COX II inhibitor use than matched controls taking the same medicine without experiencing an adverse event. This paper by Clark *et al.* also discussed possible future directions for linking pharmacoepidemiology studies with pharmacogenetic investigations.

Currently (2012–2013) the IMMP is conducting a study of bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is a serious and potentially disfiguring adverse event. The IMMP is asking dentists to report all cases of BRONJ during a 1-year period. Patients identified with BRONJ are being invited to supply samples for pharmacogenetic testing. This study is being undertaken in collaboration with the Carney Centre for Pharmacogenomics in Christchurch, NZ.

#### COMMUNICATING RESULTS OF INTENSIVE MEDICINES MONITORING PROGRAMME STUDIES

Effective communication of results from IMMP studies to prescribers and patients is an important aspect of PEM in NZ. Every spontaneous report submitted receives a detailed individual reply that includes summary information from the IMMP databases. Similarly, information is provided in response to telephone, email, or other enquiries as required. During assessment of follow-up questionnaires, IMMP clinical assessors may contact doctors or other health professionals again to discuss cases and obtain further information as needed. Our experience over many years has been that medical colleagues in NZ are usually interested and willing to discuss cases, provide information where possible, and work with the IMMP to improve patient safety in our local environment.

Summaries of IMMP work on particular medicines are regularly provided to pharmacists (with

the regular data requests) and to prescribers in regular IMMP communications with health centers. In addition, new research papers or other summaries are provided to individual doctors or those working in a specialist area – for example, a summary of work on the Mirena IUD was emailed to all family planning clinics in NZ via the Family Planning Association network.

Within NZ, the IMMP communicates results more widely by publication of articles in local professional magazines (e.g., *NZ Doctor* and *Pharmacy Today*) and also by publication of summaries in the Medsafe publication *Prescriber Update*. Outside NZ, the key method of risk communication is by publication of research papers (approximately four per year in peer-reviewed journals) and letters to international journals on specific issues. The IMMP also regularly shares results with international groups, including the WHO and International Society of Pharmacovigilance and with groups in other countries, including the Canadian Institute for Safe Medication Practice and Lareb in the Netherlands (Van Grootheest *et al.*, 2011).

Whilst many IMMP studies have identified issues of concern (e.g., new signals of ADRs), other studies may provide reassurance regarding the level of risk associated with a certain medicine. This said, the issues of most interest to the media tend to be the “scare stories”! Risk communication in pharmacovigilance is a complex process that should also include some assessment of the benefits of the medicine in question. However, as the primary objectives of PEM studies are safety outcomes rather than effectiveness or benefits, this information may have to be drawn from other studies. A complete appraisal of the risk/benefit ratio of any particular medicine may require information from many different studies and is usually undertaken by organizations such as regulatory bodies, rather than PEM units like the IMMP.

## CONCLUSIONS

PEM in NZ is a valuable method of postmarketing surveillance that has been well integrated in systems of pharmacovigilance in this country for many

years. It is recognized that PEM methods are particularly useful for calculation of rates of adverse events, as patient exposure may be accurately defined from dispensing data. In this chapter it has been outlined how, in NZ, the IMMP is the only national unit that can collect dispensing data for any prescribed medicine, whether or not it is subsidized. These data may be used for nationwide medicine utilization studies in addition to safety studies.

The NZ IMMP has adapted and enhanced PEM to perform many different pharmacoepidemiology studies. The intensive methodology, where adverse events are identified from multiple sources, has been effective for signal identification, and this has been enhanced by the symbiotic relationship of the IMMP with the NZ spontaneous reporting program as outlined in Chapter 16a.

Once cohorts have been established, follow-up may be conducted in the whole population or in specific subgroups. Studies to further investigate signals identified or specific safety issues may be conducted, and examples of these studies have been given in this chapter. The range of investigations conducted by the IMMP shows that the methodology of PEM in NZ is highly adaptable.

The information obtained from IMMP studies is useful to patients and doctors when evaluating the benefits and risks of medicines. The additional value of data collected in PEM studies is that it is derived from “real-life” use of medicines. The populations studied are generally more representative of normal clinical practice, without the exclusion criteria of premarketing clinical trials.

There is much potential to further enhance the methodology of the IMMP. Electronic capture of prescription dispensing data has now been established (the “EIMMP” system) as described in this chapter. There is also scope to investigate different methods for identifying events; for example, by using web-based technologies and by encouraging patient reporting. In the future, it is hoped that the IMMP will be able to continue to develop and enhance different methods of identifying adverse events.

Although NZ has a population of only 4 million people, the IMMP has produced results that have usefully informed national public health systems

and which have also contributed to pharmacovigilance worldwide. Internationally, there is scope for PEM methods to be used much more widely, and pooled information from several centers would provide added value. The enhanced and adapted PEM methodology of the NZ IMMP should continue to be an important component of the pharmacovigilance toolbox of the future.

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# A Description of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance as a Global Resource for Pharmacovigilance and Pharmacoepidemiology<sup>1</sup>

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## INTRODUCTION

With the new pharmacovigilance legislation (EU, 2010a,b) the landscape of pharmacovigilance and post-authorization medicines regulation in the EU has changed significantly. There is now a strong legal basis for regulators to request and oversee post-authorization studies aimed at resolving

safety and efficacy questions that have not been answered at the time of authorization. Pro-active benefit-risk management planning has been substantially strengthened with the new legislation, and the EU Risk Management Plan will play an even more important role as a tool to ensure that benefits outweigh risks once a new medicine has been approved. In 2006, to facilitate the conduct of high-quality and independent post-authorization studies and to support regulatory decision making, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was launched with the support of the European Medicines Agency (EMA). ENCePP is a pivotal

<sup>1</sup>The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

initiative within the European Risk Management Strategy (ERMS; HMA/EMEA, 2007) aimed at strengthening the science and methodology that underpins pro-active pharmacovigilance measures for better benefit–risk monitoring throughout the lifecycle of medicines. ENCePP is a voluntary and collaborative network of excellence that brings together the European expertise and experience in the fields of pharmacoepidemiology and pharmacovigilance. The guiding principles of the network are based on *transparency*, scientific *independence*, and highest *methodological standards* in post-authorization research with particular focus on noninterventional studies, a key component of the post-authorization risk management strategy. ENCePP thereby complements existing initiatives in pharmacoepidemiological research, such as good pharmacoepidemiology practice guidelines (ISPE, 2008) and the STROBE (von Elm *et al.*, 2008) statement all designed to ensure robust post-authorization research for the benefit of public health.

### **THE EUROPEAN NETWORK OF CENTRES FOR PHARMAEOPIDEMOLOGY AND PHARMACOVIGILANCE DATABASE OF RESEARCH RESOURCES**

The ENCePP network consists of research and medical-care centers, healthcare databases, electronic registries, and European networks dedicated to certain rare diseases, therapeutic areas, or adverse drug events of special interest. By September 2013 more than 180 research resources in 18 EU/European Free Trade Association (EFTA) countries had joined the network and have registered their details regarding expertise and experience in post-authorization study design, therapeutic areas, and available data sources in the ENCePP Database of Research Resources (see Figure 24.1). The database is a convenient tool for study sponsors and investigators to identify research centers and data sources for the conduct of or collaboration in pharmacoepidemiological research in Europe. Accessible free of charge via the ENCePP website ([www.encepp.eu](http://www.encepp.eu)), the database can be searched using various criteria of interest. The participating centers, networks, or

data source providers are responsible for maintaining their data record. Any organization based in one of the EU/EFTA countries that is not a pharmaceutical company and which undertakes research primarily focused on pharmacoepidemiology and pharmacovigilance can join ENCePP. This also includes for-profit organizations that perform studies commissioned by third parties. Registration is subject to providing evidence of expertise and research experience; for example, through publications in peer-reviewed journals.

The implementation of the network's priorities and objectives is overseen by the ENCePP Steering Group, the decision-making body consisting of elected ENCePP partners and representatives from the International Society for Pharmacoepidemiology ([www.pharmacoepi.org](http://www.pharmacoepi.org)), the International Society for Pharmacovigilance ([www.isoponline.org](http://www.isoponline.org)), the Heads of Medicines Agencies, the EMA and its Committee for Medicinal Products for Human Use and Pharmacovigilance Risk Assessment Committee, the Committee on Orphan Medicinal Products, and the EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations. The network is supported organizationally by the ENCePP Secretariat at the EMA.

To underpin the three pillars of the network – transparency, scientific independence, and state-of-the-art methodological standards – working groups with experts from participating centers have developed a set of operational rules and guidance documents for best practice in pharmacoepidemiology and pharmacovigilance.

### **THE EUROPEAN NETWORK OF CENTRES FOR PHARMAEOPIDEMOLOGY AND PHARMACOVIGILANCE CODE OF CONDUCT**

Post-authorization studies investigating the benefits and risks of medicinal products in clinical practice have sometimes faced criticism because of a lack of clarity in the relationship between sponsors and investigators, casting doubts on the scientific independence of the results. The ENCePP Code of Conduct provides a set of rules to maximize

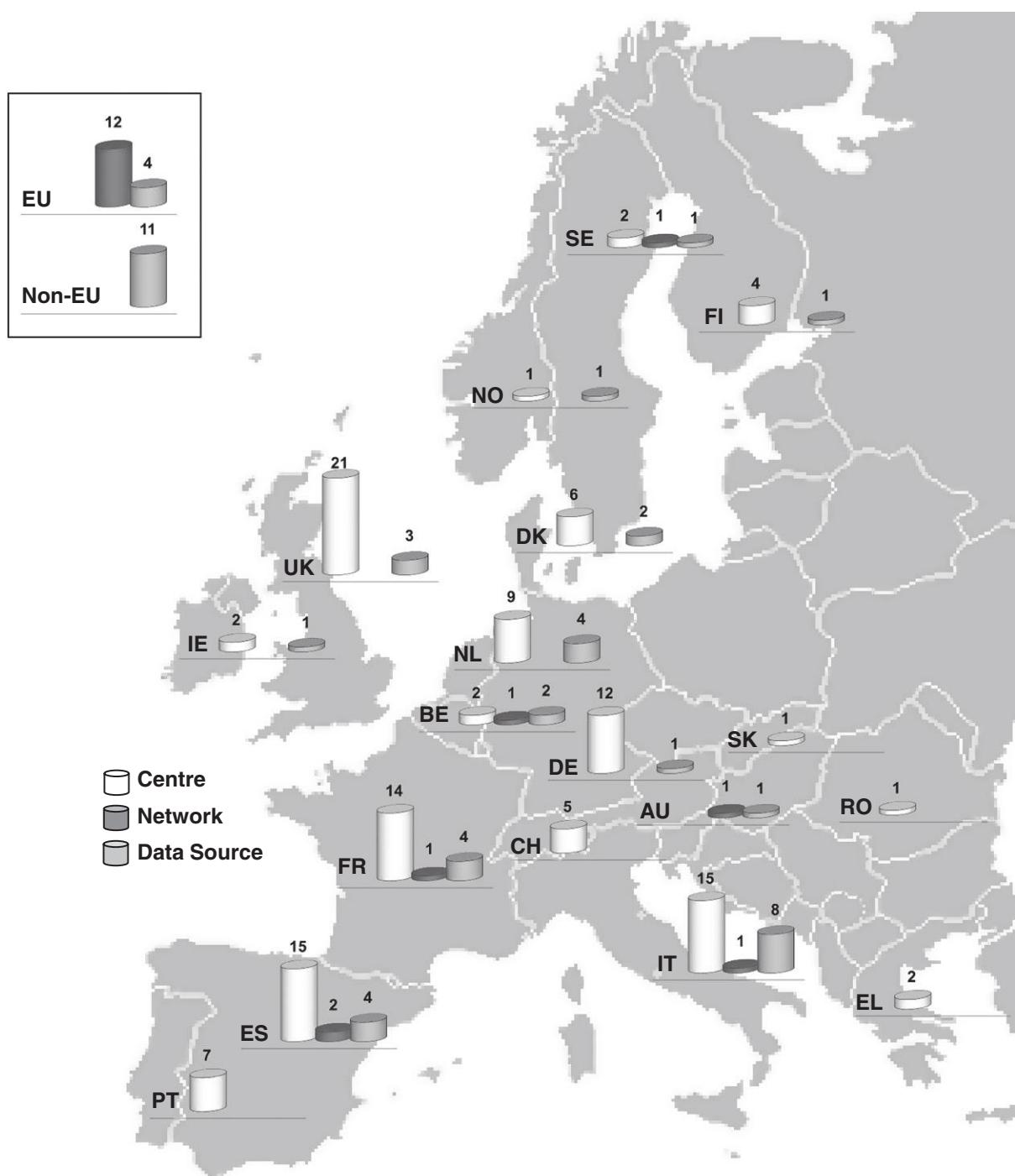


Figure 24.1 The ENCePP network includes 119 centers, 7 national and 12 international networks across 18 EU/EFTA countries. The ENCePP database also includes 48 data sources (September 2013).

scientific independence by making available study protocols prior to study start, registering the study in a public register, namely the ENCePP E-Register of Studies, allowing sharing of study data for the purpose of audit or corroboration, and the obligation to publish upon completion the study outcome without delay and irrespective of whether the results are positive or negative. The code's primary concern is to achieve a high level of public scrutiny to increase confidence in the integrity and value of pharmacoepidemiology and pharmacovigilance research. To this end the code seeks to make explicit the levels of involvement of study sponsors and investigators throughout the research process (planning, funding, conduct, and reporting), including the requirement for investigators to declare any interests of a personal, commercial, and financial nature before the study starts. Another important aspect of the code relates to the sharing of study data to strike the right balance between maximum levels of transparency, patient data protection, and protection of intellectual property. Initial concerns about the practical implications of sharing study data and complying with data protection legislation have been addressed by defining criteria for data sharing and a procedure for handling third parties' access requests.

#### **THE EUROPEAN NETWORK OF CENTRES FOR PHARMAEOPIDEMOLOGY AND PHARMACOVIGILANCE GUIDE ON METHODOLOGICAL STANDARDS AND THE CHECKLIST FOR STUDY PROTOCOLS**

In line with the objective to facilitate the conduct of multicenter, independent, and robust pharmacoepidemiological studies, a systematic review of pitfalls in study design and analysis was conducted which resulted in the publication of the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology* ([http://www.encepp.eu/standards\\_and\\_guidances/methodologicalGuide.shtml](http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml)) together with the *ENCePP Checklist for Study Protocols* ([http://www.encepp.eu/standards\\_and\\_guidances/checkListProtocols.shtml](http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml)). The guide is a tool for reviewing and providing direct electronic access to established methodological guidance in the area of pharmacoepidemiology and pharma-

covigilance. Its main purpose is to provide in one place signposts to the best existing scientific guidelines and to address identified gaps; for example, in the areas of statistical analysis planning and in quality control and assurance. Rather than just compiling existing guidelines, this single overview document provides a framework for learning and raising awareness of the latest methodological developments and study designs based on internationally agreed guidelines, articles, and textbooks. Researchers are encouraged to use the corresponding checklist to consider the most important methodological questions when developing a study protocol. The checklist equally promotes transparency about methodologies and designs applied in pharmacoepidemiological studies when it is made publicly available in line with the provisions of the code.

#### **THE EUROPEAN NETWORK OF CENTRES FOR PHARMAEOPIDEMOLOGY AND PHARMACOVIGILANCE E-REGISTER OF STUDIES**

The electronic ENCePP Register of Studies (E-Register also known as EU PAS Register) is a public database accessible from the ENCePP website. It increases transparency in observational post-authorization research by promoting the disclosure of information at an early stage, preferably before the study has actually started. Such *a priori* study registration allows comparison between initial and final protocols once the study has been completed. Providing access to study protocols, information on possible conflicts of interest, and reports of study results contributes to reducing publication bias and increases the credibility of pharmacoepidemiological study results overall. Further benefits of study registration include the possibility of closer collaboration within the scientific community and making optimal use of available pharmacoepidemiological and pharmacovigilance resources, thus preventing unnecessary duplication of research. The registration of studies in the E-Register is on a voluntary basis and is only mandatory if investigators apply for the ENCePP seal.



Figure 24.2 ENCePP study seal requirements.

## THE EUROPEAN NETWORK OF CENTRES FOR PHARMACOEPIDEMIOLOGY AND PHARMACOVIGILANCE SEAL

To provide visibility to studies adhering to the principles of the Code of Conduct and the methods checklist, the concept of the “ENCePP seal” has been developed. Any pharmacoepidemiological or pharmacovigilance study can apply for the seal provided the primary (lead) investigator belongs to a registered ENCePP resource and the application is submitted to the ENCePP Secretariat before the study starts. In addition, an ENCePP seal study must be registered in the ENCePP E-Register prior to its start and its status as an “ENCePP seal study” will be displayed by the corresponding seal (see Figure 24.2) if all the aforementioned requirements are met.

The ENCePP seal indicates to the general public that the study will be conducted in accordance with the provisions of the code taking due account of the methodological research standards described in the *ENCePP Checklist for Study Protocols*. Beyond that, the seal displays a commitment to a maximum level of transparency with regard to protocol agreement and the communication of results, including relevant milestones. The primary objective(s) of an ENCePP seal study should have potential impact on science or public health and should not be aimed at promoting the use or sale of medicines. Transparency with respect to the roles of investigator and sponsor in a clearly defined research contract is of paramount importance, as is the commitment to always publish the study results, preferably in a peer-reviewed journal, or to make them publicly available (e.g. E-Register) within reasonable time frames. Ultimately, the ENCePP seal is expected to increase

confidence in the study results and the research processes themselves, thus raising the standards in pharmacoepidemiology. However, the seal award does not guarantee the scientific quality of the study, as its award is independent from an assessment of the study protocol and results. Once the seal is awarded, the investigator has the duty to inform the ENCePP Secretariat without delay of any deviations from the protocol or any breaches of the code that could lead to the removal of the ENCePP seal from the E-Register of Studies.

## SUMMARY AND OUTLOOK

Since its launch, ENCePP has developed into a network of European experts and resources in pharmacoepidemiology and pharmacovigilance with the ENCePP Research Resource Database and the E-Register of Studies at its core. ENCePP provides a unique opportunity to further strengthen post-authorization monitoring of medicinal products in Europe by facilitating the conduct of multicenter, independent, post-authorization studies focusing on safety and on benefit–risk balance. ENCePP is expected to raise trust in pharmacoepidemiological research through studies conducted in adherence to its guiding principles – transparency, scientific independence, and robust methodological standards – enshrined in the Code of Conduct and the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*. With a strengthened legal basis for EU regulators to request and oversee post-authorization safety studies for medicines, ENCePP will help to provide the capacity, expertise, and standards to tackle the predicted increased number of post-authorization studies. With increasing globalization of the pharmaceutical industry and the universal nature of the science involved, serving as a global resource will be a key challenge for ENCePP.

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# Overview of North American Databases

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## INTRODUCTION

Large electronic databases can often meet the need for cost-effective and efficient means of conducting surveillance after a new drug is marketed, and for establishing baseline data prior to marketing (Strom, 2012). Such databases can be used to assess signals from trials and from spontaneous reports, and, given adequate power and design, the results of such assessments generally are more credible than evidence from spontaneous reports of the same problem (Edwards *et al.*, 2005). Large databases are often needed to address acute and serious regulatory, commercial, and public health crises. Postmarketing studies of drug effects must generally include at least 10 000 exposed persons, preferably within a definable population base.

In North America, databases able to meet this need are primarily administrative in origin, generated by the request for payments, or claims, for clinical services and therapies. Large databases of

electronic medical records, like the General Practice Research Database and The Health Improvement Network in the UK (Ogdie *et al.*, 2012), do not exist yet in North America. The resulting databases of health insurance claims are inherently different from medical record databases (Strom, 2012).

Health insurance in the USA is typically obtained through one's place of employment, and does not always include coverage for prescription drugs. The US healthcare programs described in this chapter are primarily employer based. Instability in these systems is then caused by employees changing jobs and employers changing health plans and coverage for specific employees and their families. The opportunity for longitudinal analyses is thereby hindered by the continual enrollment and disenrollment of plan members.

Beyond the employer-based health insurance programs are the US Medicaid program, which funds medical care, including prescription drug coverage, for economically disadvantaged and

disabled persons, and the Medicare program, which funds healthcare primarily for persons aged 65 and older, including access to prescription drugs. The latter benefit became available under the Medicare Prescription Drug, Improvement, and Modernization Act that was enacted in 2003, resulting in Medicare Part D starting in 2006 ([http://www.ssa.gov/legislation/legis\\_bulletin\\_121103.html](http://www.ssa.gov/legislation/legis_bulletin_121103.html)).

In contrast to the variety of healthcare systems for selected eligible subsets of populations in the USA, provinces in Canada provide a publicly funded health system for all of their residents.

To meet the needs of drug surveillance and pharmacoepidemiologic studies, claims data from multiple sources (drug purchases, visits to physicians, hospital stays, etc.) must be linked on a patient-specific basis. Depending on the nature of the study, records from the following sources may need to be included: inpatient and outpatient care, emergency care, mental health care, laboratory and radiological tests, alternative therapies, and prescribed and over-the-counter medications. The size of the population covered by the database must be large enough to permit discovery of rare events for the drug(s) (in surveillance studies). Questions such as the stability of the population and the completeness of therapies and clinical services obtained solely through the health plan may be considerations in study design. Although it is generally preferable for the population included in the database to be representative of the general population from which it is drawn, it may sometimes be advantageous to emphasize the more disadvantaged groups that may have been absent from premarketing testing and may be absent from employer-based health databases. The drug(s) under investigation must, of course, be present in the formulary and be prescribed in sufficient quantity to provide adequate power for analyses. Additional considerations are that the records are verifiable and are reliable. The ability to conduct chart review to confirm outcomes is a necessity for most studies, as diagnoses entered into an electronic database of paid claims may be of uncertain validity (West *et al.*, 2012). Information on potential confounders, such as smoking and alcohol consumption, and such information as time of menarche and meno-pause, may only be available through chart review

or, more consistently, through patient interviews. With appropriate permissions and confidentiality safeguards in place, access to patients is sometimes possible. Information on drugs taken intermittently for symptom relief, over-the-counter drugs, herbal products, and drugs not on the formulary must also be obtained directly from the patient.

The advantages of a claims database remain; that is, data do not have to be collected *de novo*, investigations can be completed more efficiently and more economically, and data on exposures are not subject to recall or interviewer bias. Although data on drugs dispensed are of extremely high quality (West *et al.*, 2012), the quality of disease data may be less so. With the caveat of the need to confirm outcomes, the availability of such databases is an important asset for postmarketing surveillance.

In the following sections we will discuss the databases associated with four major US health programs (Saunders *et al.*, 2005; Andrade *et al.*, 2012; Hennessy *et al.*, 2012; Seeger and Daniel, 2012) and one Canadian provincial health plan (Moride and Metge, 2012). Each of these is presented just as an example, since the proliferating number of available databases makes an exhaustive presentation impractical. Many of them are being aggregated into the FDA Sentinel System (Platt and Carnahan, 2012; Racoosin *et al.*, 2012). Readers are referred to Strom *et al.* (2012) for more details on these and other databases, as used for pharmacoepidemiology hypothesis testing studies.

### **EXAMPLE OF HEALTH PLAN DATA: GROUP HEALTH COOPERATIVE OF PUGET SOUND**

Group Health Cooperative of Puget Sound (GHC) is presented as an example of data from health plans, and one which has been used frequently for pharmacoepidemiologic research – see Saunders *et al.* (2005) for more complete information. GHC is a health maintenance organization (HMO), established in 1947, which provides healthcare on a prepaid basis to over 674 000 persons in Washington State and Idaho, in the northwest USA ([http://www.ghc.org/about\\_gh/co-op\\_overview/index.jhtml](http://www.ghc.org/about_gh/co-op_overview/index.jhtml)). Nearly two-thirds of members receive care

at Group Health medical centers. About 30% of all enrollees belong to a subsidiary of GHC, established in 1990, which provides a “point of service” option that permits care from community providers other than Group Health providers. As the point of service coverage is more expensive than that provided by Group Health providers, most of the coverage remains within the Group Health network. Although the majority of enrollees receive health benefits through their place of employment, coverage has been extended to 54 000 Medicare recipients, 18 000 Medicaid recipients, and about 9000 Washington Basic Health Plan recipients, thereby expanding its membership to include elderly and low-income residents (Saunders, personal communication, September 2011).

GHC offers comprehensive healthcare coverage for outpatient care, inpatient services, emergency care, mental health services, and prescribed drugs. Nearly all benefit plans require small co-payments for services, such as prescriptions, outpatient visits unrelated to preventive care, and emergency treatment. Coverage for outpatient drugs is controlled by GHC's drug formulary.

At GHC, each enrollee is assigned a unique number, which remains with that person even if the individual drops out of the plan and then rejoins the health system at a later date. Multiple databases have been developed from the main database, with an individual's records linked through their unique number.

Group Health has a slightly higher proportion of women (53%) than the regional community (50%) and the nation (51%). Group Health members are also older (46%  $\geq$ 45 years) than the regional community (38%) and the nation (39%). Compared with the rest of the country, Group Health members are more likely to be Asian or Pacific Islanders (9% versus 4%), but less likely to be African American (4% versus 12%) or report Hispanic ethnicity (4% versus 15%). The Group Health racial and ethnic composition broadly represents the Puget Sound region (Saunders, personal communication, September 2011).

Multiple database files exist, and date from varying time-points. The current enrollment file consists of some 674 378 individuals; historical files contain records for some 2.5 million persons

enrolled in GHC at any time since 1980 (Saunders, personal communication, September 2011). The pharmacy file, dating from 1977, contains records generated when prescriptions are filled. Drug data include drug number, therapeutic class, drug form and strength, date dispensed, quantity dispensed, cost to GHC, and refill indicator. The file includes a field for number of days the medication should last. The hospital database, dating back to the early 1970s, includes diagnoses, procedures, diagnostic-related group, and discharge disposition. Laboratory data are available since 1986, and specify, in both inpatient and outpatient settings, the test ordered, the date ordered, specimen source, results, and date of the results. All radiographic studies performed at GHC facilities, including magnetic resonance imaging and computed tomography scans, are now available in the outpatient visits file. Beginning in the early 1990s, diagnosis and procedure data were incorporated into the outpatient registration database, which also includes date of visit, the provider seen, the provider's specialty, and the location of care.

As a longtime participant in the National Cancer Institute's Cancer Surveillance, Epidemiology and End Results (SEER) program, GHC receives a data file of all newly diagnosed cancers among its enrollees, including anatomical site, stage of diagnosis, and vital status at follow-up. This file covers a reporting area of 13 contiguous counties of northwest Washington State, and is maintained by the Fred Hutchinson Cancer Research Center in Seattle, one of the 17 SEER population-based registries in the USA (see <http://seer.cancer.gov/registries/list.html>).

GHC has developed a death file that covers enrollees from 1977. Data are also available from the Community Health Services department, from an immunization database, and from claims databases for services purchased from non-GHC providers. Cost information is available through the Utilization Management/Cost Management Information System, developed in 1989.

Turnover in membership at GHC varies widely (from 5% to 35%) depending on age, health status, and type of insurance (Saunders personal communication, September 2011). Since Group Health has been in existence for over 65 years, a subset of

enrollees can be identified whose tenure spans decades.

The GHC databases have been widely used for pharmacoepidemiologic research (Saunders *et al.*, 2005). Limitations to the GHC databases include its relatively small size, a disadvantage in the study of uncommon outcomes as most drugs are used by only a small percentage of the population; the lack of information on some important confounders, such as smoking and alcohol consumption; and limitations of the GHC formulary, especially with regard to newly marketed drugs, since GHC may decide not to add a new drug or may delay its adoption until it has been on the market for a while. Drugs that offer little therapeutic or cost advantage over drugs already listed on the formulary may be excluded. Non-formulary drugs as well as over-the-counter drugs would be purchased for use outside the GHC pharmacy system, and therefore would not be represented in the database.

### **EXAMPLE OF HEALTH PLAN DATA: KAISER PERMANENTE MEDICAL CARE PROGRAM**

The Kaiser Permanente Medical Care Program is presented as another example of data from health plans that have been used frequently for pharmacoepidemiologic research – see Selby *et al.* (2005) and Andrade *et al.* (2012) for a more complete description. Kaiser is the largest and one of the oldest prepaid group model healthcare systems in the USA. With 8.9 million members in eight states and the District of Columbia, the program is divided into eight administrative regions, each of which has its own research center (Alan S. Go, personal communication, August 2011). The two oldest research centers, in operation since the 1960s, are the Division of Research of Kaiser Permanente Northern California and the Center for Health Research of Kaiser Permanente Northwest (KPNW), and each is presented as an example. Both centers have made major contributions to pharmacoepidemiology, including developing strategies for dealing with methodologic issues endemic to the use of clinical data for research, and developing approaches to overcoming biases present in

clinical databases, at least as applied to Kaiser Permanente databases.

### **KAISER PERMANENTE NORTHERN CALIFORNIA**

Kaiser Permanente's largest and oldest regional entity is in northern California, which now serves approximately 3.3 million enrollees in a 20-county area that includes the Oakland–San Francisco Bay and Sacramento metropolitan areas. Of the population covered by this region of Kaiser Permanente, 81.4% are enrolled mainly through employment, and 5.3% receive Medicare coverage (Alan S Go, personal communication, August 2011). Race/ethnicity information is not collected routinely, but special member surveys and other sources show a close similarity to the distribution of the general population, based on census data (Selby *et al.*, 2005). Comparisons of household income of the membership with census data show a slight underrepresentation at the highest and lowest income levels (Krieger, 1992; Selby *et al.*, 2005). After the first year or two of membership, during which there is a relatively high turnover, enrollees tend to stay with the program for relatively long periods of time (average length of enrollment retention is 9.9 years). A unique medical record number is used for all encounters with the Kaiser Permanente program, making possible the linking of various records. Computerized membership files contain records of all members at a given point in time.

The Pharmacy Information Management System has been operational in Kaiser pharmacies since 1994, recording information on approximately 25 million prescriptions per year (as of 2009). Information on each prescription is entered into the database prior to it being dispensed, and includes patient and prescribing physician identification numbers, drug name, national drug code (NDC), dose, therapeutic class, date dispensed, and prescription cost. As this is an integrated care delivery model, 100% of members receive drug benefits (Alan S. Go, personal communication, August 2011).

Other databases include hospitalizations, available since 1971; laboratory, pathology, and radiology/diagnostic imaging data, stored since 1992; and information on outpatient visits, stored since 1994.

Review of medical records has not been obviated, however, and is recommended for validation of certain computerized data.

A recent example of a study that utilized this database investigated the risk of bladder cancer among diabetic patients treated with pioglitazone (Ferrara *et al.*, 2011; Lewis *et al.*, 2011).

### KAISER PERMANENTE NORTHWEST

KPNW serves over 480 000 members, approximately 18% of the population of the membership area (Alan S. Go, personal communication, August 2011), which includes northwest Oregon and southwest Washington. The distribution of the membership by age, race, and gender proportionately reflects that of the area population. Services provided by KPNW include hospital and surgical care, maternity care, X-rays, mammography, laboratory testing, allergy testing, home healthcare, doctor office visits, well-baby care, mental health, and, unique to KPNW, dental care. All the members are covered by a prepaid drug benefit.

Databases available at KPNW include the Outpatient Pharmacy System, which began in 1986 and records all prescriptions dispensed by its outpatient pharmacies. Data include drug name, NDC, quantity dispensed, days supplied, refill number, date, and other product information. The automated Inpatient Medication System captures all inpatient medication orders, storing the history of each hospitalization in a unique hospital stay number that is generated on admission.

The KPNW also maintains an Adverse and Allergic Drug Event Reporting database, from which it prepares reports for the local KPNW Formulary and Therapeutics Committee, and submits data to the MedWatch system of the US Food and Drug Administration (FDA).

Other data systems include The Inpatient Admission/Discharge/Transfer System, which provides data on hospitalizations in Kaiser and non-Kaiser hospitals, and includes information on ambulatory surgical and other major procedures performed in the hospitals since the mid 1960s. EpicCare® is an automated medical record system useful for clinicians providing direct patient care. It has been used for all outpatient care since 1997, and

contains records for 480 000 KPNW members (Selby *et al.*, 2005; Alan S. Go, personal communication, August 2011). Spinoffs of subsets of these files can make these data accessible for research purposes.

EpicCare has served as the prototype for Health-Connect®, which was implemented across the Kaiser Permanente Program, creating an electronic health record for 8.6 million members from 36 hospitals and 454 medical offices (<http://xnet.kp.org/newscenter/aboutkp/healthconnect/index.html>). This new software collects information not collected previously under a claims-based system, such as orders for prescriptions (whether or not they were filled) and laboratory tests (whether or not they were completed), and telephone consults, information that is useful for studies of adherence to therapy and quality of care and of safety in large populations (Selby *et al.*, 2005). Additional databases cover the areas of dental care, emergency psychiatric calls and contacts, emergency department visits, laboratory, cytology and histology procedures and results, patient-specific radiology department data, including radiology, ultrasound, magnetic resonance imaging, nuclear medicine, and computerized tomography, prenatal screening, immunization, and a continuing-care service database of home care services for homebound members. A Medicare Plus II Database contains data from questionnaires, distributed annually to participants, which measure levels of functioning and depression using standardized instruments.

Multiple disease registries are maintained by KPNW as well, including cancer, benign breast disease, breast cancer family registry, diabetes, and rheumatology registries.

The KPNW Center for Health Research also maintains multiple databases that provide data on outpatient utilization, information on health status and behaviors of members, satisfaction with care provided, and other information obtained from surveys based on a sampling of the KPNW membership. The Common Control Pool database contains basic demographic and eligibility data for virtually all people who have been members of KPNW. A pregnancy registry identifies pregnant KPNW members, using laboratory data, ultrasound reports, and clinic visits, enabling the tracking of all

pregnancy outcomes. The KPNW immunization database contributes data to the Vaccine Safety DataLink Project, funded by the US Centers for Disease Control and Prevention.

The KPNW membership mostly reflects the population of the area it serves, although again the poor and the very wealthy are underrepresented. The membership is relatively stable after 1 year; the average length of enrollment retention is 8.2 years. The use of a unique medical record number allows the linkage of drug dispensing with inpatient and outpatient files, and it is possible to calculate prevalence and incidence rates. Access to primary medical records permits validation of diagnostic information and gathering of information on confounding and demographic variables, which, with the exception of age and gender, are absent from the available databases.

The Kaiser Permanente formularies are limited, with the newest and/or most expensive drugs unlikely to be listed. It is also likely that only one brand of a particular drug is available.

## **EXAMPLE OF COMMERCIAL DATA: UNITEDHEALTH GROUP**

UnitedHealth Group is presented as an example of a commercial database – see Shatin *et al.* (2005) and Seeger and Daniel (2012) for a more complete description. UnitedHealth provides a continuum of healthcare and specialty services to about 70 million members throughout the USA through HMOs, point-of-service arrangements, preferred provider organizations, managed indemnity programs, Medicare and Medicaid managed care programs, and senior and retiree insurance programs. Specialized services include mental health, substance abuse, utilization management, specialized provider networks, third-party administration services, employee assistance services, managed pharmacy services, and information systems. Although the plan structures vary and range from staff or group models to independent practice associations, affiliated health plans are typically the latter, with open access to a wide network of providers. Participating providers include more than 3300 hospitals and more than 400 000 physicians.

These health plans were begun in 1994, representing predominantly employer-based clients, and also Medicaid and Medicare recipients (Shatin *et al.*, 2005). The electronic administrative claims data of all UnitedHealth-affiliated healthcare plans are linked. Ingenix, now called OPTUMInsight™, a UnitedHealth Group subsidiary, maintains the research database, with over 60 million people enrolled during 1994–2010, including large numbers of special populations (children, pregnant women, and persons aged 65 years and older). The annual patient turnover within the database is 30–35%, with average enrollment duration of 2 years or less (Seeger and Daniel, 2012). Unique member identifiers allow for tracking across enrollment periods, so that a member can be followed through disenrollment and re-enrollment.

Most of the commercial and Medicaid members have a drug benefit. Medicare drug benefits vary depending on the plan, so the pharmacy files may not capture all prescriptions in this age range. The elderly are underrepresented in other databases as well, since most UnitedHealth members are enrolled in employment-based plans.

The research databases are compiled from linkable files of membership data, medical and pharmacy claims, and health professional data. Data elements in the membership file include, besides the unique member identifier, date of birth, gender, place and type of employment, benefit package, and links to dates of enrollment and disenrollment. Medical claims include outpatient as well as inpatient, emergency room, surgery, specialty, preventive, and office-based treatment, including laboratory services and diagnostic imaging. Claim forms must be submitted by a healthcare provider in order to receive payment for a covered service. Pharmacy claims typically are submitted electronically by the pharmacy at the time a prescription is filled. The data submitted specify the patient's and pharmacy's identifiers, drug name, date dispensed, dosage of medication dispensed, duration of the prescription in days, and quantity dispensed. Provider data include physician specialty, enabling researchers to locate medical records for the collection of detailed information not provided in the claims data. The resulting files have been incorporated into software developed by UnitedHealth to

facilitate the investigation of questions such as those regarding drug exposures and adverse drug events. Research capabilities include performing record and file linkages, constructing longitudinal histories, identifying denominators to calculate rates, identifying specific treatments at a particular point in time, and calculating person-time at risk and time of event occurrence.

Given the large size of the databases available to UnitedHealth, it is possible to detect rare exposures and rare outcomes. Feasibility studies have been conducted using these data to evaluate drug usage and to study adverse events that are first identified through the spontaneous reporting system of the FDA.

UnitedHealth has no data on drugs that cost less than the copayment amount, and inconsistent data on those eligible for Medicare. Not all drugs are on the preferred drug list. Medical record retrieval is still necessary for obtaining information such as race/ethnicity, confirming a diagnosis, obtaining information on risk factors and outcomes, or determining whether a member is deceased. Another limitation is the time lag in receiving information from claims data, which can be 1 month for pharmacy claims but up to 6 months for physician and facility claims.

## **EXAMPLE OF US GOVERNMENT PROGRAM: MEDICAID DATABASES**

The US Medicaid Program is a health insurance system created in 1965 to provide access to medical care for economically disadvantaged and disabled persons (Hennessy *et al.*, 2012). It is supported jointly by federal and state funds, and managed by states with federal oversight. Benefits are available for members of three groups: (1) low-income pregnant women and families with children; (2) persons with chronic disabilities; and (3) low-income elderly, including those receiving benefits from the federal Medicare (65 years and older) program. In addition to these categories for eligibility, individual states may set up their own programs for specific groups of persons who do not qualify for federally supported programs. Services provided by the states under the federal Medicaid program include inpatient

hospital services, outpatient hospital services, and physician services. All states provide outpatient prescription drugs for at least some categories of enrollees, even though this coverage is not federally mandated. Rather than serving as a direct provider of healthcare services, Medicaid functions as a payer for eligible services provided by participating physicians, hospitals, and pharmacies. Of the US population, 22% (70.4 million persons) received healthcare services through Medicaid in 2011, serving as the largest health insurance program in the USA (<http://cnsnews.com/news/article/record-704-million-enrolled-medicaid-2011-1-out-every-5-americans>; <http://www.infoplease.com/ipa/A0004986.html>). Compared with the overall US population, the Medicaid population has a disproportionate number of children, females, and non-whites. Income and disability status are also not representative of the total population. Of course, these are the populations that are often underrepresented in premarketing randomized trials. The Medicaid program is administered by the Centers for Medicare and Medicaid Services (CMS), which has established a mechanism for researchers to obtain data that have been received from the individual states and have undergone editing and range checks. A lag-time of 4 years currently exists for the availability of the cleaned Medicaid Analytic Extract (MAX) files; crude data from the Medicaid Statistical Information System are also available. Support for the process of obtaining files and technical assistance in the use of the data are supplied through a contract with the University of Minnesota's Research Data Assistance Center (ResDAC), instituted in its School of Public Health. ResDAC's description of the CMS data and of its services is publicly available through its website: <http://www.resdac.umn.edu/>. Data can also be obtained through commercial data vendors or by contacting individual state Medicaid programs directly (Hennessy *et al.*, 2012).

Five types of MAX files are available for CMS Medicaid data, separately by year and by state: personal summary, inpatient, prescription drug, long-term care, and other therapy. The personal summary file contains one record per person enrolled in the specific state's Medicaid program for any part of the specific year. It includes demographic data, namely date of birth, sex, race, and

zip code of residence, and identifies the months in which the person was enrolled in the plan. The inpatient file contains information on hospitalizations, including admission and discharge dates, discharge status, up to nine diagnoses, up to six procedures, and payment information. Drugs used during hospitalization are not available in this file. The prescription drug file contains records for drugs reimbursed for outpatient or nursing home prescriptions. NDCs provide information on the manufacturer and the name, strength, and dosage form of the drug. Data elements include date and quantity dispensed, whether the drug was new or a refill, and cost information. The long-term care file contains information on care provided by skilled nursing, intermediate care, and independent psychiatric facilities. Data elements include type of facility, dates of service, diagnosis, and discharge status. The other therapy file contains records for physician, laboratory, radiology, and clinic services. Date, type of service, diagnosis, and procedure codes (where applicable) are recorded. Although the types of laboratory and radiology testing are recorded, their results are not reported. Medicaid data have been linked to other databases, such as Medicare data (for persons eligible for both programs), the National Death Index, and state vital statistics registries.

The quality of the Medicaid database has been evaluated for six states. Results suggest the need for macro-level descriptive analyses of the parent dataset, with a particular focus on the number of medical and pharmacy claims over time, checking for gaps, assessing the validity of markers for hospitalization, and evaluating the accuracy of diagnostic and demographic data (Hennessy *et al.*, 2003).

The strengths of the Medicaid databases are their large size, permitting the study of infrequently used drugs and rare outcomes, and the accuracy of the drug data. Sixteen states have over a million Medicaid recipients each (e.g., California 7.0 million, New York 4.4 million, Texas 3.3 million, Florida 2.4 million, Illinois 2.3 million, Ohio and Pennsylvania over 1.9 million each); prescriptions for the top three medications dispensed numbered 7 million, 6.4 million, and 4.4 million (for hydrocodone, amoxicillin, and ibuprofen, respectively) for the total Medicaid program in 2010. Far down the

list, ranked at number 50, were prescriptions for hydrocortisone, accounting for 1 million prescriptions (<http://www.cms.gov/MedicaidDrugRebateProgram/SDUD/list.asp>).

As a claims database (similar to most of the other databases described), information is lacking on variables often needed to control for confounding, such as smoking, body mass index, environmental exposures, illicit drug use, alcohol use, occupation, family history, and use of over-the-counter and herbal drugs.

The International Classification of Disease Ninth Revision – Clinical Modification (ICD-9-CM) is the coding scheme for diagnoses, with the implementation of the Tenth Revision (ICD-10-CM) scheduled for October 1, 2014. Together with factors such as the level of accuracy of the clinical diagnosis and need for information on potential confounding variables, experience suggests that investigators should obtain medical records in at least a sample of outcomes to confirm the diagnosis and characterize the severity of the disease, in addition to obtaining information on potential confounding variables. A Health Insurance Portability and Accountability Act-compliant mechanism was developed to request hospital records of specific patients without patient contact, yielding 70–75% of inpatient hospital and emergency department records for some studies (Hennessy *et al.*, 2012). Studies where primary record confirmation is less important are those that focus on drug-to-drug relationships, or studies that can use drugs or procedures as markers of diagnoses.

## **EXAMPLE OF CANADIAN GOVERNMENT PROGRAM: HEALTH DATABASES IN SASKATCHEWAN**

Data from Saskatchewan are presented as an example of Canadian provincial data, and the database of this type that has been used for pharmacoepidemiology the longest – see Downey *et al.* (2005) and Moride and Metge, (2012) for more information. Saskatchewan is a province in western Canada with a stable population of about 1 million

people, or about 3.1% of the total population of Canada. The province provides a publicly funded health system for its residents, who are each assigned a Health Services Number upon registration that uniquely identifies that person, and which is captured in records of health service utilization, enabling the linkage of computer databases. Only a very small percentage (less than 1%) of the population of Saskatchewan is excluded from the health registry. Prescription plan coverage excludes about 10% of the population, primarily Indians, who are covered by another government agency. Hospital services and most physician services are available to all persons in the health registry. The population registry captures demographic and coverage data on every member of the eligible population, including gender, marital status, date of birth, and date of death.

Drugs covered by the drug plan are listed in the Saskatchewan formulary; non-formulary drugs are generally not covered. The drugs listed are intended for outpatient use, although the database includes prescriptions to residents of long-term care facilities. The formulary is updated semi-annually; as of July 2011, 4200 drug products were listed ([http://formulary.drugplan.health.gov.sk.ca/PublNs/Formularyv62\\_17fw.txt](http://formulary.drugplan.health.gov.sk.ca/PublNs/Formularyv62_17fw.txt)). The drug database contains information from September 1975, with an 18-month hiatus in 1987–1988 when data were incomplete. The database includes patient, prescriber, pharmacy, and cost information. Drug information includes pharmacologic–therapeutic classification, using the American Hospital Formulary Service classification system, active ingredient, generic and brand names, strength and dosage form, drug manufacturer, and date and quantity dispensed. Unavailable is information on non-formulary drug use, over-the-counter drugs, use of professional samples, and in-hospital drugs. The database also does not provide information about the dosage regimen prescribed, the reason the drug was prescribed, or patient compliance. Over 10.9 million prescription claims were processed by the drug plan in fiscal year 2009–2010 (<http://www.health.gov.sk.ca/adx/aspx/adxGetMedia.aspx?DocID=e7f43b12-82dc-47b0-9081-690029244fa6&MediaID=5129&Filename=drug-plan-annual-report-2009-10.pdf&l=English>).

Data from hospitalizations, including day surgeries, include discharge diagnoses (ICD-9 codes until 2006 and ICD-10 codes since then), procedures, an accident code, admission and discharge dates, and attending physician and surgeon (where applicable). Procedures are coded using the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures. There is a lag time of about 6 months from date of discharge to the date when hospital data are available electronically (Moride and Metge, 2012).

Physician services data are obtained from claims, and include diagnoses and procedures (coded from a fee-for-service payment schedule established by the Health Registry and the provincial medical association). These data are limited, however, in that diagnostic data are not mandatory for payment, and only one code is recorded per visit.

Linkage can be made to the Saskatchewan cancer registry, which is required to record all persons diagnosed with cancer, including non-melanoma skin cancers and *in situ* cancers, and suspected as well as confirmed cancers. A lag time of 6 months exists from date of diagnosis to availability of the data.

Vital statistics data are also maintained by Saskatchewan Health; all birth, death, stillbirth, and marriage data are collected. Although cause of death is initially coded as received on a death registration form, it is updated if an autopsy diagnosis is received. The underlying cause of death is recorded electronically as well, and is defined as the disease or injury that initiated the sequence of events that led to death. Other information available includes institutional long-term care and home care services, mental health services that cover both inpatient psychiatric care and community-based outpatient care, alcohol and drug abuse treatment data, and microbiologic and biochemical laboratory records.

Hospital medical records are retrievable after the appropriate approvals are obtained, with patient identifiers removed from the record. Hospital record retrieval rates often exceed 95%. Outpatient record retrieval has not approached that level of success. Information on potentially important confounders is only available in patient records or through direct patient contact.

## THE FUTURE

As US Medicare has begun paying for drugs for the elderly for the first time, it has the potential for becoming the largest database yet created; it is beginning to become available to researchers. However, it may create huge gaps in the other US databases. This will need to be watched closely as the program evolves.

The growing adoption of electronic medical record systems in the USA portends exciting opportunities for future pharmacoepidemiologic and clinical research. The ability to link claims from prescription fills to the physician's issuing of the prescription will expand studies of adherence to drug therapy. Access to health indicators such as vital signs, height and weight, alcohol consumption, and smoking will enhance our capability of controlling for such confounders. Although records maintained for clinical rather than research purposes have inherent biases, lessons can be learned from the experience in the UK (Ogdie *et al.*, 2012). Systems must be established to monitor the quality of data entry by healthcare personnel, and other potential sources of errors in the use of electronic systems (Koppel *et al.*, 2005). As with claims data, validation analyses and consistency checks must be implemented. Despite the inevitable challenges posed by an electronic medical record system, the result could be a rich complement to claims data for future pharmacoepidemiologic research. The largest issue is that, in the USA, in contrast to the UK or Canada, these are not likely to be population-based systems, given the decentralized healthcare system in the USA and its much larger size. The lack of a national identification number and the lack of a standardized method for recording medical record data also limit the potential for a national database.

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# The Clinical Practice Research Datalink: The New 54 Million Fully Integrated Research Data and Clinical Trial System

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## INTRODUCTION

In the second edition of this book (Parkinson *et al.*, 2007), we said:

It is difficult to predict how this future system will work related to NHS data, but these changes offer unique opportunities for the GPRD to maximise the use of the UK population based cradle to grave data for pharmacovigilance and other pharmacoepidemiological studies. The [Medicines and Healthcare Products Regulatory Agency] MHRA is an Executive Agency of the Department of Health and as such is working closely with those involved in implementing these obviously beneficial IT changes.

We are proud of the fact we have actually achieved massive changes, as you will see.

The General Practice Research Database (GPRD) has for good reasons, related to safeguarding and improving health, become a far larger

enterprise working in partnership with the National Health Service (NHS) National Institute for Health Research (NIHR). The new Clinical Practice Research Datalink (CPRD) operation remains housed with the UK Medicine and Devices regulator, the MHRA, and will play a larger role in all aspects of pharmacovigilance, including risk management and the tracking of all coded drugs and devices available in the UK.

GPRD was the world's largest record-linked computerized database of well-validated longitudinal patient records collected via the universal primary care system operated within the UK NHS. Additional primary care population cover and links to many, full-population, 52 million based data sources mean that the new CPRD system will continue to act as one of the key drug and device safety databases used by regulators, academics, and commercial companies. There is also a belief that this access to significant population-cover primary and secondary care data, in close to real time, offers the

potential to change the way pharmacovigilance is undertaken; time will tell.

What has made such a system possible is having the universal healthcare provider, the NHS, in which almost all inhabitants are registered with a single general practice and have a unique patient identifier. This together with privacy enhancing technologies (PETs) within an extensive data stewardship program is used to link data from various NHS and non-NHS sources. Hospitals have always been required to inform general practitioners (GPs) of any significant medical events that occur in their patients, but now with CPRD linked to the actual NHS hospital-episode statistics (HES) record, this provides a high level of coded detail on every hospitalization, is richer, and has the potential for greater validation. Long-term care of chronic conditions is typically managed by GPs; as a consequence, patients' medical records contain longitudinal information on all significant medical events and prescribing. Now, in the new system, with links to a whole range of registries, far more detailed information is available on key aspects related to early and highly interventional stages of many diseases. As well as the HES data, information on drugs used in hospital will also be available.

CPRD takes the already excellent GP coded record, uses a natural programming language to enrich this with text, and then enriches the data further with other information from other sources. The CPRD system essentially contains the life-long record for each patient, including secondary care information as well as laboratory, other investigations, and details of all medications prescribed within general practice and now in many cases drugs used in hospital. It should be noted that it is not a single database; rather, it is a federation of data sources linked, as required, for research.

The CPRD contains unique information for research based upon the very large 54 million population of England (85% of the population of the UK). The original GPRD contained the anonymized patient medical records from GPs who use the Vision IT system from InPractice System Ltd; the new CPRD system will contain data from all five main (99%) electronic health record IT systems. The new system also runs detailed quality control

checks to ensure that data is up to standard. Only practices that meet continuous quality standards are included into the CPRD.

## HISTORICAL OVERVIEW

The original history of the GPRD, since its creation in 1987, has been well documented elsewhere (Lawson *et al.*, 1998; Wood and Coulson, 2001). Since 2000, the database has been managed by the MHRA under its remit to safeguard public health. It is used within the MHRA to provide evidence for the evaluation of risks and benefits of marketed medicines. As such, the GPRD forms a critical part of the UK MHRA drug safety system. Signals obtained through the spontaneous reporting scheme for suspected adverse drug reactions (known as the Yellow Card Scheme in the UK) may be tested in the GPRD. Such hypothesis testing in GPRD is not only conducted by the MHRA, but also by pharmaceutical companies, academics, and other regulators.

In 2005 the MHRA made major input to a report looking at how NHS data could be used more extensively in research and surveillance to safeguard and improve health in the UK, as well as in other countries, by the application of the research outputs. This report was adopted by government and led to the setting up of the Research Capability Programme that in late 2011 led to the partnership between the NHS NIHR and the GPRD group at the MHRA; that is, CPRD.

Given the importance of real-world data to public health, the MHRA, together with its partner the NHS NIHR, is making an extensive investment in staff and information technology to ensure the full potential of NHS record linked data is not only enabled but also made usable to the full range of pharmacovigilance and devico-vigilance researchers. For instance, data volumes are becoming so large that we are taking measures to reduce the byte volume, without altering the significance of the data to researchers.

CPRD provides worldwide users with online access to a data warehouse. This was developed as not every researcher has access to the large data storage capabilities required to house the full

dataset or the experience of using powerful data manipulation and analysis tools as available in SAS or STATA. Researchers can access, via the CPRD data warehouse, anonymized coded data alongside markers relating to the quality of the data, which are set during the data loading process. These markers include:

- 1 the acceptable patient flag, which relates to the internal consistency of key patient data, including age, gender, and registration status;
- 2 the practice up-to-standard date, which defines the first date at which the practice to which the patient is registered met the CPRD-derived minimum standards for data recording quality (Wood and Martinez, 2004).

In addition to the quality markers, a variety of other parameters that increase the research utility of the data are calculated during the data loading process. Owing to the rapid increase in size of the CPRD dataset and the volume of queries being run across the web system, the CPRD has recently become available in a variety of other formats. This includes flat files for large subsets of the CPRD as required for a particular protocol that can be loaded into statistical software packages.

## **CLINICAL PRACTICE RESEARCH DATALINK: PRIMARY CARE DATA**

The list below provides the key characteristics of CPRD data. It should be recognized that GPs use their computers primarily to create electronic medical records for the purpose of managing their patients. However, contributing GPs are provided with recording guidelines that define what information should be recorded electronically, so making the research undertaken in CPRD more valid:

- demographics, including the patient's age and sex;
- medical diagnosis, including free-text comments;
- all prescriptions and immunizations as given in primary care;
- referrals to hospitals or specialists;

- laboratory results, including microbiology;
- treatment outcomes, including hospital discharge reports where patients are referred to hospital for treatment;
- key patient information (e.g., smoking status, height, and weight);
- date and cause of death;
- pregnancy-related information.

Following receipt and processing of a data collection, the CPRD Group provide feedback reports to the contributing practice on the completeness of data in key areas (e.g., date and cause of death and patient registration details), to enable practices to address any deficiencies they have with their recording. In addition, the quality of recording across the entirety of data contributed by a practice is assessed by means of the "up to standard" audit, which assesses the completeness, continuity, and plausibility of data recording in key areas, in accordance with the recording guidelines issued to practices. Where data quality is found to be acceptable, the practice is judged to be "up to standard" and marked as such in the database; this marker can be used to identify those practices where data recording is considered by the CPRD Group to be of sufficient quality for research purposes.

In April 2004, the Quality Outcomes Framework (QOF) was introduced into UK general practice. This framework provides incentives to practices for the provision of high-quality care that naturally involves improved data documentation. Given the key role of practice records in supplying the data needed to assess practice achievement/performance, there is now even more emphasis for practices to ensure that their records are complete, particularly in areas related to QOF indicators. This can only be of benefit to research.

The CPRD is a unique public health research tool, which has been used widely for drug safety studies and many other types of pharmacoepidemiological research. There are now over 800 CPRD-based peer-reviewed publications, a total of over 2000 peer review impact points, and an ever-expanding international user base. Numerous independent validation studies have confirmed a high level of completeness and validity of the data in the CPRD. A large study recently examined the validity

of the computerized diagnoses of autism in the CPRD. Anonymized copies of all relevant available clinical reports, including GPs' notes, consultant, speech therapy and educational psychologists reports, were evaluated for 318 subjects with a diagnosis of autism recorded in their electronic general practice record. For 294 subjects (92.5%) the diagnosis of pervasive developmental disorder was confirmed after review of the records, providing evidence that the positive predictive value of a coded diagnosis of autism recorded in the CPRD is high (Fombonne *et al.*, 2004). Another study compared the distribution of cause of death in CPRD with national mortality statistics and concluded that they were broadly similar. This provides further evidence that the CPRD population is broadly representative of the general population (Shah and Martinez, 2004).

#### **CLINICAL PRACTICE RESEARCH DATALINK: SECONDARY AND OTHER DATA**

CPRD has access to hospitalization data, called HES, that contains International Classification of Diseases (ICD) disease codes and Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS)-4 procedural codes together with dates of admission and discharge for each ward type in which the patient is treated. The HES data from 2013 is linked with data on drugs used in hospitals. Additionally, CPRD has access to a whole range of disease registries and audit datasets covering many key diseases. Central national death data with dates and causes is available within the system, and it is also hoped to gain access to the central birth records. Good demographic is available, and recording of ethnicity is rapidly expanding, aided in part by linkage across different datasets. Other data that are available include air-pollution data and some local datasets.

#### **CLINICAL PRACTICE RESEARCH DATALINK: RESEARCH**

Recent research includes a case-series analysis of the risks of myocardial infarction and stroke after common vaccinations and naturally occurring

infections. It found that there was no increase in the risk of myocardial infarction or stroke in the period after influenza, tetanus, or pneumococcal vaccination. However, the risks of both events were substantially higher after a diagnosis of systemic respiratory tract infection and were highest during the first 3 days, suggesting that acute infections are associated with a transient increase in the risk of vascular events (Smeeth *et al.*, 2004). A study by Martinez *et al.* (2005) compared the risk of nonfatal self-harm and suicide in patients taking selective serotonin reuptake inhibitors (SSRIs) with that of patients taking tricyclic antidepressants; no evidence was found that the risk of suicide or nonfatal self-harm in adults prescribed SSRIs was greater than in those prescribed tricyclic antidepressants. There have been concerns that pioglitazone may be associated with an increased risk of bladder cancer. A propensity score matched analysis found that pioglitazone was significantly associated with an increased risk of bladder cancer in patients with type 2 diabetes (Wei *et al.*, 2012). Another study investigated whether there is an association between use of angiotensin receptor blockers and risk of cancer. In a cohort of 377 649 new users of angiotensin receptor blockers or ACE inhibitors, it was found that use of angiotensin receptor blockers was not associated with an increased risk of cancer overall. Observed increased risks for breast and prostate cancer were small in absolute terms, and the lack of association with duration of treatment meant that noncausal explanations could not be excluded (Bhaskaran *et al.*, 2012). A study of daily medical contacts from 1999 to 2005 in a population of school-aged (5–16 years) children with a diagnosis of asthma found that returning to school after the summer break is associated with a sharp increase in unscheduled medical contacts in school-aged children, particularly in those with asthma. The authors concluded that at least part of the excess numbers of unscheduled contacts in children with asthma is because they do not maintain their inhaled corticosteroids over the summer holidays (Julious *et al.*, 2011).

A recent systematic study assessed the validity of diagnostic information in CPRD as reported in the literature. It found that estimates of validity were high overall. However, the quality of reporting of

the validations was often inadequate to permit a clear interpretation. This study made recommendations for methodology and reporting to strengthen further its use in research (Herrett *et al.*, 2010).

Most of the drug safety research in the CPRD has concerned the estimation of relative rates; that is, the rate of outcomes in exposed patients divided by that in control patients. But relative rates do not convey the public health importance of a safety issue. Large relative rates for rare events may not be of major concern, while small relative rates for frequent events may potentially have large implications. An example for this may be the cardiovascular risk of selective cyclooxygenase-2 inhibitors, which may have affected a large number of patients. Recent research developed methods to estimate, in the CPRD, individual long-term probabilities specific for a patient's age, sex, and clinical characteristics. This was done for estimating the long-term risk of fracture in patients using oral glucocorticoids. As an example, it found that a woman aged 65 years with rheumatoid arthritis, low body mass index, and a previous history of fracture and falls, who used 15 mg glucocorticoids daily, would have a 5-year fracture risk of 47% (a man with similar history, 30.1%) (van Staa *et al.*, 2005). This approach to quantify individualized long-term probabilities can help to better quantify the risks and benefits associated with a treatment.

## DATA PRIVACY AND CONFIDENTIALITY ISSUES

Data privacy and confidentiality issues are a key part of a key data stewardship program for CPRD.

These activities ensure the provision of data to researchers is in an effectively anonymized format, so protecting the confidentiality of patients and healthcare professionals. The system in operation employs many PETs and also ensures there are adequate legal arrangements to ensure researchers fully follow the operating procedures required of data use.

The data leaves each GP practice and the coded data fields are loaded into CPRD in a suitably anonymized "data subject" format with a practice iden-

tifier and a patient code (names, address, post code, and full date of birth are not downloaded with the data from each patient's record). However, there are text fields within the download that, by their nature, may contain potential identifying information. The text data is an important element in some research studies as it holds levels of data that help ensure validity of the research being undertaken – specifically, in many instances providing additional data that either could not be coded or easily coded under the pressure of a consultation. This text data is kept separate from the coded data fields and is only made available to researchers once it has been fully stripped of potential identifiers via parsing and manual checking.

On the basis that CPRD deals with "anonymized data subjects," consent is not technically required. However, in order to keep CPRD operating at the highest level of governance, patients can opt out from allowing their data to be exported to CPRD. The rate of opt out is very low and not at a rate that might be considered to introduce a bias.

## CURRENT AND FUTURE DEVELOPMENTS IN CLINICAL PRACTICE RESEARCH DATALINK

The following programs have been developed to allow even better use of the CPRD:

- *Risk management programs.* Pharmaceutical companies are now required to submit risk management plans to regulatory authorities for newly approved drugs, dose changes, and new indications. Systematic data collection on a large cohort of drug users in routine clinical practice is an important element of risk management. The CPRD Group has developed the Risk Management Knowledge and Tracking program, which allows monitoring of outcomes in drug users and, importantly, the key background information required for case assessment.
- *Surveillance programs.* Patients prescribed a drug can be followed for selected outcomes. Further information (including hospitalization records) may then be requested. This information can then be used to assess the causality of

the individual cases and also to estimate overall risks.

- *Randomized simplified trials.* Subject to appropriate approval (including the patient's informed consent and approval by an ethics committee), it will be possible in selected practices to randomize patients in normal clinical care to various treatments. Patients can then be followed using routine data collection to evaluate the outcomes. Confounding by indication is a major concern in pharmacoepidemiological research, and this randomization can overcome bias due to baseline differences.
- *Prospective data collection.* Subject to appropriate approval (including the patient's informed consent and approval by an ethics committee), additional information can be obtained through the GP. This can include genetic samples. Pharmacogenetic studies could be conducted to evaluate the effect of genetic polymorphisms on the response of drug treatment.

## STRENGTHS AND WEAKNESSES OF THE CLINICAL PRACTICE RESEARCH DATALINK

The inherent strengths in the CPRD stem mainly from the single NHS system of healthcare delivery, which essentially provides cradle to grave healthcare delivery. GPs are the central healthcare providers in the UK and, thus, have longitudinal medical records for their patients kept within powerful electronic health record systems using a standard coding for medical conditions and drugs. Electronic links to laboratories and increasingly to hospitals ensures that secondary care data are within the GP record.

CPRD is a central research record linkage system for the >54 million population of England. This makes it one of the largest systems (perhaps the largest) in the world that ensures accuracy of linkage by using the NHS unique identifier and methodologies available to CPRD to distinguish invalid and not officially allocated numbers.

The data subjects included in CPRD are broadly representative of the UK population as a whole with respect to age, sex, socio-economic class, and

UK region. Unlike databases based on health insurance claims, the CPRD includes a relatively stable population with good information on start and stop of data collection. The possibility to obtain further information from GPs and validate computerized information and to collect prospective data and samples is an additional major strength of this dataset. The record linkages further enhance the ability to undertake very detailed research projects. The CPRD is used by several regulatory authorities and numerous pharmaceutical and device companies, and is available for use by academics.

Some of the traditional weaknesses of the CPRD have been associated with the level of completeness of data recording due to the way data were transferred between secondary and primary care. This weakness is rapidly diminishing due to the linkages discussed earlier. Drag-and-drop data entry into a patient's record is now becoming the norm for laboratory data as well as hospitalizations. In the future, it will become fully automated.

A limitation of the CPRD, in the same way as for most databases, is that the information on factors such as over-the-counter medication, diet, and exercise is limited. Also, detailed information on disease severity may not always be available or may not be recorded in a routine and standardized manner. Another challenge is for researchers to understand the complexity of this dataset and to take into account the huge variability of patient characteristics and drug use.

A summary of the key characteristics of CPRD is presented in Table 26.1.

## CONCLUSION

The CPRD is a widely used resource for studies in drug safety and pharmacoepidemiology. The CPRD is maintained and developed by the MHRA. The challenge is that analyses of CPRD data require a deep understanding of both the CPRD and the UK healthcare system. Collaboration with researchers who understand the CPRD and the UK healthcare system may be helpful.

The CPRD is used by researchers internationally in academia, the pharmaceutical industry, the

Table 26.1 Summary of key characteristics of CPRD.

Data source	The English NHS: >52 million population. Some data are also available from Scotland, Wales, and Northern Ireland.
Size	>52 million for many datasets. Some may be lower population cover. CPRD will provide denominator for any study.
Geographic cover	Good cover regardless of actual population cover.
Access to data and/or research	Via a variety of means, online, flat file, or data cubes for own research use. CPRD has a large in-house team of epidemiologists, statisticians, and data-cutters.
Quality of data	Metadata provides details of quality.
Longitudinal nature	The NHS as a single system provides cradle-to-grave care
Standard information in CPRD, primary care data	Registration file, drug prescribing, primary care diagnosis, laboratory data, immunizations, hospital discharge and referral summaries, death data, lifestyle factors. Most of this information is coded.
Coding of data	Read Clinical Terms are currently used for coding of primary care medical data. This has been matched to the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The Multilex dictionary is used for coding prescription information. Hospital data are ICD and OPCS4 coded.
Additional information on request	Anonymized free-text data as entered in the medical records. Additional information can be gained from the GP or patient (patient-reported outcomes)
Governance	Full data stewardship approvals gained by CPRD team.
Users	Worldwide regulatory authorities, pharmaceutical industry, academics, and public health departments.

NHS and UK Government departments, for research in areas such as disease epidemiology, drug/vaccine utilization and safety, pharmacoeconomics and resource utilization. Its value in pharmacoepidemiology is highlighted by its ongoing use by drug regulatory authorities – namely the USA's Food and Drugs Administration, as well as the Post Licensing Division of the MHRA. A bibliography can be found on the CPRD website ([www.CPRD.com](http://www.CPRD.com)).

CPRD is indebted to the many GPs, other data providers, and IT companies that help to enable such a system, and the members of the Independent Scientific Advisory Committee who give necessary oversight to all research conducted in CPRD.

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# Active Surveillance: The United States Food and Drug Administration's Sentinel Initiative

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## INTRODUCTION

In September 2007, the US Food and Drug Administration (FDA) was mandated by Congress to establish a postmarket risk identification and analysis surveillance system to monitor drug safety. This mandate came in the form of the Food and Drug Administration Amendments Act (FDAAA) (FDA, 2007), which also required that the FDA establish methods to obtain access to electronic data sources to conduct this surveillance (Platt *et al.*, 2009; Behrman *et al.*, 2011). In light of this mandate the FDA announced the *Sentinel Initiative* in 2008. It is a long-term effort to create a national

electronic system for monitoring FDA-regulated medical product safety (i.e., drugs, biologics, vaccines, and devices), the *Sentinel System*. The *Sentinel System*, which is being developed and implemented in stages, will ultimately expand the FDA's existing postmarket safety surveillance capabilities by enabling it to actively gather information about the safety of its regulated medical products once they reach the market.

In 2009, the FDA, in collaboration with the Harvard Pilgrim Health Care Institute and 24 partner organizations, launched the Mini-Sentinel pilot, a smaller working version of the future *Sentinel System*. The Mini-Sentinel pilot helps inform

and facilitate the development of the fully operational Sentinel System to fulfill the mandate included in the FDAAA. This active surveillance system will utilize existing electronic healthcare data, derived from healthcare claims generated in the administration of insurance plans, electronic health records created for patient care, and other sources of electronic information, such as registries. These data can be used to track exposure to FDA-regulated medical products and health outcomes associated with their use. This allows the FDA to evaluate safety signals identified by passive surveillance systems or other mechanisms, and to assess the impact of the FDA's regulatory actions on the use of medical products and on subsequent health events. An additional goal is proactive use of these routinely collected data to identify and characterize the risk of both anticipated and unexpected serious adverse effects earlier in the life cycle of FDA-regulated medical products than would otherwise occur, allowing the FDA to intervene if necessary to prevent further harm.

The FDA's ability to perform active safety surveillance of approved medical products was limited prior to its efforts to develop the Sentinel System. It is often difficult to identify rare adverse events before products are introduced into general use since the number of people exposed is limited. The FDA largely relied on passive surveillance systems to monitor the safety and performance of its regulated medical products after they were approved and reached the market. The *active surveillance* vision of the Sentinel Initiative complements the largely *passive surveillance* safety systems currently in use by the FDA. These passive surveillance systems rely on reports submitted to the FDA by industry, consumers, and healthcare professionals. The FDA Center for Drug Evaluation and Research's Adverse Event Reporting System (AERS) captures reports of suspected adverse drug reactions and medication errors. The FDA Center for Biologics Evaluation and Research's Vaccine Adverse Event Reporting System (VAERS) captures reports of suspected vaccine-related adverse reactions. The FDA Center for Devices and Radiological Health's Manufacturer and User Facility Device Experience (MAUDE) system captures reports of suspected medical device-related adverse

reactions. Industry reporting to these systems is mandatory. The FDA's MedWatch program enables healthcare professionals and consumers (i.e., patients, family members, caregivers) to voluntarily report suspected adverse drug reactions and medication errors (FDA, 2010).

Sentinel's active surveillance system will enable the FDA to utilize existing electronic healthcare data quickly, a key advantage to more quickly evaluating and understanding a safety issue. Additional advantages of an active surveillance system include the ability of FDA staff to evaluate safety issues in targeted subgroups of patients (e.g., the elderly) and also to have the capability to evaluate adverse events occurring commonly in the general population (e.g., myocardial infarction, fracture) that tend not to get reported to the FDA through its passive reporting systems.

Electronic healthcare data is used to evaluate the relationships between medical product exposures and outcomes. This has similarities to standard pharmacoepidemiologic studies that also use this type of data, but the system poses unique opportunities and challenges. Unique opportunities stem from the large number of individuals on whom data is available, frequent updates of data, relatively rapid access to data, and a large network of investigators who can be quickly mobilized to conduct signal refinement or generation activities. Challenges include understanding the validity of the data, and its other strengths and limitations; determining the best way to conduct sequential analyses to monitor for a large number of exposure–outcome pairs without producing false positive results; and evaluating strategies to analyze distributed data sets, a model used to maximize the privacy of individuals' confidential healthcare data. The goal of this chapter is to overview the active surveillance efforts of the FDA's Sentinel Initiative and to discuss the vision for the fully operational Sentinel System (Platt *et al.*, 2012; Robb *et al.*, 2012).

## COMPONENTS OF THE SENTINEL INITIATIVE

The Sentinel Initiative is comprised of several components intended to inform and facilitate the

development of the FDA's fully operational active surveillance system, the Sentinel System. The Sentinel System will increase the FDA's capability to conduct active surveillance on the safety of FDA-regulated medical products.

The *Mini-Sentinel pilot* is giving the FDA the opportunity to develop the data infrastructure and scientific operations needed to conduct active safety surveillance of medical products within a working model of a distributed data system which will inform the development of the fully operational Sentinel System ([www.mini-sentinel.org](http://www.mini-sentinel.org)). It is described in more detail below, and is the major focus of this chapter since it is laying the primary foundation for the Sentinel System. In brief, it is a collaboration of the FDA, academic institutions, and data partners that provides access to healthcare data on over 125 million people, and the expertise needed to use it to meet the goals of the Sentinel Initiative (Mini-Sentinel, 2011a; Platt *et al.*, 2012).

The *Federal Partners Collaboration*, with the Veteran's Health Administration, Department of Defense, and Centers for Medicare & Medicaid Services, enables the FDA to query publicly held automated healthcare data, including administrative claims data and electronic health records. These federally held data sources are used to conduct safety assessments, and also to develop methodologies necessary for active surveillance (FDA, 2010).

The *Observational Medical Outcomes Partnership* (OMOP) contributes to the Sentinel Initiative through methods evaluation and development (see Chapter 28). OMOP is a public-private partnership with a goal to improve the monitoring of drugs for safety. The partnership includes representatives of the pharmaceutical industry, academic institutions, other nonprofit organizations, the FDA, and other federal agencies. Research conducted or funded by OMOP is directed at developing and testing analytic methods to detect and evaluate drug safety issues. Its work focuses on the use of administrative claims data and electronic health records for this purpose. OMOP works with data providers who supply deidentified data for analysis in a centralized repository, and with other organizations that conduct analyses using patient-identifiable information within their own environments (<http://omop.fnih.org/>).

Finally, the *Engelberg Center for Health Care Reform* at the Brookings Institution has served the Sentinel Initiative by gathering stakeholder input on active medical product surveillance. Activities have included expert stakeholder conferences, public workshops, medical product surveillance roundtables, and active surveillance implementation meetings. These activities serve to ensure the transparency of Sentinel Initiative activities, and enhance these activities by collecting valuable input from a broad range of stakeholders. (FDA, 2010)

## MINI-SENTINEL

Mini-Sentinel is the pilot program developing a system to conduct near-real time active surveillance and other signal generation and refinement activities. It is laying the foundation for the fully operational Sentinel System. Mini-Sentinel is a collaboration between the FDA and over 30 academic institutions and data partners who contribute the broad range of expertise required to achieve its goals (Table 27.1) (Platt *et al.*, 2012). It draws on, and extends, surveillance methods of the Vaccine Safety Datalink Project, funded by the Centers for Disease Control and Prevention (DeStefano, 2001). Activities are led by the Mini-Sentinel operations center based at the Harvard Pilgrim Health Care Institute; it includes scientists to manage day-to-day operations and support staff. Leadership activities are distributed throughout Mini-Sentinel, including cores that focus on data, methods, and protocol development. A planning board includes representatives from all collaborating institutions and the patient community, and provides the opportunity for broad input on Mini-Sentinel activities and policies. It also includes committees to provide guidance on safety science and on policies and procedures. A privacy panel, comprised of health data privacy experts provides guidance on procedures for protection and use of confidential medical data. FDA scientists are actively involved in all facets of Mini-Sentinel (Forrow *et al.*, 2012). The following description covers activities that were completed, in progress, or planned in early 2012.

Table 27.1 Mini-Sentinel collaborating institutions.

Aetna: Aetna Informatics
America's Health Insurance Plans: Clinical Affairs Department
Brigham and Women's Hospital Division of Pharmacoepidemiology & Pharmacoconomics in the Department of Medicine
The Center for Health Care Quality at Cincinnati Children's Hospital Medical Center
Columbia University: Department of Statistics
Critical Path Institute
Duke Clinical Research Institute
HealthCore, Inc.
HMO Research Network
● Group Health Research Institute
● Harvard Pilgrim Health Care Institute
● HealthPartners Research Foundation
● Henry Ford Health System
● Lovelace Clinic Foundation
● Marshfield Clinic Research Foundation
● Meyers Primary Care Institute
Humana: Competitive Health Analytics, Inc.
Kaiser Permanente
● Colorado
● Georgia
● Hawaii
● Mid Atlantic
● Northern California
● Northwest
Outcome Sciences, Inc.
OptimInsight (United Healthcare)
Rutgers (The State University of New Jersey): Center for Health Services Research on Pharmacotherapy, Chronic Disease Management, and Outcomes in the Institute for Health, Health Care Policy, and Aging Research
University of Alabama at Birmingham
University of Illinois at Chicago: Department of Pharmacy Administration; Department of Pharmacy Practice; Department of General Internal Medicine; Department of Biostatistics
University of Iowa: Department of Epidemiology in the College of Public Health
University of Pennsylvania School of Medicine: Center for Clinical Epidemiology and Biostatistics in the Department of Biostatistics and Epidemiology; Cardiovascular Medicine Division and Division of General Internal Medicine in the Department of Medicine.
Vanderbilt University Medical Center
Weill Cornell Medical College: Department of Public Health

Data are analyzed in a distributed fashion, with each data partner analyzing its own data and providing aggregated results that the Mini-Sentinel operations center compiles. Data are identically transformed at each site using a common data model, which allows programs to be written centrally and distributed to the data partners so they can analyze their data locally, behind their secure firewalls. This allows data partners to maintain control of their data and ensure the privacy of their health plan members. It also promotes efficient use of programming time and provides a measure of quality control (Curtis *et al.*, 2012).

Mini-Sentinel's activities have been classified as public health practice operating on the FDA's public health authority, rather than research. Institutional review board approval is thus not required for its activities. Mini-Sentinel adheres to the public health provisions of the Health Insurance Portability and Accountability Act (HIPAA). (McGraw *et al.*, 2012).

Mini-Sentinel's developmental activities are focused on two major aspects of active surveillance: signal refinement and signal generation. Signal refinement involves further characterization of potential risks that have been identified through other mechanisms. Signal generation is targeted at risks that have not been previously identified. Initial development of Mini-Sentinel capabilities has focused on signal refinement activities, which allows the FDA to prioritize safety questions that have emerged from premarket or postmarket safety data sources (e.g., experience with other drugs in the same class, clinical trial data, spontaneous adverse event reports) for evaluation. However, the goal is that the Sentinel System will ultimately also generate signals of adverse events that may be associated with medical products.

Signal refinement activities vary from simple to complex. Simple queries can be performed using modular programs that are easily adaptable to answer questions about exposure and outcome rates that are necessary for most risk assessments. These can provide the data needed to calculate risk associated with medical products, adjusted for basic characteristics such as age and sex. They can be used to quickly evaluate the potential for serious risks to public health when preliminary safety

signals are identified. More complex analyses currently require protocol development to ensure control for important confounders, such that they can provide more conclusive results about risk associated with medical products.

The goal of signal generation activities is to allow for hypothesis-free assessments that attempt to identify unanticipated adverse effects. Activities are ongoing to better understand how to perform these assessments in a data environment like the Mini-Sentinel's. Initial efforts have focused on evaluating the relationship of vaccines with multiple outcomes of interest (Platt *et al.*, 2012).

In addition to Mini-Sentinel's signal refinement and generation activities, much of its work is focused on improving methods, understanding the capabilities and limitations of the data, and building capacity to perform semi-automated surveillance activities or more rapid complex assessments (Platt *et al.*, 2012). The next section overviews some of the methods used to conduct active surveillance activities in the Mini-Sentinel pilot and ongoing work to improve capabilities, inform study design, and better understand results.

## METHODS FOR ACTIVE SURVEILLANCE IN A DISTRIBUTED DATA SYSTEM

Mini-Sentinel uses a distributed database, with collaborating data partners maintaining physical and operational control over their own data in their existing environment. In the aggregate, these represent over 125 million health plan members who have both medical and pharmacy benefits coverage. Data partners are also able to obtain full text records when these are needed to confirm exposures, outcomes, or risk factor status. These data partners process healthcare administrative claims data using programs distributed by the Mini-Sentinel Operations Center (Curtis *et al.*, 2012). Mini-Sentinel did not establish a centralized data repository for various reasons, including concerns about maintaining the privacy of confidential medical data. (FDA, 2010; McGraw *et al.*, 2012). Additionally, by allowing data partners to maintain control of their data and its uses, the distributed model avoids or reduces many of the security, proprietary, legal, and

privacy concerns of data partners, including those related to complying with HIPAA, thus ensuring that only the minimum data necessary are shared with the FDA. The use of claims data and the distributed data structure require special considerations and methods to facilitate analysis and understand the validity of findings.

## COMMON DATA MODEL

The Mini-Sentinel common data model provides a standardized table structure into which data partners transform their data so that the same queries, or executable programs, can be used to process and analyze data across all sites. Formatted data are periodically refreshed at each data partner site to ensure the capability for rapid responses to queries with nearly current data. Data quality has been evaluated across all sites. This includes analysis of data completeness, determining consistency of findings across sites, and seeking explanations for any notable variations from expected patterns (Curtis *et al.*, 2012).

The common data model was designed to maintain the level of detail provided in original claims for important variables, but to include only information necessary for surveillance. The first version includes data on enrollment, demographics, outpatient pharmacy dispensing, healthcare encounters, diagnoses, and procedures. Date and cause of death from the National Death Index are available from some data partners. Encounter data include one record for each time an individual sees a healthcare provider or is hospitalized. Diagnosis and procedure codes are linked to the encounter data in a one-to-many fashion such that all available claim codes are included. Mini-Sentinel is expanding its surveillance capabilities by adding electronic health record and laboratory-based variables, which are available from a subset of the data partners (Curtis *et al.*, 2012).

## EXPOSURE IDENTIFICATION

Outpatient pharmacy dispensing records include National Drug Codes, which can accurately identify most drug products obtained in the outpatient setting. They also include information on the

quantity dispensed and the day's supply entered by the pharmacy, which serve as proxies for determining the dose and duration of drug exposure. Limitations include the inability to be certain about whether or for how long a drug dispensed was actually taken, inability to capture samples or drugs that are dispensed but not submitted to the pharmacy benefits plan, and inability to capture over-the-counter drugs or dietary supplements. These are limitations typical of claims data, not unique to the Mini-Sentinel environment.

Currently, inpatient drug exposures can only be evaluated if they include a corresponding procedure code. This limits Mini-Sentinel's capacity to examine the safety of drugs received in inpatient settings. It also raises questions about the ability to examine the short-term safety of medications often started in inpatient settings. Procedure codes can also be used to identify administration of some types of drugs and other medical product exposures. As previously mentioned, claims data are unable to identify other products, such as specific models of medical devices. There is also uncertainty about the ability of these data to accurately identify other exposures of interest, such as blood products. Future efforts will explore identification of some of these exposure types. Electronic health records may serve as a useful source of data to examine the safety of inpatient exposures.

## OUTCOME IDENTIFICATION AND VALIDITY ASSESSMENT

Health outcomes of interest in safety surveillance include new-onset disease, hospitalizations for specific conditions, procedures representing a particular health outcome (e.g., surgery revision), changes in laboratory values or vital signs, death, and cause of death. Most outcomes are identified using diagnosis codes, currently *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. Procedure codes and mortality information may also be used (Carnahan, 2012; Curtis *et al.*, 2012). Laboratory and vital signs data are available from some data partners (Platt *et al.*, 2012). Pharmacy claims may be used in combination with diagnosis codes to improve the accuracy of an algorithm to identify a condition (Carnahan,

2012). For example, an algorithm to identify new-onset diabetes may require both an ICD-9-CM code for diabetes and dispensing of a hypoglycemic agent to achieve a higher positive predictive value than either criterion would achieve alone. Such an algorithm would also likely require a disease-free baseline period during which a person was receiving healthcare benefits from a data partner, such that diagnosis and medication claims could be observed, but had no claims with a diabetes diagnosis code and no claims for hypoglycemic drugs.

The goal of algorithms to identify health outcomes of interest is to maximize the balance between positive predictive value (PPV) and sensitivity in their ability to accurately identify the outcome. The PPV of an algorithm is usually easier to estimate than sensitivity. Studies to determine PPVs involve identifying a condition using one or more algorithms and then reviewing medical records, redacted of directly identifiable personal information, to determine whether the condition was actually present. In contrast, the most efficient strategy to determine sensitivity is to start with a set of confirmed cases and then determine whether they are identified in claims. This requires a registry or other case-identification method that does not depend on claims or diagnosis codes. Thus, studies estimating the PPV of algorithms are more common than those estimating sensitivity (Carnahan, 2012). It is important for the FDA to understand the validity of algorithms in order to determine whether the findings of surveillance activities are valid or subject to misclassification bias.

Mini-Sentinel and OMOP have conducted systematic reviews of studies that have examined the ability of claims data to accurately identify health outcomes. OMOP commissioned systematic reviews on 10 outcomes. (<http://omop.fnih.org/HOI>) Mini-Sentinel performed such reviews on 20 additional outcomes (Carnahan, 2012), and is following up with additional reviews (Mini-Sentinel, 2011b). In addition to the overall PPV of algorithms, the reviews examine the influence on the validity of codes or algorithms of factors such as clinical setting of diagnosis (inpatient, emergency department, outpatient), position of diagnosis in a claim (principal versus secondary), and characteristics of the study populations. These reviews have identified

some outcomes that can be identified from claims data with relative confidence, and others for which algorithms have substantial limitations or evidence is insufficient (Carnahan, 2012). Additional efforts are devoted to validating algorithms to identify health outcomes in Mini-Sentinel data sources. This requires the ability to access the minimum necessary component of redacted medical records as a gold standard for algorithm validation (Cutrona *et al.*, 2012).

This ability to retrieve original medical records, both to adjudicate outcomes using standardized definitions and to obtain risk factor information that is not captured in electronic data, is an important capability, since some important outcomes are not currently identifiable with sufficiently high predictive value. Mini-Sentinel has developed policies and procedures for obtaining medical records from hospitals, redacting identifying information, abstracting required data elements, and performing adjudication by a panel of experts (Cutrona *et al.*, 2011, 2012). In its first test of this process, for individuals with a coded diagnosis of acute myocardial infarction, 143 of 153 requested records were obtained (Cutrona *et al.*, 2011).

Nonspecific outcomes, such as all-cause mortality or all-cause hospitalizations, are generally not preferred for surveillance because causality is more difficult to establish. Risk assessments examining nonspecific outcomes provide little insight into the exact nature of the adverse effects of a medical product, which makes it difficult to assess biologic plausibility. It is also more difficult to ensure that any association between an exposure and a nonspecific outcome is not the result of unmeasured confounding (Ray, 2005). Therefore, Mini-Sentinel assessments focus on specific outcomes in the majority of cases.

#### STUDY DESIGN/CONTROLLING FOR CONFOUNDING

Mini-Sentinel has created a taxonomy of observational study design options for different types of exposure–outcome pairs. The classification uses exposure persistence, onset and duration of exposure risk window, strength of within-person and between-person confounding, and the background

frequencies of the exposure and outcome to guide design choices. These choices include both cohort and self-controlled designs. New user designs are generally preferred, since prevalent user designs may include people who have tolerated adverse effects of drugs or are at low risk. Cohort designs are favored when the exposure persistence is long or the onset of the health outcome under study is insidious. Self-controlled (case only) designs may be particularly useful when the duration of exposure is short and the onset of adverse effects of interest is rapid, as is sometimes true for studies of vaccine adverse effects. Self-controlled designs have the advantage of controlling for time-invariant within-person confounding. They may also be helpful when there is no logical active control drug for comparison, or the active control may pose its own risk (Gagne *et al.*, 2012; Maclure *et al.*, 2012). Mini-Sentinel is also examining the strengths, weaknesses, and applicability in distributed data of different analytic approaches to adjust for confounding, such as disease risk scores, propensity scores, and high-dimensional propensity scores (Fireman *et al.*, 2012; Nelson *et al.*, 2012; Rassen and Schneeweiss 2012).

#### UNIQUE STATISTICAL CHALLENGES

Mini-Sentinel safety assessments include both one-time analyses and sequential analyses. The primary statistical approaches for one-time analyses using observational data are fairly well understood. Sequential analyses, in contrast, have typically been applied in randomized clinical trials. However, they are vital for conducting active surveillance, since the goal is to monitor a product's safety as it enters the market and detect any serious adverse effects early to prevent future avoidable harm. Mini-Sentinel investigators are working to better understand the challenges of applying sequential approaches in safety assessments using observational data (Nelson *et al.*, 2012).

Several factors pose unique challenges when applying sequential methods to distributed observational data, in contrast to randomized controlled trials. The lack of a randomized control group requires that methods control for confounding. The uncertain rate at which exposure will accrue in

observational data raises questions about how often to assess adverse event rates. Missing data and misclassification also need to be considered. The distributed data environment of Mini-Sentinel complicates application of some methods. Finally, when adverse safety outcomes are rare, risk estimates may be unstable and require small sample testing strategies (Nelson *et al.*, 2012). Mini-Sentinel investigators have conducted simulations to compare the performance of sequential methods to evaluate safety outcomes in distributed data, considering a variety of outcome, exposure, and confounding conditions to inform the choice of method (Cook *et al.*, 2012).

### MODULAR PROGRAMS

Reusable (modular) programs are designed to facilitate rapid response to commonly recurring types of queries in the Mini-Sentinel distributed database. Query parameters are specified for standardized and quality-tested programs to allow rapid queries on drug utilization and outcome rates. The modular programs have been designed to reduce duplicate programming effort required to conduct the types of queries that need to be run regularly in Mini-Sentinel's distributed database. Use of the Mini-Sentinel common data model allows for distribution of the same modular program to all data partners with no need for local customization. Results are then returned to the operations center and compiled into summary tables. This method allows for rapid response to FDA requests for queries while maintaining confidentiality of the protected health information housed with each data partner (FDA, 2010; Curtis *et al.*, 2012). Examples of modular programs include (Curtis *et al.*, 2012):

- 1 Description of outpatient pharmacy dispensing of specific drugs over time by characteristics such as age, sex, and year, including ability to specify new use of the drugs. The population can be restricted to individuals with specified pre-existing conditions identified by diagnosis codes.
- 2 Evaluation of the rate of incident health events, identified by diagnosis codes in new users of

specified drugs. Results may be stratified by characteristics such as age, sex, and year.

These modular programs can be useful for feasibility analyses to inform design and analysis of formal risk assessments. They can also be used for rapid assessment of exposures and outcomes. These can sometimes assist in making regulatory decisions or inform the prioritization of future actions. The number and complexity of modular programs will increase over time to address a wider range of FDA's needs.

### CONCLUSION

The Sentinel Initiative is still evolving, but it has begun to provide valuable information to complement FDA's safety monitoring capabilities. The Sentinel System augments, rather than replaces, the FDA's existing postmarket safety monitoring systems. The combination of both active and passive safety surveillance systems provides the FDA a more comprehensive means of monitoring FDA-regulated medical products in the USA. The FDA's vision of the Sentinel System is that it will eventually become part of a large national infrastructure that supports regulatory responsibilities, but also facilitates the work of academicians and regulated industry. The fulfillment of the mandate to develop an active surveillance system will ultimately help the FDA continue its mission to protect and promote the health of the public.

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# Leveraging Routinely Collected Healthcare Data to Scale Up Drug Safety Surveillance: The EU-ADR Experience

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## INTRODUCTION

Knowledge of the safety profile of drugs prior to marketing is limited because of the small and selective groups of individuals included in clinical trials. Careful observation and systematic monitoring is thus continued postmarketing to determine the effects of drugs in actual practice. The prevailing system of postmarketing surveillance is via spontaneous reporting systems (SRSs), where suspected adverse drug reactions (ADRs) are reported to national authorities by physicians and other healthcare practitioners, as well as patients and caregivers. The reliance of the SRS on voluntarily delivered information makes the system susceptible to various limitations, however. These limitations include underreporting, lack of information on user popu-

lation and patterns of drugs use, and reporting bias from excessive media attention (Goldman, 1998; Stephenson and Hauben, 2007; Molokhia *et al.*, 2009).

Safety-related warnings and market withdrawal of prominent drugs in recent years have fueled efforts to consider other data sources for surveillance and to develop new methodologies in order to supplement existing pharmacovigilance systems. One of the important resources posited to have enormous potential for proactive safety surveillance are electronic healthcare records (EHRs). Across the globe, various public and private initiatives have been launched to investigate the secondary use of EHRs for this purpose. These potential resources include electronic medical records containing detailed clinical information, such as

patients' symptoms, physical examination findings, specialist care referrals, diagnostic tests, and prescribed medications or other interventions. In addition, data on pharmacy dispensations, diagnostic procedures, hospitalizations, and other health services are now routinely recorded electronically by health maintenance organizations for audit and reimbursement purposes. Data from EHRs reflect actual clinical practice and, as such, have been employed to characterize healthcare utilization patterns, monitor patient outcomes, and carry out formal drug safety studies (Garcia Rodriguez and Perez Gutthann, 1998; Hennessy 2006; Suissa and Garbe, 2007). Being routine by-products of the healthcare delivery system, the use of these databases offers the advantages of efficiency in terms of time necessary to conduct a study, manpower, and financial costs. Combining multiple EHR databases from different locations and settings to support traditional systems is an emerging paradigm in pharmacovigilance.

### STRENGTH IN NUMBERS

Timely detection of safety issues requires monitoring of large populations that are representative of the entire spectrum of medication users as well as an extensive observation period, particularly for events that are rare or have a long latency (Meyboom *et al.*, 1999). Moreover, new drugs (or infrequently used drugs for rare diseases) that slowly penetrate the market will require a greater amount of patient data to comprise a significant user population within a reasonable period of time. Although it took 5 years for rofecoxib (Vioxx®) to be withdrawn from the market, it has been suggested that if the medical records of 100 million patients had been available for safety monitoring then the adverse cardiovascular effect would have been discovered in just 3 months, given the drug utilization patterns in the USA (McClellan, 2007).

### OPPORTUNITY IN DIVERSITY

The predisposition to, and manifestations of, disease often vary in certain populations, because

of ethnicity or exposures that are peculiar to a group. Different patients react differently to healthcare interventions, including drug therapy and vaccination. One of the presumed benefits of combining disparate healthcare databases for safety surveillance is the ability to assess exposures to a larger variety of drugs and to characterize use of drugs within a wider range of the population. There is much knowledge and understanding to be gained regarding disease progression and health management from networks of databases that are diverse not only in physical location (i.e., different healthcare systems), but also in structure and content (i.e., outpatient versus inpatient care, medical records versus insurance claims).

### THE EU-ADR PROJECT

The EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge, <http://www.euadr-project.org>) was launched in 2008 under the auspices of the European Commission's Seventh Framework Programme (Coloma *et al.*, 2011). EU-ADR is a collaboration of 18 public and private institutions representing academic research, primary care practice, health services administration, and the pharmaceutical industry. A computerized integrated framework for the detection of drug safety signals was developed in EU-ADR (Figure 28.1) from eight population-based databases (both administrative claims and general practitioner (GP) records) in four European countries: Denmark, Italy, Netherlands, and the UK. The databases contain demographic information, details of registration and utilization of services within the healthcare system, clinical data (including diagnoses, symptoms, procedures, some laboratory results), and drug prescription and/or dispensing information (Table 28.1). The safety signals initially identified from EHR data are then substantiated by semantic mining of literature and computational analysis of pharmacological and biological information on drugs, molecular targets, and pathways (Bauer-Mehren *et al.*, 2012).

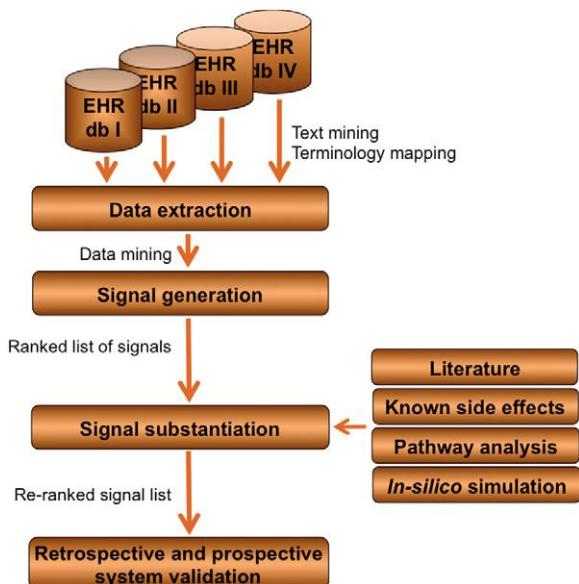


Figure 28.1 EU-ADR Project framework. Adapted from Trifirò *et al.* (2009) Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? *Pharmacoepidemiol Drug Saf*, **18** (12), 1176–1184.

#### WHERE AND HOW TO FOCUS EFFORTS IN SURVEILLANCE USING ELECTRONIC HEALTHCARE RECORD DATA

With active surveillance using EHR databases being an emerging science still in its infancy, there are important issues that are being encountered for the first time. When using data mining to detect signals in EHR databases, a decision needs to be made about the type of approach, which can be drug-based or event-based. In a drug-based approach, specific groups of drugs are monitored for their association with all possible events. In an event-based approach, specific groups of events are evaluated for their association with all possible drugs. In the EU-ADR Project, an event-based approach was adopted because the definition of drugs across databases in various countries can be harmonized more easily, compared with the definition of events. Moreover, the event-based approach enables investigation of events that are considered important from a public health perspective irre-

spective of the drug associated with the event. However, there was nothing in the published literature that prescribed what would be the primary events of interest for intensive monitoring in pharmacovigilance when applying data mining techniques. EU-ADR laid the groundwork in a study where such a list of events was created (Trifirò *et al.*, 2009). Peer-reviewed publications, medical textbooks, and websites of regulatory agencies were reviewed to create a preliminary list of events that are deemed important in pharmacovigilance. Two teams of pharmacovigilance experts independently rated each event on five criteria: “trigger for drug withdrawal,” “trigger for black box warning,” “leading to emergency department visit or hospital admission,” “probability of event to be drug related,” and “likelihood of death.” An initial list comprising 23 adverse events was identified and a ranked list subsequently established (Table 28.2). The five top-ranked events were (1) bullous eruptions (collectively consisting of Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme), (2) acute renal failure, (3) anaphylactic shock, (4) acute myocardial infarction, and (5) rhabdomyolysis. This shortlist of events served as the initial focus of signal detection in the EU-ADR Project. Although the prioritization of adverse events for drug safety monitoring done was based on thorough evaluation of evidence from various sources of information by pharmacovigilance experts, this list of events and their ranking are by no means definitive and will need to be updated as new data come along.

Data from EHRs can be used to monitor drug safety, but in order to compare and pool data from various databases of different countries and constructs, the extraction of potential adverse events must be standardized to a certain extent. Each of the eight databases in EU-ADR has unique characteristics depending on its primary objective and local function (i.e., administrative/claims, medical records) and contains medical information coded according to different languages and terminologies. Databases in EU-ADR use one of four nomenclature systems to describe the events: the International Classification of Diseases (ICD9-CM and ICD10); the International Classification of Primary

**Table 28.1** Characteristics of the databases in the EU-ADR network. Adapted from Coloma *et al.* (2011) Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. *Pharmacopidemiol Drug Saf*, **20**, 1–11.

Characteristics	Pedianet (Italy)	HSD (Italy)	Lombardy Regional (Italy)	Tuscany Regional (Italy)	IPCI (Netherlands)	PHARMO (Netherlands)	QRESEARCH (UK)	Aarhus (Denmark)
Current source population	160 000 children 2003–2007	1 500 000 2003–2007	9 000 000 General practice database	3 500 000 2003–2005 Administrative	1 500 000 2003–2006 Administrative	3 000 000 1996–2006 General practice database	4 000 000 1998–2007 Hybrid (administrative and medical record/registries)	1 800 000 2001–2006 Administrative
Years covered for this study								
Type of database	General practice pediatric database		From 15 onwards 47.2	All ages 48.8	All ages 49.6	All ages 45.8	All ages 49.6	All ages 49.9
Age range	0–14							
Males (%)	52.2							
Demographic information available	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of registration	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of transferring out	Yes	MM-YY	DD-MM-YY	DD-MM-YY	MM-YY	DD-MM-YY	YY	MM-YY
Date of birth	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gender	No	No	No	No	No	No	No	No
Ethnicity/Race								
Drug information available								
Product coding								
Active international principle coding system								
Date of prescription/ dispensing	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dosing regimen	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Quantity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Indication of use	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Outcome information available								
Symptoms (Yes/No)	Yes, as free text/codes	Yes, as free text/codes	No	No	Yes, as free text/codes	Yes for some codes	Yes, as codes	No
Outpatient primary care diagnoses	Yes, as free text/codes	Yes, as free text/codes	No	No	Yes, as free text/codes	No	Yes	No
Outpatient specialist care diagnoses	Yes, as free text/codes	Yes	No	No	Yes	No	Yes	No
Hospital discharge diagnoses	Yes, as free text/codes	Yes, as free text/codes	Yes	Yes	Yes, as free text/codes	Yes	Yes	Yes
Diagnosis coding scheme	ICD-9CM	ICD-9CM	ICD-9CM	ICD-9CM	ICPC	ICD-9CM	RCD	ICD-10
Diagnostic procedures	Yes	Yes	Yes	Yes	No	Yes for in-hospital interventions	Yes	Yes, in-hospital only
Laboratory tests	Yes	Yes	No	No	Yes	Yes subset	Yes	Yes, in-hospital only

ICPC: International Classification of Primary Care; ICD9-CM: International Classification of Diseases – 9th Revision Clinical Modification; RCD: READ CODE Classification; ICD-10: International Classification of Diseases – 10th Revision; MINSAN: Italian Ministry of Health.

Table 28.2 List of events considered important in pharmacovigilance, grouped according to system/organ involved. Adapted from Trifirò *et al.* (2009) Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? *Pharmacoepidemiol Drug Saf*, **18** (12), 1176–1184.

System/organ	Event
Hematologic	Hemolytic anemia Aplastic anemia/pancytopenia Neutropenia Thrombocytopenia
Cutaneous	Maculopapular erythematous eruptions Bullous eruptions (Stevens–Johnson syndrome, Lyell's syndrome)
Liver and gastrointestinal	Acute liver injury Acute pancreatitis UGIB
Cardiac and vascular	Acute myocardial infarction QT prolongation Cardiac valve fibrosis Venous thrombosis
Neurologic/musculoskeletal	Convulsions Peripheral neuropathy Extrapyramidal disorders Rhabdomyolysis
Psychiatric	Mood changes: depression and mania Confusional state Amnesias Suicidal behavior/attempt
Renal	Acute renal failure
Multi-systemic	Anaphylactic shock

Care (ICPC); and the READ Code (RCD) classification. For these reasons, queries for data extraction concerning potential adverse events had to be created based on local expertise. Owing to structural, syntactic, and semantic heterogeneity of the databases, it was not possible to construct a single query for data extraction that could be used as such in all databases. In the context of large-scale drug safety monitoring using EHRs, the event data extraction from different databases required harmonization; that is, a process geared towards reaching a common definition of events that is both clinically sound and agreeable to all stakeholders.

Such a process would also facilitate transparency in the extraction of the events of interest and understanding of differences between databases. An iterative harmonization process for data extraction was implemented in EU-ADR (Avillach *et al.*, 2013). The Unified Medical Language System (UMLS) was used to identify concepts and corresponding codes in each terminology. UMLS is a biomedical terminology integration system handling more than 150 terminologies (Lindberg *et al.*, 1993; Humphreys, 1994). Feedback interaction with the database holders was employed at various stages to refine the extraction queries, and age-adjusted incidence rates were used to support harmonization of the data extraction process across databases. This exercise showed how automatic extraction of event data may differ across databases and how different choices impact on the estimated incidence of the events. Furthermore, it reiterated the view that use of EHR databases requires an understanding of how the healthcare data are generated from the initial patient encounter all the way to completion of the database entry.

#### COMMON DATA FRAMEWORK AND DISTRIBUTED DATA PROCESSING

Founded on the basic governance principle that data holders must be involved in the elaboration of data as they best understand the context within which the data are recorded, a distributed network approach was adopted in EU-ADR (Figure 28.2). Standardized input files (patient, drug, and event data files) are created locally and are subsequently managed by purpose-built software Jerboa<sup>®</sup>, which has been tested against different scripts. Jerboa<sup>®</sup> uses flat text files as input and is written entirely in Java<sup>TM</sup> to ensure that it will run in a wide variety of computational environments. The software queries patient-level data in the different databases, which are later aggregated, de-identified, and sent in encrypted format to a central repository for evaluation and further analysis. This repository is managed by the Department of Medical Informatics at Erasmus Medical Center in the Netherlands, the project's coordinating center.

In combining the data of the various databases it was crucial to take into account ethical issues

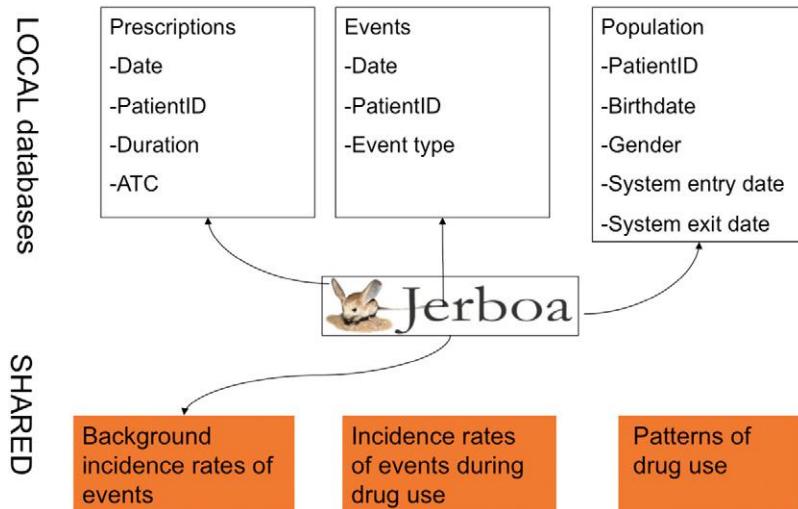


Figure 28.2 Distributed data processing. Adapted from Coloma *et al.* (2011) Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. *Pharmacoepidemiol Drug Saf*, **20**, 1–11.

regarding the processing of anonymized healthcare data. The databases in EU-ADR have well-developed safeguard mechanisms ensuring compliance with the European directives and national regulations as well as database governance rules. Since no new data are collected, other than those made available by the participating databases, the cornerstone of ensuring proper ethical and legal conduct is set down in the rules and regulations that govern each database. Rather than imposing a “one size fits all” approach and compel data holders to restructure their data, the diversity of the databases was used as an opportunity to use local expertise and maximize extraction of relevant information. Within this distributed network system, databases retain ownership of their respective data, extraction being done locally, and only the aggregated, non-identifiable data are shared with the rest of the network. Revisiting the known association of upper gastrointestinal bleeding (UGIB) and nonsteroidal anti-inflammatory drug (NSAID) use, it has been shown that data sharing can take place within a distributed networking system to provide consistent incidence rates and detect a known drug–adverse event association. A statistically significant age- and sex-adjusted association between use of any NSAID and increased risk for UGIB was confirmed in all databases, incidence rate ratio (IRR)

from 2.0 to 4.3, which is consistent with what has been described in the literature (Hernandez Diaz and Garcia Rodriguez, 2000; Coloma *et al.*, 2011).

#### POWER FOR SIGNAL DETECTION

Data mining on healthcare databases generates statistical associations between drug exposure and adverse outcomes and may be able to augment the current passive–reactive system and facilitate earlier detection of potential safety issues. Such an approach for safety surveillance is promising; now the question arises as to what this type of surveillance can add to existing systems and whether these database platforms have enough power to adequately detect safety signals. Database size (variously measured as total population, total follow-up time, or total exposure time to drugs) is important in understanding its capability for meaningful signal detection. The overall size of a database is not the determinant of the statistical power to detect safety signals, but rather the drug exposure data (Hammond *et al.*, 2007). Hence, it is not sufficient to know the total number of individuals contributing to the database; it is also important to determine whether drug exposure in the database is “big enough” that an adverse effect of such magnitude as to be scientifically significant will also be

statistically significant. In EU-ADR it was estimated for how many and for which types of drugs safety signals might be detected as a function of actual drug use, minimal detectable relative risk (RR), and incidence rates of events as observed in the database network (Coloma *et al.*, 2012). Data from almost 20 million individuals with 60 million person-years of follow-up who used 2289 drugs in the EU-ADR network showed that for a frequent event such as acute myocardial infarction there are 531 drugs (23% of total) for which an association with  $RR \geq 2$ , if present, can be investigated. For a rare event such as rhabdomyolysis, there are 19 drugs (1% of total) for which an association of same magnitude can be investigated. Although linking of healthcare databases for active drug safety surveillance is feasible in Europe, the leverage to do so may be too low for very rare events and for drugs that are infrequently used, or captured, in the databases, and a system such as EU-ADR may be better at detecting signals with lower strength of association for events that have a relatively high background frequency (such as acute myocardial infarction and UGIB). Following on the premise that an increase in the size of the database network would translate to an increase in the power to detect safety signals, a simulation was also performed to determine how the percentage of drugs that can be monitored would change if more data become available. Data simulation showed that if the EU-ADR platform were to be expanded to 10 times its current size, assuming the same patterns of use, the maximum percentage of drugs that can be investigated for acute myocardial infarction with adequate power is about 50% for relatively frequent events such as acute myocardial infarction and UGIB and less than 10% for rare events such as rhabdomyolysis.

Because the prevalence and nature of many diseases are not the same in children as in adults, and because of age-related variation in drug pharmacology and drug utilization (Le *et al.*, 2006; Rashed *et al.*, 2012; Mason *et al.*, 2012), a separate study was conducted to determine the capabilities of the system for pediatric drug safety signal detection (de Bie *et al.*, 2012). Findings revealed that drug use in children, as documented in the databases, is rare and shows little variation: only 18 out of the total

2170 prescribed drugs make up half of the total exposure to drugs in the pediatric population in EU-ADR. The number of drugs with enough exposure to detect potentially drug-induced adverse events using EHRs for rare events in children and adolescents is limited. Mining within EHR databases seems especially promising for events that have a high background incidence in the pediatric population and for drugs with a large amount of exposure. Furthermore, there is a need to develop a “priority list” of adverse events to monitor that is specific for children.

## TESTING THE SYSTEM

Although several drugs have been withdrawn post-marketing by regulatory authorities after scientific evaluation of harms and benefits, there is no definitive list of confirmed signals (i.e., list of all known adverse reactions and which drugs can cause them). As there is no true gold standard, prospective evaluation of signal detection methods remains a challenge. Within the context of methods development and evaluation in the EU-ADR Project, a surrogate reference standard of drug–adverse event associations was developed based on existing scientific literature and expert opinion. The reference standard was constructed for 10 top-ranked events judged as important in pharmacovigilance (Coloma *et al.*, 2013a). A stepwise approach was employed to identify which among a list of drug–event associations are well recognized (known positive associations) or highly unlikely (“negative controls”) based on MEDLINE-indexed publications, drug product labels, spontaneous reports made to the World Health Organization’s pharmacovigilance database, and expert opinion. Only drugs with adequate exposure in the EU-ADR database network to allow detection of an association were considered. Ninety-four drug–event associations comprised the reference standard, which included 44 positive associations and 50 negative controls for the 10 events of interest: (1) bullous eruptions; (2) acute renal failure; (3) anaphylactic shock; (4) acute myocardial infarction; (5) rhabdomyolysis; (6) aplastic anemia/pancytopenia; (7) neutropenia/agranulocytosis; (8) cardiac valve fibrosis; (9) acute liver injury;

and (10) UGIB. For cardiac valve fibrosis, there was no drug with adequate exposure in the database network that satisfied the criteria for a positive association. It is important to realize that this reference standard must be considered dynamic and needs to be reassessed periodically as knowledge on drug safety evolves over time and new issues in drug safety arise.

To evaluate the relative performance of different statistical methods for identifying drug–adverse event associations from EHR data, RR estimates were computed for drug–event pairs using 10 different methods, including those developed for SRSs, cohort methods such as the longitudinal gamma Poisson shrinker (LGPS), and case-based methods like case–control (Schuemie *et al.*, 2012). The method “Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs” (LEOPARD), developed in EU-ADR (Schuemie, 2011), was used to remove associations likely due to protopathic bias. Data from the different databases were combined by pooling of data and by meta-analysis for random effects. The previously mentioned surrogate reference standard of known positive associations and “negative controls” was used to evaluate method performance. The area under the receiver operating characteristic (AUC) curve (which is equal to the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one) was obtained for each method, both with and without LEOPARD filtering. The highest AUC (0.83) was achieved by the combination of either LGPS or case–control method with LEOPARD filtering, but the differences in performance among the different methods were marginal. LEOPARD increased overall performance, but flagged several known ADRs as caused by protopathic bias. Based on this preliminary evaluation, it was concluded that combinations of methods demonstrate good performance in distinguishing known ADRs from negative controls, and that these methods may also be used to detect new drug safety signals.

Accuracy of outcome assessment is crucial to ensure validity when mining multiple EHR databases for drug safety signal detection. Twin studies evaluated the accuracy of various coding-based algorithms used to identify cases of UGIB and

acute myocardial infarction in the databases in EU-ADR (Coloma *et al.*, 2013b). Cases were identified from GP and medical specialist diagnoses as well as from primary hospital discharge diagnoses and death registries using predefined coding algorithms in three disease terminology systems: (1) ICPC; (2) International Classification of Diseases–9th Revision – Clinical Modification (ICD9-CM); and (3) ICD 10th revision. Unstructured (free) text search using key words consistent with the UMLS concepts was also employed. Manual review of medical records and hospitalization charts was performed using a standardized questionnaire implemented as computerized data-entry algorithm using custom-built software Chameleon<sup>®</sup>, locally installed in each database. Positive predictive values were calculated overall and for each code and free-text query. These two studies showed that EHR databases present a potentially good source of identifying patients with acute myocardial infarction and UGIB and that further studies are needed to optimize the value of free-text search in the identification of events in EHR databases.

To further explore how EHR databases can augment safety surveillance, EU-ADR responded to a request from the Dutch Medicines Evaluation Board to study the background epidemiology of progressive multifocal leukoencephalopathy (PML). PML is a rare central nervous system demyelinating disease caused by reactivation of the JC virus and occurs almost exclusively in immunosuppressed individuals such as patients with HIV/AIDS, leukemia, tumors, or those undergoing organ transplants (Tan and Koralnik, 2010). The disease has recently generated widespread concern after reports of PML allegedly developing after treatment with several new biologic agents (Carson *et al.*, 2009). Because of its rarity, few data are available regarding the incidence of PML in non-immunocompromised populations. Using demographic and clinical data from six databases in three countries within EU-ADR, estimates of the incidence of PML in the general population were calculated. Cases of PML were identified from primary and secondary hospital discharge diagnoses as well as death registries (claims databases) and from GP or specialist diagnoses (medical records databases) using diagnostic codes and free text. Case validation by medical

chart/records review was performed in a subset of cases.

### SIGNAL TRIAGE AND EVALUATION

Like any signal detection system, there is a need to establish “rules” on how to trigger an alert and when to consider a signal likely enough to be true to warrant follow-up or even to require immediate health policy intervention. A strategy for combining evidence from different data sources has been proposed in EU-ADR to prioritize signals that may represent genuine risk and, hence, necessitate further investigation and formal pharmacoepidemiologic studies (Coloma *et al.*, 2013c). Association estimates are ranked according to magnitude of risk, also taking into account temporality and confounding effects. Consistency of the association among drugs of the same class and the number of excess cases attributable to the drug exposure are further assessed to prioritize the list of potential signals. Finally, signal filtering and signal substantiation are done using different bioinformatics workflows to determine the novelty and plausibility of the identified signals (Oliveira *et al.*, 2013). This signal triage strategy can be further tested using other EHR data sources and other adverse events. While the automated signal filtering and signal substantiation streamlined the triage and greatly reduced manual work, full automation of the signal prioritization process is still not possible at this time. Manual verification of the output produced by these workflows, in terms of both accuracy and completeness, remains a crucial step.

### HOW SIGNAL DETECTION USING ELECTRONIC HEALTHCARE RECORD DATA FITS INTO THE BIG PICTURE

In order to better understand what could be the niche of EHR data in the current practice of pharmacovigilance, it is useful to examine the nature and characteristics of safety signals triggering withdrawal of drugs from the market, particularly the type of data that provide the basis for these withdrawals (Coloma *et al.*, 2013d). Of the 25 safety-based withdrawals in the USA or the EU in the last

10 years, 10 (40%) were for adverse cardiovascular events and seven (28%) were for gastrointestinal, primarily hepatic, adverse events. Drugs acting on the gastrointestinal system comprised the majority (28%, 7 out of 25) of all drugs withdrawn, while drugs acting on the neuropsychiatric and musculoskeletal systems each comprised 20% (five drugs) and 17 % (four drugs), respectively. Eleven out of the 25 drugs (44%) were withdrawn from both the US and EU markets. Characterization of these safety-based withdrawals in terms of background frequency, latency or temporality, type of ADR, and source of information used as the basis for the withdrawal revealed that the majority of safety-based withdrawals concern rare events that have a delayed onset and that cannot be predicted based on known pharmacological action. It is also clear that spontaneous reports have been an important resource contributing to the decision to take regulatory action, case reports (both published and unpublished) being the primary source of information in 11 of the 25 withdrawals (44%). In two instances (8%), clinical trials were the sole source of the safety information, but for the rest of the withdrawals a combination of case reports and/or clinical trials and/or observational studies contributed to the regulatory action. While all these data resources remain important and indispensable for safety surveillance, there remain gaps that may be filled by observational data derived from safety surveillance using EHRs. Potential risk associated with medication use has to be evaluated both with respect to risk to the individual and the population frequency, which requires knowledge of the level and duration of exposure. The longitudinal nature of routinely collected EHR data may allow identification of adverse events that have a long delay between exposure and clinical manifestations, particularly in databases with long patient follow-up and low turnover. While most spontaneous reports usually involve newly marketed drugs, EHR data may be able to highlight new risks associated with old drugs (as a consequence of new indications of use or new generation of users), as well as adverse events that have high background incidence rates and events that are not pharmacologically predictable and are less likely to be suspected as drug induced, and hence less likely to be reported. Data

from EHRs further provide greater detail regarding patient demographics, drug use, and utilization of healthcare services that permit evaluation of the benefit–risk profile of drugs, hence putting safety issues in a broader perspective and fostering sound regulatory decisions.

## METHODOLOGICAL CONSIDERATIONS

While the impetus for putting together data from different sources primarily comes from the need to investigate drug safety in larger populations (there is strength in numbers), the enormity and multidimensionality of the data present various challenges, both in the methodology and in the interpretation of results.

## ENSURING PATIENT CONFIDENTIALITY AND DATA PROTECTION

The common data framework, implemented via the custom-built software Jerboa<sup>®</sup>, and the choice of a distributed data network were crucial steps in the development of the EU-ADR system. This distributed network takes advantage of multiple, routinely collected, aggregated healthcare data while minimizing sharing of confidential patient-level information. A similar concept of distributed processing of healthcare data has been employed by other research collaborations, albeit with different research objectives. This model has previously been described in bioterrorism and syndromic surveillance, as well as vaccine safety surveillance (Lazarus *et al.*, 2006; Brown *et al.*, 2007; Lieu *et al.*, 2007). The ongoing Sentinel Initiative of the US Food and Drug Administration (FDA) is also adopting a distributed data architecture for combining healthcare databases to improve drug safety monitoring (Robb *et al.*, 2012). While the scale may be comparable, there are issues in combining data that are unique to Europe. Challenges stem from the fact that different countries have distinct natural languages, aside from having different drug and disease coding systems. The diversity of healthcare systems throughout Europe makes merging data from databases a more complex task that requires striking a balance between international cooperation and

adequate protection of patient confidentiality (Rynning, 2007).

## THE PROBLEM OF MULTIDIMENSIONALITY

One of the presumed benefits of combining international healthcare databases for safety surveillance is the ability to assess exposures to a larger variety of drugs and to characterize use of drugs within a wider range of the population. It is, however, a monumental task to undertake active monitoring of all drugs for all possible events in all members of the population (including children and the elderly) under all actual circumstances of medical care. Signal detection in multiple EHR data requires striking a balance between customization of methodologies for particular outcomes (immediate reactions such as anaphylaxis versus more insidious events such as UGIB or aplastic anemia) and increasing applicability. Optimization of methods for signal detection, taking into account variations in exposure and outcome assessment, among others, is an ongoing work in EU-ADR, in collaboration with other international initiatives.

## PERENNIAL THREAT OF FALSE ALARMS

The advantages of automated surveillance and quantitative signal detection are obvious, but there is a legitimate concern that such data mining on a grand scale may generate more signals than can be followed up effectively with currently available resources. The unpleasant implications of spurious and unsubstantiated signals for public health, as well as for regulatory agencies and the pharmaceutical industry, cannot be underestimated and is an important consideration (Waller, 2003; Hauben *et al.*, 2006; Avorn and Schneeweiss, 2009). In EU-ADR, some limits to unconstrained data mining were set by initially monitoring only the events considered to be most relevant from a public health and pharmacovigilance perspective. In addition, signal detection methods that allow shrinkage of the risk estimates were employed so that those supported by large data are given more weight than those supported by sparse data. In the estimation of how much drug exposure data would be necessary for signal detection, a 5% significance level was

used, which is generally deemed desirable for the purpose of minimizing the probability of observing false-positive associations. This value is fairly arbitrary, however. Although this significance level is customarily employed in most epidemiologic studies seeking to confirm drug–event associations, such requirement may not be appropriate in the context of exploratory signal detection.

### CAVEAT

Secondary use of data for purposes other than they have originally been intended for brings with it many opportunities as well as challenges. The literature is replete with discussions on the merits and challenges of recycling routinely collected EHR data, including how the type of database influences the structure and content of the data (Hennessy, 2006; Suissa and Garbe, 2007). Potential associations are inferred outside the actual patient–physician encounter that leads to suspicion of an ADR – something that is inherent in SRSs. Data in medical records databases, recorded in the course of routine clinical care, provide a different perspective from data in databases that document claims for utilization of healthcare services. With use of multiple databases from different countries and different healthcare systems, the issue of accuracy of information vis-à-vis heterogeneity is even more formidable and potential misclassification of both drug exposure and outcome must be taken into account. EHR data derived from reimbursement claims, for example, are affected by a lack of incentive to record sufficient data to allow proper case classification. Drug utilization patterns derived from population-based EHR data reflect “real-world” conditions, but are thereby also influenced by changes in clinical practice, including changes brought about by preferential prescribing and disease management guidelines, and may lead to underestimation of risks.

### FUTURE PERSPECTIVES AND CHALLENGES

The increasing complexity of research in healthcare and medicine demands new forms of collaboration

to enable cooperation and exchange of expertise across disciplines. Beyond the expected increase in data heterogeneity and statistical power, database networking is also about capacity building and performance efficiency. Concerted efforts in data retrieval and management, as well as methods development, avoid many redundancies in the conduct of research. Collaboration among research institutions and healthcare databases is desirable and is becoming more feasible with the establishment of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (Blake *et al.*, 2012).

The EU-ADR Project was officially finished in 2012, but the EU-ADR Alliance has been created as a stable collaboration framework for conducting drug safety studies in a federated manner, especially when the participation of several EHR databases is required. EU-ADR is expanding its network and expertise through the EU-ADR Alliance, within which safety studies are currently being conducted for the European Medicines Agency. There are ongoing collaborations with other safety surveillance initiatives across the continent, including the FDA Mini Sentinel and Observational Medical Outcomes Partnership.

An EHR-based signal detection system, like any other surveillance system, provides no definitive answers. There are still a lot of spots to cover before rational decisions can be made, including weighing the implications of potential risks against the benefits of therapy, as well as risk communication and its many complexities. There are further opportunities to evaluate comparative effectiveness and risk management activities in EHR databases, and such opportunities are worthwhile to explore.

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# Development and Evaluation of Infrastructure and Analytic Methods for Systematic Drug Safety Surveillance: Lessons and Resources from the Observational Medical Outcomes Partnership

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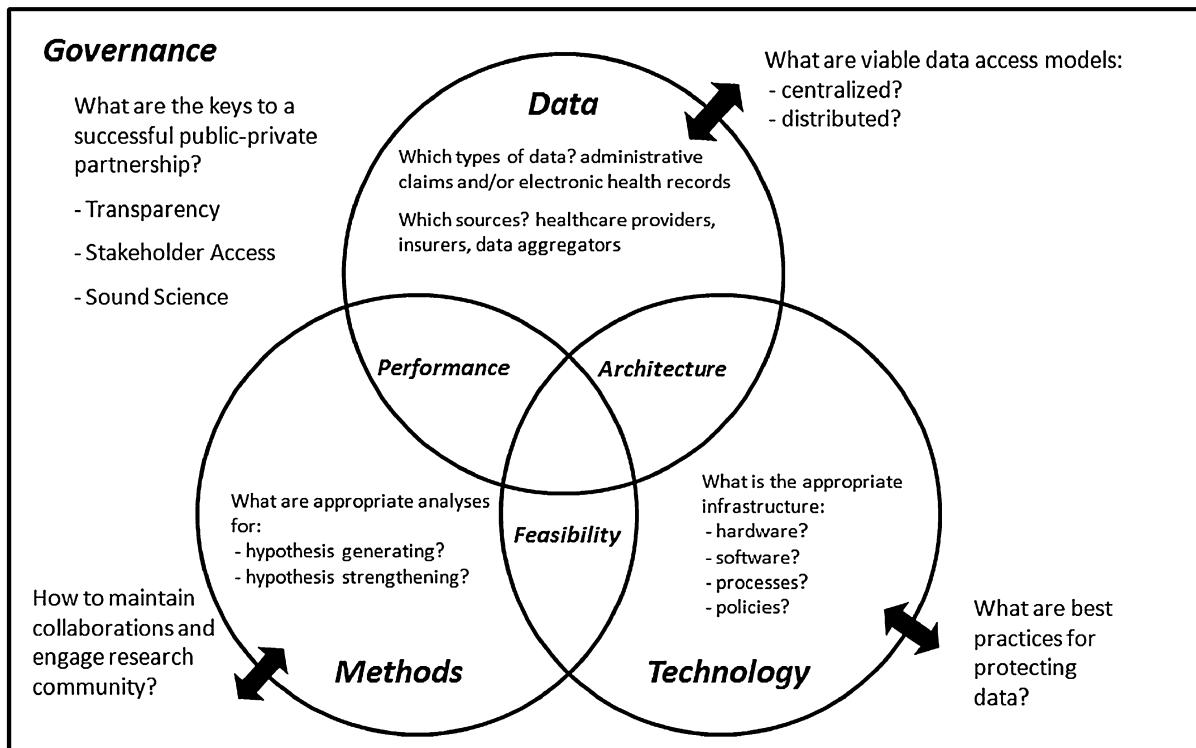


Figure 29.1 Interactions between data, analytic methods, technology, and governance that has driven OMOP's research agenda.

## THE OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP: STRUCTURE AND OBJECTIVES

The Observational Medical Outcomes Partnership (OMOP) is a public–private partnership between the US Food and Drug Administration (FDA), the Foundation for the National Institutes of Health (FNIH), the Pharmaceutical Research and Manufacturers Association, data owners, and academia. The OMOP research program is administered by the FNIH with consortium funds from a number of manufacturers. The OMOP program has a number of unique features, including its public–private governance, its open innovation approach, and the transparency of its research processes and findings (Stang *et al.*, 2010).

The OMOP research program is intended to advance the science of active safety surveillance of medical products. The ultimate goal is to develop a

systematic process for identifying associations between medical products and outcomes using healthcare claims data or electronic health records data. In contrast to spontaneous reports, these data offer the advantage of representing a defined population with known denominators and potentially more robust medication and outcome information. Toward that goal, research has focused on the development and investigation of data sources, analytic methods, technology, and outcome definitions. Figure 29.1 illustrates some of the relationships between these elements and how they have driven the OMOP research agenda.

As constituted, the OMOP has three principal objectives:

- 1 Develop tools and capabilities for transforming, characterizing, and analyzing disparate observational data from a broad range of sources representing the spectrum of healthcare settings.

- 2 Conduct research to evaluate the ability of analytic methods to accurately identify associations between medical products and health outcomes using observational data.
- 3 Establish resources to be shared with the broader research community for advancing the science of safety surveillance.

Comprehensive safety surveillance of medical products requires evidence from clinical trials, spontaneous adverse event reports, and other sources, including the analysis of observational databases. The analysis of these databases can potentially inform many components along the spectrum from “risk identification” to “amplification,” from “systematic” or “automated” epidemiology to formal “evaluation”; however, there are known issues in these data (including biases and unmeasured confounders) that over the years have caused confusion when interpreting study results or attempting to reconcile differing results across studies. The risk identification system being tested by the OMOP is intended to complement, not replace, existing safety surveillance systems or data sources by empirically testing and understanding the performance and characteristics of the underlying data, definitions, and methods. The insights gained should help inform the scientific community on the boundaries and optimal implementation of these analyses in a comprehensive safety surveillance program.

## GENERAL APPROACH

Fundamentally, our studies focus on heterogeneity and its impact across the science of observational database research: data capture and the populations they represent (Ryan *et al.*, 2010), the definitions of exposures and outcomes, selection of comparators, study design decisions, and execution of the analysis using the methods and choices of parameter “settings” within a method. Characterizing heterogeneity and the performance of methods will provide insights into how best to achieve more robust approximation of the true relationships between exposures and health outcomes of interest (HOIs) with the goal that observational research

can credibly contribute another source of information to inform clinical decisions by identifying associations in larger defined patient populations.

Attempts to analyze data from multiple sources must contend with additional issues such as inconsistent data structures and vocabularies. A major aspect of the OMOP research program involves either minimizing such issues (e.g., creating a consistent data structure and vocabularies) or understanding them and how they affect data analysis and results. To identify and address issues related to inconsistent data structures, access, and vocabularies, we established a network of disparate data sources that included both central (housed in the OMOP research lab) and distributed (data remained with collaborators) databases. These databases consisted of claims data and electronic health records. Each database was converted to a standards-based common data model (CDM) (OMOP, 2009a; Overhage *et al.*, 2012) with a standard structure and vocabulary (OMOP, 2010) to which we applied a set of epidemiological and statistical methods (OMOP, 2009b) that were identified in searches, discussions, and contests. A set of “known associations” was identified and served as our “true positive” test cases; similarly, a set of associations believed to represent “true negatives” was also identified and together formed the associations used to test the performance characteristics of the methods.

A typical epidemiologic analysis uses a single data source and applies a specific analytic method to the data in a specific manner, using specific definitions for exposures and outcomes (possibly subject to a validation procedure). In practice, researchers usually consider myriad choices among data sources, analytic methods, and definitions of exposure and outcomes, then select a single choice for each based on the research question, the nature of the data sources, and other considerations. Each of these choices can be considered fine-tuning as one may do across dials in an attempt to optimize output (we will refer to them as “parameter settings”). Considerable evidence suggests that these choices differ by investigator, and results may not be reliably reproduced from other data sources or analytic methods that are equally valid.

Rather than choosing a single database or analytic method, we attempted to empirically evaluate

the consistency of findings across databases, analytic methods, and definitions to identify optimal choices of each. Overall, the evaluation involved testing 14 analytic methods, each with up to 162 parameter settings, against 35 outcome definitions, across 10 databases. The output of this analysis consisted of quantitative estimates of association for 1.4 million drug-outcome association estimates.

## **EXPERIMENTAL INFRASTRUCTURE FOR SYSTEMATIC SURVEILLANCE**

To achieve OMOP's mission, it was necessary to establish an organizational and technical infrastructure that served as a prototype for an automated system for active safety surveillance. That infrastructure had to meet several requirements, including satisfying the needs of an ambitious research program; modeling the governance and operating characteristics of a final system; incorporating data from multiple, disparate environments; interacting with multiple stakeholder organizations; and performing ongoing monitoring of medical products and health outcomes of interest across databases within the network. This infrastructure design departs from traditional safety studies, which typically examine associations between a single drug and a small number of outcomes using a single data source. These studies typically involve a carefully designed protocol that includes the parameter settings and other design characteristics tailored to the unique drug-outcome situation of interest.

### **COMMON DATA MODEL**

A standard data environment was established that consisted of three primary elements: a CDM, specifications for standards-based terminology, and design guidelines for developing analytic methods within the common framework. The CDM (OMOP, 2009a; Overhage *et al.*, 2012) was designed to accommodate data from a variety of sources, including electronic health records and administrative claims databases. It incorporates standard terminology and standard definitions of drug exposure

and outcomes. By following the guidelines for design of analytic methods and the CDM, researchers can perform an analysis against all available databases without having to customize the programming code for each database, thereby reducing programming errors and increasing efficiency.

Methods developed to the CDM specifications are run across all available databases within the OMOP network without modification. The network of data sources consisted of five central datasets and five distributed datasets, included both administrative claims and electronic health records, and covered de-identified patient-level data for more than 200 million people.

### **RESEARCH COMPUTING LAB AND SOFTWARE TOOLS**

The five central datasets are housed within a research computing lab that currently exists in the Amazon Elastic Compute Cloud (Amazon EC2). This infrastructure provides secure computational resources for methods development and testing, data storage, and data management (OMOP, n.d.). The five distributed datasets were housed by their respective partners: the Department of Veterans Affairs Pharmacy Benefits Management Center for Medication Safety (VAMedSAFE); Humana, Inc.; Partners HealthCare System; Regenstrief Institute affiliated with Indiana University School of Medicine; and SDI Health. Each of these partners established an instance or copy of their dataset that complied with the OMOP CDM and vocabulary specifications (OMOP, 2011a).

OMOP investigators have developed several software tools to systematically assess and summarize the data. These include (OMOP, 2009c–e):

- OSCAR (Observational Source Characteristics Analysis) – summarizes the characteristics of the data source;
- NATHAN (Natural History Analysis) – reveals insights into the natural history of diseases;
- RICO (Regularized Identification of Cohorts) – identifies cohorts of interest in the dataset;
- GROUCH (General Review of OSCAR Unified Checking) – assesses the quality of the central and distributed datasets.

In addition, OMOP investigators developed the Observational Medical Dataset Simulator (OSIM), a software tool for creating simulated datasets that are scalable and compliant with the OMOP CDM. The OSIM utility can create datasets containing predefined drug–outcome associations of prespecified strength, allowing researchers to test the performance of analytic methods using datasets containing known drug–outcome associations (OMOP, 2009b; Murray *et al.*, 2011). The source code for all software tools and analytic methods developed by the OMOP research team are available on the OMOP public website.

## ANALYTIC METHODS

A community of methods developers contributed 14 analytic approaches (see Table 29.1) for estimating the strength of association between exposure to medical products and the occurrence of health outcomes of interest. The programming code for each of the analytic methods was designed to be configurable for any drug or health outcome of interest and was written to be compliant with CDM specifications (OMOP, 2009a; Overhage *et al.*, 2012). Each of these analytic methods (OMOP, 2009b) was tested within the OMOP research lab before being made available to the distributed partners for implementation.

## HEALTH OUTCOMES OF INTEREST

Before assessing the performance of an analytic method, it was necessary to establish a set of gold standards against which each method could be tested. This entailed identifying a set of health outcomes known to be associated with specific drugs or drug classes (e.g., warfarin and bleeding) against which the performance of databases, statistical methods, and health outcome of interest definitions could be assessed empirically. We performed systematic literature reviews to develop a spectrum of definitions for 10 health outcomes of interest (OMOP, 2009f; Stang *et al.*, 2012) that are central to the safety and pharmaceutical outcomes community, paired with 10 drugs/drug classes for which there was evidence from other observational studies and product information of an association. These

became our “positive controls” (e.g., drug–outcome pairs where the drug is believed to cause the outcome) and our set of “negative controls” (e.g., drug–outcome pairs where we could find no evidence of an association for which any method should not produce an association). These positive and negative controls became the “truths” used to test the various epidemiological/statistical methods and allowed us to estimate the empiric performance of a given method in a given dataset using specific parameter definitions; in other words, a good method should consistently identify the “true” associations and not identify an association for the “negative controls” (see Figure 29.2).

There was no single search strategy that effectively identified all of the relevant articles, due in part to the lack of a specific subject heading that consistently and completely identifies observational database studies (OMOP, 2009f; Stang *et al.*, 2012). We found during our literature reviews that case definitions used by previous researchers to identify specific events of interest were often not published and rarely validated, which made the idea of testing multiple definitions more important. Furthermore, most researchers had focused only on showing that their chosen case definition was viable, without determining whether it was the optimal case definition for the outcome of interest.

Consistent with our empiric approach, we developed several definitions of each health outcome of interest. These definitions were based on other observational studies in the literature and were defined based on ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification), CPT® (Current Procedural Terminology, 4th edition) and LOINC® (Logical Observation Identifiers Names and Codes) codes. Definitions are available from the OMOP website (OMOP, 2009f). Each definition then entered our research effort to be tested with the different types of data to identify the optimal definition for each outcome of interest.

## GOVERNANCE

An executive board and two advisory boards were constituted to implement the governance requirements of the partnership’s research program and

Table 29.1 Fourteen analytical methods applied across 10 databases in the OMOP experiment.

Method name	Disproportionality analysis	Case-based methods	Exposure-based methods	Sequential testing methods	Contributor
Bayesian logistic regression (Hauden <i>et al.</i> , 2005; Gernkin <i>et al.</i> , 2007)	X				Rutgers University/ Columbia University
Bayesian multivariate self-controlled case series (Whitaker <i>et al.</i> , 2005)	X				Columbia University
Case-control surveillance (Rosenberg <i>et al.</i> , 2005)	X				Eli Lilly and Company
Case-crossover (Schneweiss <i>et al.</i> , 1997)	X				University of Utah
Conditional sequential sampling procedure (Li, 2009)	X			X	Harvard Pilgrim/ Group Health
Disproportionality analysis (Almenoff <i>et al.</i> , 2003; Gould, 2007; Curtis <i>et al.</i> , 2008; Hochberg <i>et al.</i> , 2009)	X				Columbia University/ Merck & Co., Inc.
High-dimensional propensity score (Schneweiss <i>et al.</i> , 2009)	X				Columbia University
High-throughput screening (Janzen, 2002)	X				
IC temporal pattern discovery (Norén <i>et al.</i> , 2008, 2010)	X				Regenstrief Institute/ Indiana University
Incident user design (Ray, 2003; Schneweiss <i>et al.</i> , 2009)			X		Uppsala Monitoring Centre
Longitudinal gamma Poisson shrinker (LGPS) and Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs (LEOPARD) (Schuemie, 2011)	X				University of North Carolina
Maximized sequential probability ratio test (Brown <i>et al.</i> , 2007; Kulldorff <i>et al.</i> , 2007)		X		X	Erasmus University Medical Center Rotterdam
Multi-set case control estimation (Breslow and Day, 1993)					Harvard Pilgrim/ Group Health
Observational screening (Ryan and Powell, 2008; Ryan <i>et al.</i> , 2009)		X			Columbia University/ GlaxoSmithKline/ ProSanos/ GlaxoSmithKline

	Angioedema	Aplastic Anemia	Acute Liver Injury	Bleeding	Myocardial Infarction	Hip Fracture	Mortality after MI	Renal Failure	GI Ulcer Hosp
OMOP ACE Inhibitor									
OMOP Amphotericin B									
OMOP Antibiotics									
OMOP Antiepileptics									
OMOP Benzodiazepines									
OMOP Beta blockers									
OMOP Bisphosphonates									
OMOP Tricyclic antidepressants									
OMOP Typical antipsychotics									
OMOP Warfarin									

**Positive control**  
**Negative control**

Figure 29.2 Positive and negative controls used in initial OMOP experiments.

operations. The composition of the executive board reflects the public–private constituency of the OMOP. The executive board sets policies for the research effort, guides the general execution and direction of the OMOP, and sets research priorities with input from the advisory boards and research investigators. The advisory boards provide input to the executive board and are responsible for oversight of the scientific and technical aspects of the OMOP.

### NETWORK COORDINATION AND MANAGEMENT

Fundamental to the OMOP research program is the network of central and distributed data sources. To facilitate network access to the databases and other resources, we chose to use several collaboration platforms to coordinate the distribution of analytic methods, software tools, and results among partners and the core team. The primary mechanism used for coordinating activities, resolving issues, and tracking progress across the research core team, methods developers, and distributed partners was frequent dialog via regular conference calls and status reports. This mechanism allowed the distributed partners to take an active role in the experimental process while maintaining control over access to their data and analysis results.

### INITIAL RESULTS

Our initial results indicate that no single analytic method was consistently superior to others, and

that each method offered tradeoffs between false-positive rates and false-negative rates. At 50% sensitivity, the methods we tested had false-positive rates that ranged from 16% to 30%. If parameters were changed to achieve a false-positive rate of 10%, sensitivity declined to 9% to 33%.

At an organizational level, the experience of working across central and distributed data sources generated important insights into policies, processes, and skills needed within each participating organization to effectively and efficiently operate as an automated safety surveillance network.

### RESOURCES AVAILABLE TO THE SCIENTIFIC COMMUNITY

Consistent with the open innovation and transparency tenets of the OMOP research program, all processes, procedures, techniques, and results are posted on the OMOP website (<http://omop.org>). A number of technical reports, presentations, and white papers are also available on the website. Relevant scientific papers are published in the peer-reviewed literature.

### SUMMARY AND FUTURE EFFORTS

The OMOP project is an ongoing research endeavor that continues to explore the interactions between data, analytic methods, outcome definitions, technology, and governance. The data being used in OMOP are observational data that are generally

based on a defined population where you can actually quantify incidence, prevalence, and apply methods that would not be applicable in other data sources. We have completed the investigation of analytic methods, parameter settings, and datasets for a small number of test cases using statistical techniques to evaluate the performance of each analytic method. At the time of this writing, we are evaluating these methods across a broader array of experiments, expanding the exploration of test cases against both real and simulated data. Although empiric investigation should provide insight into the optimal methods, data sources, and definitions for identifying drug–outcome associations, we do not expect to find a one-size-fits-all solution for every safety issue.

We have already learned that researchers need to be cautious in interpreting results from a single study design or single statistical method in a single database. Furthermore, replication of results using a different method and dataset cannot ensure the validity of the results. Further empirical research is needed to develop a reliable, automated process for systematic surveillance of drug safety using observational data.

## NOTE FOR READER

Since the writing of this book chapter, OMOP has been transitioned from the Foundation for the National Institutes of Health to the Reagan–Udall Foundation for the Food and Drug Administration (Evans *et al.*, 2013).

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## **Part IV**

# **PHARMACOVIGILANCE AND DRUG/SYSTEM ORGAN CLASSES**



# Mechanisms of Adverse Drug Reactions

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## INTRODUCTION

An *adverse drug reaction* may be defined as (Edwards and Aronson, 2000):

an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.

More recently, the new EU Pharmacovigilance legislation has extended the definition to include medication errors and also drug misuse and abuse (European Commission, 2010). This chapter focuses on adverse reaction occurring while the drug is being used within its therapeutic indication.

By the time a drug is marketed, only about 1500–3000 patients may have been exposed to the drug (Rawlins, 1995; Asscher *et al.*, 1995). Thus,

only those adverse reactions occurring at a frequency of greater than 1 in 500–1000 will have been identified at the time of licensing. Assessment of adverse drug reactions, therefore, is likely to represent an important aspect of drug therapy for many years to come; indeed, with the development of new biotechnology compounds, the pattern of these reactions is also changing. Furthermore, through the use of gene and protein screening technologies, many new targets are likely to be discovered in the future. As new drugs are developed to modulate the function of these targets, it is very unlikely that we will fully understand the biology of the new target molecule(s), and this will lead to unforeseen adverse reactions. For example, adverse effects such as exacerbation of multiple sclerosis, systemic lupus erythematosus (SLE), and blood dyscrasias that have been reported with anti-tumor necrosis factors (TNF) biologics (Sharief and Hentges, 1991; Furst *et al.*, 2000) may not have been expected given the *known* pharmacology of these therapies.

## IMPORTANCE OF ADVERSE DRUG REACTIONS

Adverse drug reactions are a major clinical problem (Einarson, 1993; Bates *et al.*, 1995a,b, 1997; Classen *et al.*, 1997). A meta-analysis suggested that adverse drug reactions were between the fourth and sixth commonest cause of death in the USA in 1994

Table 30.1 The direct and indirect effects of adverse drug reactions.

Cause admission to hospitals, or attendance in primary care
Complicate hospital in-patient stay in 10–20% of cases
Responsible for deaths, possibly as high as the fourth commonest cause of death
Increase length of hospital stay
Increase cost of patient care
Major economic burden on the pharmaceutical industry
Adversely affect patient quality of life
Cause patient to lose confidence in their doctors
Occurrence of toxicity in a minority of patients will preclude use of the drug in the majority of patients
Mimic disease and result in unnecessary investigations and/or delay treatment

(Lazarou *et al.*, 1998). A large prospective study in the UK showed that adverse drug reactions were responsible for 6.5% of all hospital admissions (Pirmohamed *et al.*, 2004). In children, approximately 2.9% of admissions are due to adverse reactions (Gallagher *et al.*, 2012). Adverse drug events are associated with an increased length of stay in hospital of 2 days, and an increased cost of approximately \$2500 per patient (Bates *et al.*, 1997; Classen *et al.*, 1997). Adverse drug reactions can also have many other indirect effects (Table 30.1), which, in total, highlight the overall importance of adverse drug reactions in modern medicine.

## CLASSIFICATION OF ADVERSE DRUG REACTIONS

There are many different classifications for adverse drug reactions. For the purpose of this chapter, we will use the original classification proposed by Rawlins and Thompson (1991), which divided adverse drug reactions into two types: type A (pharmacological) and type B (idiosyncratic) (Table 30.2). The type A reactions represent an augmentation of the known pharmacological actions of a drug, are dose dependent, and, perhaps more importantly from the viewpoint of safety, are

Table 30.2 Characteristics of type A and type B adverse drug reactions.

Characteristic	Type A	Type B
Dose dependency	Usually shows a good relationship	No simple relationship
Predictable from known pharmacology	Yes	Not usually
Host factors	Genetic factors may be important	Dependent on (usually uncharacterized) host factors
Frequency	Common	Uncommon
Severity	Variable, but usually mild	Variable, proportionately more severe than type A
Morbidity	High	High
Mortality	Low	High
Overall proportion of adverse drug reactions	80%	20%
First detection	Phases I–III	Usually phase IV, occasionally phase III
Mechanism	Usually due to parent drug or stable metabolite	May be due to parent drug or stable metabolite, but CRMs also implicated
Animal models	Usually reproducible in animals	No known animal models

readily reversible on drug withdrawal, or even simply after dose reduction (Table 30.2). In contrast, the type B, or idiosyncratic, adverse reactions are bizarre, cannot be predicted from the known pharmacological actions of the drug, do not show simple dose dependency, and cannot be reproduced in animal models. The type A reactions are more common than the type B reactions (Einarson, 1993) accounting for over 80% of all reactions. Although they cause a great deal of morbidity, in general, type A reactions are proportionately less severe and less likely to result in fatalities than type B reactions.

## TYPE A ADVERSE DRUG REACTIONS

Pharmacological (type A) adverse drug reactions are the most common forms of drug toxicity (Pirmohamed *et al.*, 1998). They can be due to the primary and secondary pharmacological characteristics of the drug (Figure 30.1). More emphasis is now placed on the secondary pharmacology of new drugs during preclinical evaluation, in order to anticipate, and thus avoid, problems that might arise once the drug is introduced into humans.

The experience with fialuridine, an experimental drug for hepatitis B, highlights the need for continued development of appropriate *in vivo* and, bridg-

ing, *in vitro* test systems for the prediction of secondary pharmacological adverse effects in humans. In June 1993, during phase II trials, 5 out of 15 patients given fialuridine died, whilst two others required emergency liver transplants (McKenzie *et al.*, 1995). The toxicity was delayed, with patients presenting weeks to months after stopping fialuridine. The toxicity had not been observed in four animal species, and the only model seems to be the hepatitis B-infected woodchuck. *In vitro* studies in cultured hepatoblasts have shown that the toxicity is due to inhibition of DNA polymerase  $\gamma$  by fialuridine and its metabolites leading to mtDNA depletion and mitochondrial ultrastructural defects (Lewis *et al.*, 1996).

Factors predisposing to pharmacological adverse reactions include dose, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities, drug–drug interactions, and drug–food interactions (Pirmohamed *et al.*, 1998) (Table 30.3). In essence, type A reactions occur when the drug concentration in plasma or tissue exceeds the perceived therapeutic window. Alternatively, the drug concentration may be within the normal range defined for the population, but because of increased sensitivity of the target in the individual an adverse reaction results. There are a number of examples of drugs (e.g., captopril) that had been introduced into clinical practice at a dose that was subsequently shown to be associated with an unacceptable frequency of adverse drug reactions, and for which a lower dose was found to be both safe and effective. In general, however, the individual affected by a type A adverse reaction will have impairment of clearance or increased sensitivity as a result of the normal process of ageing, disease, concomitant drugs, concomitant foods, or genetic variation, or a combination of these factors (Brodie and Feely, 1991).

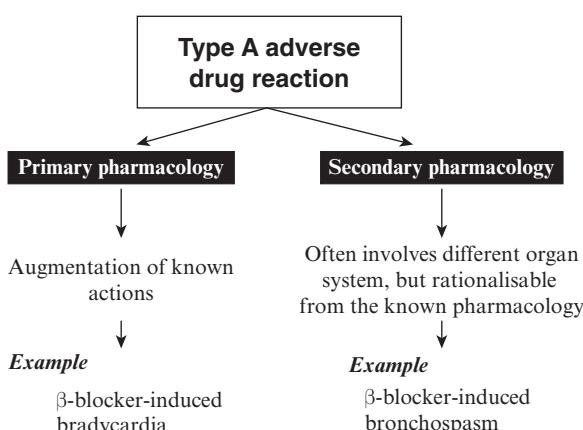


Figure 30.1 Type A adverse drug reactions can be due to the primary and/or secondary pharmacological characteristics of the drug.

## GENETIC POLYMORPHISMS AND TYPE A ADVERSE DRUG REACTIONS

A gene can be defined as exhibiting genetic polymorphisms if the variant allele exists in the normal population at a frequency of at least 1%. Genetic polymorphisms are a source of variation to drug response in the human body. In relation to type A

Table 30.3 Factors predisposing to pharmacological type A adverse drug reactions. Pirmohamed *et al.* (1998). Reproduced with permission of BMJ Publishing Group Limited.

Type	Example	Toxicity	Mechanism
Pharmaceutical	Phenytoin	Phenytoin toxicity (ataxia, nystagmus, etc.)	Increase in bioavailability as a result of a change in formulation
Pharmacokinetic (can involve absorption, distribution, metabolism, and excretion)	Digoxin	Digoxin toxicity (nausea, arrhythmias, etc.)	Decreased elimination if renal function is impaired
Pharmacodynamic Genetic	Indomethacin Nortriptyline	Left ventricular failure Confusion	Water and sodium retention Reduced hepatic elimination as a result of a deficiency of CYP2D6
Drug-drug interactions (can involve any of the above processes)	Lithium-nonsteroidal anti-inflammatory drugs	Lithium toxicity	Inhibition of excretion of lithium

Table 30.4 Genetic polymorphisms and dose-dependent adverse drug reactions. Adapted from Pirmohamed and Park (2001a). Reproduced with permission of Elsevier.

Area affected	Polymorphic gene	Example of drug affected	Adverse reaction
Phase I metabolizing enzyme	Cytochrome P450 2D6 (CYP2D6)	Metoprolol	Bradycardia
Phase II metabolizing enzyme	Thiopurine methyl transferase	6-Mercaptopurine	Bone marrow suppression
Drug transporter	P-Glycoprotein (MDR1)	Digoxin	Digoxin toxicity
Target enzyme	Acetylcholinesterase	Pyridostigmine	Neurotoxicity
Receptor	Dopamine D <sub>3</sub> receptor	Chlorpromazine	Tardive dyskinesia
Ion channel	Delayed rectifier potassium channel ( $I_{Kr}$ )	Clarithromycin	Prolonged QT interval and torsades de pointes

adverse drug reactions, polymorphisms in both pharmacokinetic and pharmacodynamic parameters can act as predisposing factors (Table 30.4).

To date, most attention has focused on genetically mediated deficiencies of the drug-metabolizing enzymes (Park, 1986; Pirmohamed and Park, 1996). A drug metabolized by this pathway will show reduced elimination from the body with a consequent increase in half-life. This will lead to dose-dependent toxicity; a typical example is neutropenia with azathioprine in patients deficient in the enzyme thiopurine methyltransferase (Lennard *et al.*, 1982).

The role of genetic variation in the metabolism of warfarin by CYP2C9 has attracted a great deal

of attention recently. Warfarin is the oral anticoagulant of choice in the UK (Hart *et al.*, 1998). The number of patients attending anticoagulant clinics has doubled over the last 15 years or so, largely because of its use in atrial fibrillation. The major risk of warfarin treatment is hemorrhage, with an incidence of 8–26 per 100 patient-years (Petty *et al.*, 1999); this is related to the intensity of anticoagulation. Minimization of the risk of bleeding depends on accurate clinical prediction of dosage requirements during warfarin therapy. However, this is difficult since there is 20-fold inter-individual variability in the dose necessary to maintain the international normalized ratio (INR) within a target range.

The S-enantiomer of warfarin, which is predominantly responsible for the anticoagulant effect, is metabolized by CYP2C9 (Rettie *et al.*, 1992). Polymorphisms in the *CYP2C9* gene result in at least two allelic variants, *CYP2C9\*2* (Arg<sub>144</sub>→Cys), and *CYP2C9\*3* (Ile<sub>359</sub>→Leu) (Furuya *et al.*, 1995), both of which have been shown to decrease warfarin clearance *in vitro* (Haining *et al.*, 1996; Takahashi *et al.*, 1998) and *in vivo* (Takahashi *et al.*, 1998). Clinically, these variants have been shown to be associated with a reduced warfarin dose requirement, greater difficulty in initiating warfarin treatment, and an increased risk of bleeding (Aithal *et al.*, 1999). CYP2C9 genotype also seems to be important with respect to warfarin-related bleeding, but the association is not as strong as that observed with dose (Sanderson *et al.*, 2005). Polymorphisms in the gene encoding vitamin K epoxide reductase complex 1 (*VKORC1*), the target for the action of warfarin, also determine dose requirements (Rieder *et al.*, 2005; Sconce *et al.*, 2005; Wadelius *et al.*, 2005). Indeed, the effect of *VKORC1* seems to be quantitatively greater than that of *CYP2C9*. A limited subset of environmental determinants (including age) and polymorphisms in the *VKORC1* and *CYP2C9* genes account for approximately 50–55% of the variance in warfarin dose requirements (Rieder *et al.*, 2005; Sconce *et al.*, 2005; Wadelius *et al.*, 2005). The International Warfarin Pharmacogenetics Consortium (IWPC) (International Warfarin Pharmacogenetics *et al.*, 2009) has developed a dosing algorithm; the algorithm, or modifications thereof, is being tested in randomized controlled trials in Europe (EU-PACT) (van Schie *et al.*, 2009) and the USA (COAG) (French *et al.*, 2010), the results of which are due to be reported in the near future.

## DRUG INTERACTIONS AND ADVERSE DRUG REACTIONS

Patients on polytherapy are more likely to have type A reactions. The likelihood of developing an adverse interaction increases with the number of drugs prescribed (D'Arcy, 1986). To date, this has largely been a problem in the elderly where polypharmacy is prevalent (Williamson and Chopin, 1980), but is becoming increasingly frequent in

younger patients with chronic diseases such as AIDS, where patients may be on 6–10 different drugs (Bayard *et al.*, 1992). An Australian study showed that 4.4% of all adverse drug reactions resulting in hospital admission were due to drug interactions (Stanton *et al.*, 1994), while a study in the UK showed that one in six of all adverse reactions causing hospital admission were due to interactions (Pirmohamed *et al.*, 2004).

Drug interactions due to effects on metabolic pathways may either be due to enzyme induction or enzyme inhibition (Brodie and Feely, 1991). Enzyme induction usually leads to increased metabolism of the drug and thus increases drug clearance. This will lead to reduced drug efficacy rather than drug toxicity (unless the adverse reaction is due to a metabolite rather than due to the parent drug). Enzyme inhibition, on the other hand, is more likely to lead to type A adverse drug reactions since the clearance of the affected drug is reduced; this is particularly likely when the affected drug has a narrow therapeutic index (Brodie and Feely, 1991). Indeed, enzyme inhibitory drug interactions have resulted in regulatory action in a number of instances. An important example was the interaction between the CYP3A4 inhibitors ketoconazole and erythromycin and the nonsedating antihistamine terfenadine (Konig *et al.*, 1992; Woosley *et al.*, 1993). This resulted in decreased conversion of terfenadine to its active metabolite (now marketed as fexofenadine). Terfenadine has been shown to affect the delayed rectifier potassium current (Chen *et al.*, 1991), which results in prolongation of Q-T interval, torsades de pointes, and sudden death. A similar interaction with cisapride and CYP3A4 inhibitors (Michalets and Williams, 2000) has also resulted in regulatory action against cisapride.

A new mechanism of adverse interaction involves drug transporters in the disposition of drugs. Many drug transport proteins are present on membranes, some of which are responsible for drug influx, some are responsible for drug efflux, while others can transport in both directions. Most of the focus to date has been on P-glycoprotein (Pgp), which is encoded by the *MDRI* gene. Overexpression of Pgp is one of the mechanisms responsible for resistance of tumors to chemotherapy (Germann, 1996). However, Pgp is also responsible for the transport

of a number of other drugs, including digoxin. Digoxin does not undergo any significant degree of metabolism, but interacts with drugs such as quinidine, verapamil, and amiodarone, all of which can precipitate digoxin toxicity. The mechanism of this interaction involves inhibition of Pgp, thereby reducing efflux of digoxin from the gut and kidney (Fromm *et al.*, 1999). As knowledge of the transporters and their drug substrates increases, it is likely that this will be identified as the mechanism underlying many adverse drug interactions.

### DRUG-FOOD INTERACTIONS

Food substances can also interact with drugs, leading to severe, and sometimes life-threatening, adverse reactions. The most famous example of this is with the irreversible monoamine oxidase inhibitors, such as phenelzine, which can interact with foods high in tyramine content, such as cheeses and red wine (Sathyanarayana Rao and Yeragani, 2009). More recently, there has been increasing concern about grapefruit juice and its ability to inhibit the metabolism of drugs metabolized by CYP3A4. Grapefruit juice contains 6',7'-dihydroxybergamottin, which can act as an irreversible inhibitor of CYP3A4 in the small intestine, increasing systemic bioavailability and the AUC of certain drugs, including simvastatin, nifedipine, nicardipine, nilotinib, and ciclosporin. Because 6',7'-dihydroxybergamottin acts as a suicide inhibitor of intestinal CYP3A4, new enzyme has to be synthesized, and thus the effect of one glass of grapefruit juice can last for up to 3 days (Pirmohamed, 2013).

### TYPE B OR IDIOSYNCRATIC ADVERSE DRUG REACTIONS

Idiosyncratic adverse reactions are less common than the pharmacological adverse reactions, but are as important, if not more so, because they are often more serious and account for many drug-induced deaths. The possible mechanisms of idiosyncratic adverse effects (Park *et al.*, 1992) are listed in Table 30.5. The toxic reactions may affect many organ systems either in isolation or in combination (Table 30.6).

Table 30.5 The mechanisms of type B or idiosyncratic adverse drug reactions.

Mechanism	Example
Pharmaceutical variation	Eosinophilia–myalgia syndrome with L-tryptophan
Receptor abnormality	Malignant hyperthermia with general anesthetics
Abnormal biological system unmasked by drug	Primaquine-induced hemolysis in patients with G6PD deficiency
Abnormalities of drug metabolism	Isoniazid-induced peripheral neuropathy in slow acetylators
Immunological	Penicillin-induced anaphylaxis
Drug–drug interactions	Increased incidence of isoniazid hepatitis with concomitant administration of rifampicin
Multifactorial	Halothane hepatitis

Taken from Park *et al.* (1992). Reproduced with permission of John Wiley.

Type B ADRs have been characterized as being dose independent (Table 30.2), or rather there is no simple relationship between dose and the occurrence of toxicity (Park *et al.*, 1998). Certainly, evaluation of patients with and without hypersensitivity to a particular compound shows very little difference in doses received; indeed, in the patients with hypersensitivity, the doses may have been lower since the drug had to be withdrawn. Furthermore, even within the hypersensitive group, there is little relationship to the occurrence and severity of toxicity and the dose administered. However, intuitively, there must some kind of dose–response relationship since if the patient had not received the drug they would not have developed the hypersensitivity reaction.

Where the type B ADR is mediated by the formation of chemically reactive metabolites (CRMs) through metabolism by P450 enzymes (a process termed bioactivation) (Park *et al.*, 1998), a relationship may exist with the “internal dose”; that is, the concentration of the toxic metabolite formed in the body. However, since these metabolites by definition are unstable, it has not been possible with the

Table 30.6 Examples of organs affected by type B or idiosyncratic adverse drug reactions.

Organ system	Type of reaction	Drug examples
Generalized reaction	Anaphylaxis	Penicillins
Generalized reaction	Hypersensitivity	Temafloxacin
Skin	Toxic epidermal necrolysis	Nonsteroidal antiinflammatory drugs
Liver	Hepatitis	Halothane
Hematological system	Aplastic anemia	Remoxipride
	Agranulocytosis	Clozapine
	Hemolysis	Nomifensine
Central nervous system	Guillain–Barré syndrome	Zimeldine
Kidney	Interstitial nephritis	Penicillins
Lung	Pneumonitis	Dapsone
Heart	Cardiomyopathy	Tacrolimus
Reproductive toxicity	Etretinate	Various fetal abnormalities

currently available technologies to evaluate the dose–response relationship. The situation is further compounded by the fact that the different sources of variation in the human body may all have a different dose–response relationship. Nevertheless, evidence for the existence of such a dose–response relationship can be gleaned from clinical situations where different doses have to be given to the same group of patients in different circumstances. For example, in HIV-positive patients, the anti-infective agent co-trimoxazole has to be given at low doses for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) (960 mg once daily), while for acute treatment of PCP a much higher dose (up to 8 g/day) may be administered. The frequency of hypersensitivity reactions is lower with the prophylactic dose (30%) than with the acute dose, where rates as high 80% have been reported (Carr and Cooper, 1995; Pirmohamed and Park, 1995). Similarly, a risk factor for statin-induced myopathy is the concomitant administration of an interacting drug that increases the overall exposure to the statin (Floyd *et al.*, 2012).

## THE ROLE OF DRUG METABOLISM IN TYPE B ADVERSE DRUG REACTIONS

In general, drug metabolism can be considered to be a detoxification process, in that it converts therapeutically active compounds to inactive metabolites, which can then be excreted harmlessly from

the body. This process may require one or more than one drug-metabolizing enzyme, which may be a phase I and/or phase II enzyme (Woolf and Jordan, 1987) (Figure 30.2). A drug may undergo sequential phase I and phase II metabolism or, alternatively, it may only undergo either phase I or phase II metabolism (Tephly and Burchell, 1990).

In certain circumstances, the drug-metabolizing enzymes can convert a drug to a toxic CRM, a process termed bioactivation (Pirmohamed *et al.*, 1994, 1996) (Figure 30.2). Bioactivation may represent less than 1% of the overall metabolism of a drug. The body is equipped with formidable defense mechanisms, and in most cases the CRM will be detoxified (a process that can be termed bioinactivation) before it can initiate tissue damage. Indeed, it is possible that most therapeutically used drugs undergo some degree of bioactivation, but do not cause toxicity because the amount of toxic metabolite formed is below a “toxic” threshold or it is promptly detoxified. Both phase I and phase II enzymes can cause drug bioactivation, but in most cases it is the former (i.e., the cytochrome P450 enzymes) that are responsible (Pirmohamed *et al.*, 1994).

Inadequate detoxication of a CRM is often the first step in the initiation of idiosyncratic drug toxicity (Park *et al.*, 1992, Pirmohamed *et al.*, 1994). This may occur if there is an imbalance between drug bioactivation and bioinactivation pathways. Tissue-specific expression of enzymes involved in drug bioactivation and drug detoxication may lead

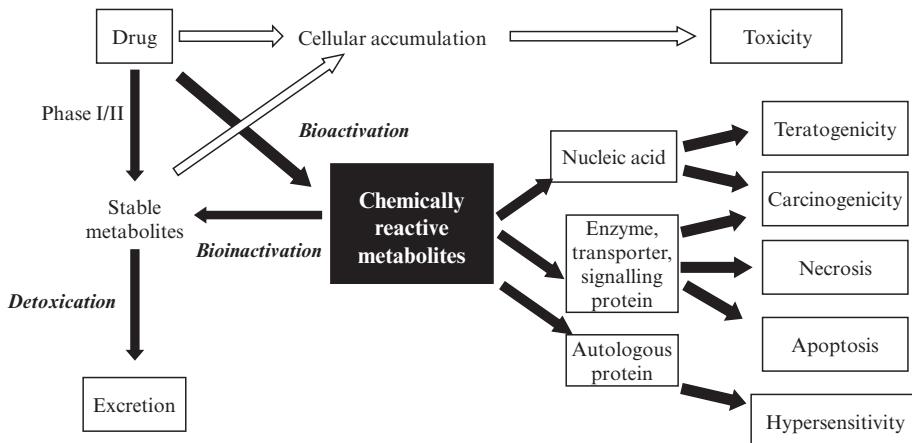


Figure 30.2 The role of metabolism in drug toxicity. Decrease in metabolism can lead to increased drug concentration and dose-dependent toxicity (which may also be due to cellular accumulation). The drug may undergo bioactivation to form CRMs, which if not adequately bioinactivated may bind to various cellular macromolecules and lead to different forms of toxicity.

to a selective imbalance in that tissue, resulting in tissue-selective toxicity (Park *et al.*, 1995). An imbalance may be the consequence of a genetically determined deficiency of an enzyme or, alternatively, it may be acquired as a result of environmental factors such as infection, diet, or concomitant drug intake. It is important to note that inadequate detoxification of a CRM, although an important first step in the occurrence of toxicity, is not necessarily the ultimate step (Pirmohamed *et al.*, 1996). Other factors, such as tissue repair enzymes, immune responsiveness, and the biochemical processes that modulate tissue injury, may all serve to determine not only whether idiosyncratic toxicity occurs, but also its severity.

An inadequately detoxified CRM can combine with or damage cellular macromolecules such as proteins and nucleic acids and result in various forms of toxicity, including teratogenicity, carcinogenicity, cellular necrosis, and hypersensitivity (Park *et al.*, 1995) (Figure 30.2). Binding of a CRM to nucleic acid may result in teratogenicity or carcinogenicity (Figure 30.2).

Binding to cellular macromolecules may result in either direct or immune-mediated toxicity (Pirmohamed *et al.*, 1994) (Figure 30.2). With direct toxicity, binding of the CRM to a protein will interfere with its normal physiological function, leading to

cellular necrosis. It has also been suggested that CRM can act as a hapten and initiate an immune reaction that may be due to a specific humoral (antibody) response, a cellular response (T lymphocytes), or a combination of both (Park *et al.*, 1987, 1998, 2001; Pohl *et al.*, 1988; Naisbitt *et al.*, 2000a). This has been postulated to be the pervading mechanism underlying penicillin allergy, where the  $\beta$ -lactam ring is chemically unstable, opens up, and forms covalent bonds with lysine residues on proteins, leading to an immune response in susceptible individuals. The factors that determine what type of toxicity is mediated by a CRM are poorly understood, but are likely to include (Gillette *et al.*, 1984; Park *et al.*, 1987; Boelsterli, 1993):

- the relative stability of the CRM, and thus its reactivity;
- the half-life of any drug–protein adducts that are formed and their concentration within the cell;
- the epitope density – that is, the number of groups of the CRM that are covalently bound to a protein molecule; and
- the nature, physiological function, and subcellular site of the carrier protein to which the CRM binds.

In most cases, the differentiation between these two forms of idiosyncratic toxicity is largely empirical, being based on symptomatology; for example, the occurrence of manifestations such as rash, fever, lymphadenopathy, and eosinophilia all suggest drug hypersensitivity (Pessayre and Larrey, 1988; Pirmohamed *et al.*, 1998). The lack of laboratory methodology by which to make a definitive diagnosis largely reflects our ignorance of the mechanism of toxicity in most cases of idiosyncratic toxicity.

#### PARACETAMOL: AN EXAMPLE OF A DRUG THAT CAUSES TOXICITY THROUGH THE FORMATION OF A CHEMICALLY REACTIVE INTERMEDIATE

For a number of drugs that undergo metabolism, CRM will be formed irrespective of the dose of the drug (Pirmohamed *et al.*, 1996). When a drug is taken in therapeutic dosage, any toxic metabolite formed will be detoxified by normal enzymatic or nonenzymatic cellular defense mechanisms. An imbalance between bioactivation and bioinactivation leading to toxicity may, however, be created by taking a drug overdose. This will lead to the formation of large amounts of CRM, overwhelm the cellular detoxification capacity, and lead to cell damage. The clearest example of this is paracetamol, which causes hepatotoxicity when taken in overdosage, and still causes about 160 deaths per year in the UK (Bray, 1993). The occurrence of liver damage with paracetamol and its severity is a function not only of the dose but also of various host factors (Pirmohamed *et al.*, 1994). Indeed, paracetamol hepatotoxicity has been reported with therapeutic drug use. For example, a study in 67 alcoholics who had sustained liver injury after paracetamol ingestion showed that 40% had taken less than 4 g/day (the maximum recommended therapeutic dose), while another 20% had taken between 4 and 6 g/day (which is also regarded as a nontoxic dose) (Zimmerman and Maddrey, 1995).

In therapeutic dosage, paracetamol is largely metabolized by phase II processes (glucuronidation and sulfation) to stable metabolites, but between 5 and 10% also undergoes P450 metabolism to the toxic *N*-acetyl *p*-benzoquinoneimine (NAPQI)

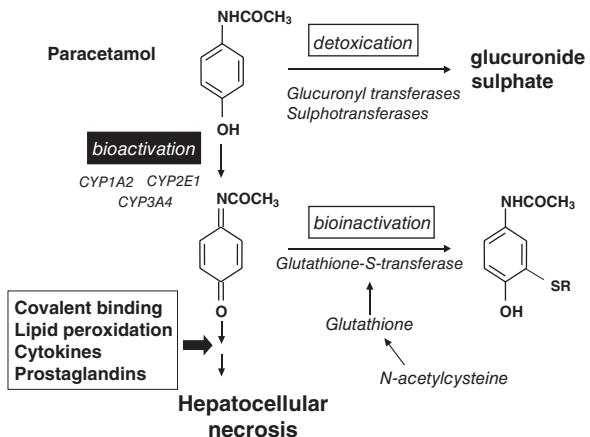


Figure 30.3 The role of metabolism in the hepatotoxicity associated with paracetamol.

metabolite (Nelson, 1990) (Figure 30.3). This is detoxified by cellular glutathione. In overdosage, saturation of the phase II metabolic pathways results in a greater proportion of the drug undergoing bioactivation. This ultimately leads to depletion of cellular glutathione and allows the toxic metabolite to bind to hepatic proteins, resulting in hepatocellular damage (Nelson, 1990). The use of *N*-acetylcysteine in the treatment of paracetamol overdosage illustrates the important point that elucidation of the mechanism of drug toxicity can lead to the development of rational therapies that will prevent the toxicity. Alcoholics show increased susceptibility to paracetamol overdosage because excess alcohol consumption results in depletion of glutathione (Lauterburg and Velez, 1988) and induction of the P450 isoform CYP2E1 (Raucy *et al.*, 1989). Studies in knockout mice have shown that CYP2E1 is the primary isoform involved in the bioactivation of paracetamol (Lee *et al.*, 1996).

Although experiments with transgenic mice have shown that in the absence of phase I oxidative pathways, and therefore of NAPQI formation, hepatotoxicity does not occur, the precise pathway leading to liver damage is still unclear (Gibson *et al.*, 1996). Several mechanisms have been proposed, including effects on plasma membrane  $\text{Ca}^{2+}$  pumps (Tsokos-Kuhn, 1989), which can lead to  $\text{Ca}^{2+}$ -induced DNA damage (Ray *et al.*, 1990), mitochondrial damage (Meyers *et al.*, 1988), resulting in glutathione

depletion and oxidative stress (Jaeschke, 1990), and apoptosis (Ray *et al.*, 1996). It has also been shown that Fas antisense oligonucleotide protects mice from paracetamol toxicity, suggesting that the ultimate cytotoxic event involves more than simply necrosis, and that cells of the immune system may be recruited in the inflammatory response (Zhang *et al.*, 2000). Interestingly, several studies have revealed that cells exposed to chemical or oxidant stress will respond with an orchestrated and robust transcriptional response aimed at detoxifying the offending chemical and preventing or repairing cellular damage (Moinova and Mulcahy, 1998, 1999; Hayes *et al.*, 1999). If unsuccessful, the culmination of this response, known as the antioxidant response, is to commit the cell to suicide through apoptosis. The target genes for the antioxidant response encode a set of enzymes and other proteins which scavenge free radicals, neutralize electrophiles, or upregulate the critical cellular thiol, glutathione. Glutathione depletion caused by a range of chemicals leads to upregulation of c-jun and c-fos mRNA, and enhances AP-1 DNA binding activity (Kitteringham *et al.*, 2000). This response was also accompanied by induction of  $\gamma$ -glutamyl cysteine synthetase. Another important mechanism of cell protection involves the nuclear translocation of redox-sensitive transcription factors such as Nrf-2, which "sense" chemical danger and orchestrate cell defense. Importantly, it has been observed that nuclear translocation occurs at nontoxic doses of paracetamol and at time-points before overt toxicity is observed. However, with increasing doses of acetaminophen, there is progressive dislocation of nuclear translocation, transcription, translation, and protein activity as the rate of drug bioactivation overwhelms cell defense through the destruction of critical proteins – at least 31 of these critical proteins have been identified (Park *et al.*, 2005).

More recently, there has been increasing interest in the development of novel, mechanism-based biomarkers that could be used as markers of liver injury. Thus, microRNA-122 (high liver specificity), high mobility group box-1 (marker of necrosis), full-length and caspase-cleaved keratin-18 (markers of necrosis and apoptosis), and glutamate dehydrogenase (marker of mitochondrial dysfunction) have been evaluated in patients who had taken a para-

cetamol overdose. These novel biomarkers outperformed alanine transaminase, INR, and plasma acetaminophen concentration in predicting acute liver injury from paracetamol (Antoine *et al.*, 2013).

## THE ROLE OF THE IMMUNE SYSTEM IN TYPE B ADVERSE DRUG REACTIONS

Based on clinical criteria, it has been postulated that many idiosyncratic adverse drug reactions are immune mediated (Park *et al.*, 1998; Pirmohamed *et al.*, 1998). Research into this area is now providing some direct evidence to support the clinical impression.

There are several possible mechanisms by which drugs lead to immune-mediated adverse reactions, the oldest of which is the hapten hypothesis (Park *et al.*, 1998) (Figure 30.2). Central to the hapten hypothesis is the assumption that small molecules such as drugs (<1000 Da) can be recognized as immunogens (i.e., a substance capable of eliciting a specific immune response) only when they become covalently bound to an autologous high molecular weight (>50 000 Da) macromolecular carrier such as a protein (Park *et al.*, 1987). The term hapten has been coined to describe such substances that are not immunogenic *per se* but become immunogenic when conjugated to a macromolecular carrier (this has been termed signal 1). The type of hypersensitive reaction will be partly determined by the nature of the immune response and the site of antigen formation. The best understood reactions are the type I hypersensitivity reactions induced by penicillins and cephalosporins and mediated by IgE antibodies directed against a drug hapten conjugated to protein (Weiss and Adkinson, 1988; Pirmohamed *et al.*, 1994). Severe anaphylactic reactions occur in only a minority of patients (1 in 2000); atopic patients are at increased risk, although the genetic basis of this and of the IgE response to penicillins remains to be elucidated.

Less well understood are the immunological mechanisms that underlie severe skin reactions such as Stevens–Johnson syndrome (SJS) and immunoallergic hepatitis. There is clear chemical evidence from *in vitro* studies that the drugs associated with these reactions can undergo oxidative metabolism to CRMs that can haptenate proteins

(Park *et al.*, 1995). In addition, both humoral and cell-mediated responses directed against drug-induced antigen have been detected in patients; for example, in halothane hepatitis (Pohl *et al.*, 1990). With some compounds, the immune response seems to be directed predominantly towards an autoantigen. For example, in tienilic acid-induced hepatitis, patients have circulating autoantibodies directed against the P450 isoform (CYP2C9), which is responsible for the bioactivation of tienilic acid (Beaune and Bourdi, 1993).

The fundamental concept that protein conjugation is an obligatory step in the process of immune recognition of drugs has been challenged by the pI (pharmacological interaction) hypothesis, prompted by the observation that T cell clones from patients hypersensitive to a number of drugs undergo proliferation in an antigen-processing-independent (but major histocompatibility complex (MHC)-restricted) manner (Schnyder *et al.*, 1997; Zanni *et al.*, 1998). This requires labile, reversible binding of drug to the MHC complexes on antigen-presenting cells. The presence of T-cell clones that proliferate only in response to parent drug rather than metabolite and the rapid downregulation in expression of the T-cell receptor upon stimulation are consistent with this mechanism.

More recently, work with the anti-HIV drug abacavir has led to new insights into the mechanism by which drugs may induce hypersensitivity reactions. Abacavir hypersensitivity is strongly associated with HLA-B\*57:01 (see below); binding of abacavir to the HLA cleft leads to a shift in the peptide repertoire with an increase in peptides with isoleucine/leucine occupying the C-terminal region (Illing *et al.*, 2012). The underlying assumption is that this leads to the presentation of novel self-proteins such that an immune response is set up against self (Illing *et al.*, 2013). However, further work is required to confirm this hypothesis, in particular the suggestion that the reaction is against novel self-antigens.

Irrespective of the mechanism of antigen presentation, T cells are of fundamental importance in the immune response against a drug (Naisbitt *et al.*, 2000a). The interaction between the T cell and the drug (antigen) in the groove of the MHC governs the immune response. MHC class I molecules bind

peptides of 8–10 amino acids and present to CD8<sup>+</sup> T-cells (Pamer and Cresswell, 1998). MHC class II molecules present longer peptide molecules (13–17 amino acids) to CD4<sup>+</sup> cells (Jensen, 1997). While class I molecules are found on all cell surfaces, class II molecules are only expressed on specialized antigen-presenting cells such as macrophages, but can become expressed on other cells such as keratinocytes in the presence of pro-inflammatory cytokines such as interferon gamma (Pichler and Yawalkar, 2000). The nature of the immune response is governed by differentiation of T cells into T helper-1 ( $T_{H1}$ ), T helper-2 ( $T_{H2}$ ), T cytotoxic-1 ( $T_{C1}$ ), or T cytotoxic-2 ( $T_{C2}$ ) subsets.  $T_{H1}$  and  $T_{C1}$  cells mediate cytotoxicity and local inflammatory reactions, while  $T_{H2}$  and  $T_{C2}$  cells stimulate B-cell-dependent antibody production (Romagnani, 1999).

It is important to note that the presence of an antigen (i.e., signal 1) in the absence of co-stimulatory molecules will lead to tolerance and T cell apoptosis (Naisbitt *et al.*, 2000a). Although the role of surface molecules such as B7.1 and B7.2 as co-stimulatory molecules has long been known, the importance of cytokines has only been recognized recently. In addition to signal 1, two other signals are required to stimulate a full immune response (Curtsinger *et al.*, 1999). Signal 2 is represented by a series of pro-inflammatory cytokines such as IL-2, TNF- $\alpha$ , and IFN- $\gamma$  that act indirectly on antigen-presenting cells to upregulate the expression of co-stimulatory molecules. Signal 3 represents polarizing cytokines that act directly on T cells. It is known that  $T_{H1}$  cells produce IL-12 and IFN- $\gamma$ , which promote the activation of macrophages and cell-mediated immunity. By contrast,  $T_{H2}$  cells produce IL-4 and IL-13; these provide help for the humoral immune response by promoting IgG to IgE class switching.

An interesting hypothesis termed the danger hypothesis has been proposed in the field of immunology to explain the basis of self-tolerance (Matzinger, 1994; Anderson and Matzinger, 2000; Gallucci and Matzinger, 2001). This can also be applied to the mechanism of drug hypersensitivity (Park *et al.*, 1998; Utrecht, 1999). This hypothesis states that the immune system responds to most antigens with tolerance, and only in the presence of a danger signal will presentation of an antigen

result in an immune response. The nature of the danger signals has not been accurately defined, but pro-inflammatory and polarizing cytokines, intracellular contents resulting from cell necrosis and exogenous proteins including those derived from viruses, are all potential candidates (Gallucci and Matzinger, 2001). With respect to drug hypersensitivity, it can be hypothesized that the CRM may not only provide signal 1 (by conjugating with a protein), but it could also provide the co-stimulatory signals 2 and 3 by activation of signaling pathways linked to oxidative stress and protein damage, including the secretion of cytokines (Park *et al.*, 2001). Furthermore, the hypothesis also allows the possibility that the co-stimulatory molecules are completely independent of the drug, and could be, for example, concomitant viral infections (see below).

### THE ROLE OF VIRUSES IN TYPE B ADVERSE DRUG REACTIONS

There is increasing evidence that concomitant virus infections can predispose to the development of idiosyncratic adverse drug reactions, particularly those reactions that are thought to be immune mediated. The mechanism of this is unclear; but as postulated above, the viruses may be acting as a source of danger signal.

Evidence for the role of viruses first came from the observation that the use of ampicillin in patients with active Epstein–Barr virus (EBV) infection (i.e., infectious mononucleosis) results in a rash in 95% of patients (Sullivan and Shear, 2001). Another member of the herpes virus family, human herpesvirus 6 (HHV6), has recently been implicated in hypersensitivity reactions associated with a number of drugs, including sulfasalazine (Suzuki *et al.*, 1998). The most comprehensive study in this area was undertaken in patients with drug reaction with eosinophilia and systemic symptoms due to carbamazepine (CBZ), allopurinol, and sulfamethoxazole (Picard *et al.*, 2010). EBV, HHV6 and HHV7 reactivation was seen in 76% of the patients, while their T cells showed increased secretion of cutaneous homing markers, TNF- $\alpha$ , and IFN- $\gamma$ . Furthermore, the CD8 $^{+}$  T cells from these patients recognized several EBV epitopes, while culprit

drugs triggered production of EBV from patient B cells. Further work is required to understand the role of viral reactivation in the pathogenesis of such reactions, and to rationalize it with the new mechanisms of antigen presentation, such as the changes in peptide repertoire profile.

Perhaps, the most striking association between viral infection and drug hypersensitivity has been observed in HIV-infected individuals. These patients had a higher frequency of hypersensitivity reactions in the pre-highly active antiretroviral therapy era with numerous anti-infective drugs, including co-trimoxazole, sulfadiazine, dapsone, clindamycin, primaquine, and thioacetazone (Koopmans *et al.*, 1995; Pirmohamed and Back, 2001). This has been best shown with co-trimoxazole that is used for the treatment of PCP. Approximately 50% of patients being treated acutely for PCP developed skin rashes, while when used for prophylaxis the figure was 30% (van der Ven *et al.*, 1991). This contrasts with a frequency of 3% in HIV-negative individuals (van der Ven *et al.*, 1991). A deficiency of thiols such as glutathione and cysteine was suggested to be responsible for the increase in susceptibility of HIV-positive patients (van der Ven *et al.*, 1991; Koopmans *et al.*, 1995). HIV-positive patients have a lower capacity to detoxify the toxic nitroso metabolite of sulfamethoxazole in the presence of plasma cysteine deficiency (Naibritt *et al.*, 2000b). However, the fact that prophylactic N-acetylcysteine did not prevent co-trimoxazole hypersensitivity (Walmsley *et al.*, 1998) suggests that the reasons for the higher frequency are likely to be more complex and multifactorial, and include the dose of the drug, changes in drug metabolizing capacity (both in bioactivation and bioinactivation), and immune dysregulation (Pirmohamed and Park, 2001b). In addition, HIV itself may act as a source of a danger signal (Park *et al.*, 1998; Uetrecht, 1999; Pirmohamed and Park, 2001b; Sullivan and Shear, 2001).

### GENETIC PREDISPOSITION TO TYPE B ADVERSE DRUG REACTIONS

Type B adverse drug reactions have typically been defined to be host dependent (Rawlins and Thomp-

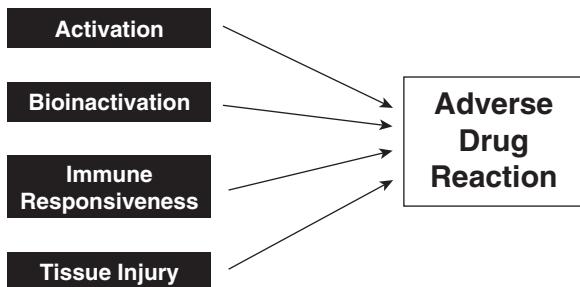


Figure 30.4 Type B or idiosyncratic drug reactions have a multifactorial etiology. Variation, which may be genetically determined, in drug *bioactivation* and *bioinactivation*, can lead to persistence of a CRM. If the adverse reaction is immune mediated, the binding of the CRM will lead to the formation of an antigen, which will be recognized by the body's immune system, resulting in an *immune response* and *tissue injury*.

son, 1991). However, the nature of this host dependency has not been defined for most drugs, although genetic factors have long been suspected. Indeed, genetic factors are also important for type A reactions, as discussed above. It is becoming clear that the genetic basis of adverse drug reactions, in most cases, is going to be multigenic (dependent on a combination of genes) and multifactorial (dependent on an interaction between genetic and environmental factors). This is going to make it difficult to unravel the genetic basis of adverse reactions and will require a concerted effort to collect suitable cases and controls as part of multicenter international collaborations (Pirmohamed and Park, 2001a).

The nature of the polygenic predisposition is unclear, but in general could theoretically be divided into several areas (Figure 30.4) as follows (Pirmohamed *et al.*, 1998; Park *et al.*, 2001; Pirmohamed and Park, 2001a):

- *Activation.* This involves activation of drug to CRMs. Bioactivation of drugs is largely mediated by cytochrome P450 enzymes, many of which have now been shown to be polymorphically expressed (Park *et al.*, 1995). Importantly, a deficiency of an enzyme will lead to reduced bioactivation of a drug and will act as a protective factor. No good examples have been identified to date. By contrast, amplification of a P450

isoform, as seen with CYP2D6 (*CYP2D6\*2xN*) (Ingelman-Sundberg *et al.*, 1999), would increase bioactivation, but again no good example has yet been identified.

- *Detoxification.* Absence or reduced activity of a detoxification enzyme would lead to a decrease in bioinactivation of the reactive metabolite (Pirmohamed and Park, 1999), and hence increase the possibility of the reactive metabolite interacting with important cellular macromolecules, resulting in different forms of toxicity. The best characterized example of this is the slow acetylator phenotype predisposing to hypersensitivity with co-trimoxazole in HIV-negative patients (Rieder *et al.*, 1991) and SLE with hydralazine and procainamide (Park *et al.*, 1992). There has also been interest in the role of the glutathione-*S*-transferase genes, many of which have been shown to be polymorphically expressed. However, although these gene polymorphisms may be important with respect to certain cancers, studies to date have not shown any association of the glutathione transferase gene polymorphisms with idiosyncratic drug reactions observed with co-trimoxazole (Pirmohamed *et al.*, 2000), CBZ (Leeder, 1998), and tacrine (Green *et al.*, 1995b; De Sousa *et al.*, 1998).
- *Immune response genes.* This is the process by which the body's immune system recognizes a drug/drug metabolite as being foreign or antigenic, and thereby mounts an immune response, conceived to be protective, but perversely leads to clinical manifestations typical of hypersensitivity. The genes encoding for immune responsiveness include MHC, T cell receptors, and co-stimulatory molecules. This is covered in more detail below.
- *Tissue injury genes.* This is the process by which an immune response is translated into tissue injury, the nature and extent of which can be counteracted by repair mechanisms that limit any tissue damage. Typical candidates include cytokines, chemokines, and prostaglandins. An example here is the association with IL4 and IL10 variant alleles and hepatotoxicity associated with the NSAID diclofenac (Aithal *et al.*, 2004).

Since the completion of the human genome project, there have been some striking findings in the MHC with respect to its role in the genetic predisposition to drug hypersensitivity. These are illustrated below with reference to two compounds, abacavir and CBZ, and further examples are provided in Table 30.7. However, it is important to bear in mind two important issues with reference to the MHC, which means that much more work is required in this area of the human genome. First, it is the most polymorphic region of the genome, and exhibits a high degree of linkage disequilibrium. Therefore, an association with one polymorphism does not necessarily mean that this is a causal association. Second, the MHC has been sequenced and initial findings suggest that over 60% of the genes in this area are of unknown function, with only 40% being involved in the immune response (The MHC Consortium, 1999).

#### ABACAVIR HYPERSENSITIVITY

Abacavir, an HIV-1 reverse transcriptase inhibitor, causes hypersensitivity, characterized by skin rash, gastrointestinal, and respiratory manifestations, in about 5% of patients (Hetherington *et al.*, 2001). These reactions can occasionally be fatal, particularly on rechallenge. Mallal *et al.* (2002) found a strong association between abacavir hypersensitivity and the haplotype comprising HLA-B\*5701, HLA-DR7, and HLA-DQ3 with an odds ratio (OR) of over 100. This association has now been shown in two other cohorts (Hetherington *et al.*, 2002; Hughes *et al.*, 2004a,b). The same association has also been shown in an African-American population despite the fact that the population frequency of the HLA-B\*57:01 allele is lower than in Caucasians (Saag *et al.*, 2008). The clinical utility of pre-treatment B\*57:01 testing has been shown in a prospective randomized controlled clinical trial (PREDICT-1) (Mallal *et al.*, 2008). *In vitro* studies have demonstrated that abacavir-treated antigen-presenting cells positive for HLA-B\*5701, but not the related alleles B\*5702 or B\*5801, can stimulate abacavir-specific CD8<sup>+</sup> T cell responses (Chessman *et al.*, 2008). The mechanistic basis of this association has been further strengthened through recent mass spectrometry studies, which have shown that

binding of abacavir leads to alteration in the peptide repertoire profile (Illing *et al.*, 2012). The drug label for abacavir has been altered by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA), which requires testing for HLA-B\*57:01 prior to the prescription of abacavir. Observational studies have shown that pre-prescription testing for HLA-B\*57:01 before the use of abacavir leads to a decrease in the incidence of abacavir hypersensitivity (Rauch *et al.*, 2006; Waters *et al.*, 2007). Furthermore, pre-prescription genotyping for HLA-B\*57:01 has also been shown to be cost-effective in the UK (Hughes *et al.*, 2004b), and subsequently in other countries (Schackman *et al.*, 2008; Kauf *et al.*, 2010; Nieves Calatrava *et al.*, 2010).

#### CARBAMAZEPINE HYPERSENSITIVITY

CBZ, a widely used anticonvulsant, causes rashes in up to 10% of patients, and in occasional cases this may be the precursor to the development of a hypersensitivity syndrome characterized by systemic manifestations such as fever and eosinophilia (Vittorio and Muglia, 1995; Leeder, 1998). Rarely, CBZ can induce blistering skin reactions, such as SJS and toxic epidermal necrolysis (TEN), two conditions associated with a high fatality rate (Rzany *et al.*, 1999). CBZ hypersensitivity is a T-cell-mediated disease (Brander *et al.*, 1995; Naissibett *et al.*, 2003). CBZ is metabolized to CRMs that have been implicated in the pathogenesis of hypersensitivity (Pirmohamed *et al.*, 1992), but the parent drug has also been shown to stimulate T cell proliferation *in vitro* (Naissibett *et al.*, 2003). To date, no polymorphisms in the drug-metabolizing enzyme gene polymorphisms have been associated with susceptibility to CBZ hypersensitivity (Gaedigk *et al.*, 1994; Green *et al.*, 1995a).

CBZ-induced SJS/TEN has shown a strong (OR > 1000) association with HLA-B\*15:02 in Han Chinese (Chung *et al.*, 2004; Hung *et al.*, 2006; Man *et al.*, 2007), Thai (Locharernkul *et al.*, 2008; Tasaneeyakul *et al.*, 2010), Malay (Ding *et al.*, 2010), and Indian (Mehta *et al.*, 2009) populations. However, it has not been shown to be important in Caucasians (Alfirevic *et al.*, 2006; Lonjou *et al.*, 2006, 2008) and Japanese (Kaniwa *et al.*, 2008; Ikeda

Table 30.7 Some of the reported HLA associations with drugs. Adapted from Alfirevic and Pirmohamed (2011).

Drug	Class of drug	HLA-allele	Population (reference)	Phenotype
Allopurinol	Uricosuric	B*5801	Han Chinese (Hung <i>et al.</i> , 2005), Thai (Tassaneeyakul <i>et al.</i> , 2009), Japanese (Kaniwa <i>et al.</i> , 2008), Malay (Ding <i>et al.</i> , 2010)	HSS, SJS/TEN
Carbamazepine	Antiepileptic	B*1502	Han Chinese (Chung <i>et al.</i> , 2004; Hung <i>et al.</i> , 2006; Man <i>et al.</i> , 2007), Thai (Locharernkul <i>et al.</i> , 2008; Tassaneeyakul <i>et al.</i> , 2010), Malay (Ding <i>et al.</i> , 2010), Indian (Mehta <i>et al.</i> , 2009)	SJS/TEN
		A*3101	Caucasian (McCormack <i>et al.</i> , 2011), Japanese (Ozeki <i>et al.</i> , 2011)	MPE, HSS, SJS/ TEN
Phenytoin	Antiepileptic	B*1502	Han Chinese (Man <i>et al.</i> , 2007), Thai (Locharernkul <i>et al.</i> , 2008)	SJS/TEN
Oxicam Sulfamethoxazole	NSAID Antibiotic	A2, B12 A29, B12, DR7	Caucasians (Roujeau <i>et al.</i> , 1987) Caucasians (Roujeau <i>et al.</i> , 1986)	SJS/TEN SJS/TEN
Abacavir	Antiretroviral	B*5701	Caucasians (Hetherington <i>et al.</i> , 2002; Hughes <i>et al.</i> , 2004b, Mallal <i>et al.</i> , 2002, 2008), African Americans (Saag <i>et al.</i> , 2008; Hughes <i>et al.</i> , 2009)	HSS
Aminopenicillins Nevirapine	Antibiotic Antiretroviral	A2, Drw52	Caucasians (Romano <i>et al.</i> , 1998)	HSS
		DRB1*01	Caucasian- Australian (Martin <i>et al.</i> , 2005)	Various, including MPE,
		DRB1*01	Caucasian-French (Vitezica <i>et al.</i> , 2008)	HSS, SJS/TEN,
		Cw8,B14	Caucasian-Italian (Littera <i>et al.</i> , 2006)	and DILI
		Cw8 B*3505 Cw4 C*04:01	Japanese (Gatanaga <i>et al.</i> , 2007) Thai (Chantarangsu <i>et al.</i> , 2009) Thai (Likanonsakul <i>et al.</i> , 2009)	
Aspirin	NSAIDs	DRB1*1302, DQB1*0609	Korean, Caucasian (Kim <i>et al.</i> , 2005; Palikhe <i>et al.</i> , 2008)	Aspirin hypersensitivity
Gold	Treatment of rheumatoid arthritis	DR5	Caucasians -Spanish (Rodriguez- Perez <i>et al.</i> , 1994)	MPE
Lamotrigine	Antiepileptic	B*5801, A*6801	Caucasians (Kazeem <i>et al.</i> , 2009)	HSS, SJS/TEN
Co-trimoxazole	Antibiotic	A30 B13 Cw6	Caucasians- Turkish (Ozkaya-Bayazit and Akar, 2001)	FDE
Feprazone Flucloxacillin Ximelagatran	Analgesic Antibiotic Antiplatelet agent	B22	Undefined (Pellicano <i>et al.</i> , 1997)	FDE
		B*5701	Caucasian (Daly <i>et al.</i> , 2009)	DILI
		DRB1*0701	Caucasian (Kindmark <i>et al.</i> , 2007)	DILI
Lumiracoxib	Antiarthritic drug	DQA1*02 DRB1*1501	Caucasian (Singer <i>et al.</i> , 2010)	DILI
Co-amoxiclav	Antibiotic	DQA1*0102 DRB1*1501	Caucasian (Hautekeete <i>et al.</i> , 1999; O'Donohue <i>et al.</i> , 2000)	DILI
Lapatinib Ticlopidine Diclofenac	Anticancer Antiplatelet NSAID	DQA1*0201	Caucasian (Spraggs <i>et al.</i> , 2011)	DILI
		A*3303	Japanese (Hirata <i>et al.</i> , 2008)	DILI
		DRB1*13	Caucasian (Daly and Day, 2009)	DILI

FDE: fixed drug eruption; DILI: drug-induced liver injury; HSS: hypersensitivity syndrome; MPE: maculopapular exanthema.

*et al.*, 2010) because of the very low population frequency of this HLA allele. A recent systematic review has shown that the overall OR of HLA-B\*15:02 in predisposing to SJS/TEN in the Chinese, Thai, and Malay population was 113 (95% confidence interval 51–251), and that 461 patients need to be tested to prevent one case of SJS/TEN (Yip *et al.*, 2012). The drug label for CBZ has been changed by several regulatory agencies, including the EMA and FDA. Apart from being ethnicity specific, the association with HLA-B\*1502 is phenotype specific, in that it is only valid for SJS/TEN, but has not been shown to be important for maculopapular exanthema and hypersensitivity syndrome (Hung *et al.*, 2006). The utility of HLA-B\*15:02 testing has also recently been shown in a prospective cohort study in Taiwan (Chen *et al.*, 2011): of the 4877 patients due to start on CBZ genotyped for HLA-B\*1502, the use of CBZ was avoided in 7.7% of patients who were positive for HLA-B\*1502, while those who were negative for this allele were given CBZ as per usual practice. After a follow-up of 3 months for all patients, no patients developed SJS, when at least 10 cases would have been expected.

A genome-wide association study has recently shown a strong association with CBZ hypersensitivity and HLA-A\*31:01 in Caucasian patients (McCormack *et al.*, 2011). Unlike the association with HLA-B\*15:02 in Chinese patients which was specific for SJS/TEN, the association with HLA-A\*31:01 seems to be important for all forms of cutaneous eruptions (maculopapular exanthema, hypersensitivity syndrome, and SJS/TEN). The association with HLA-A\*31:01 and CBZ hypersensitivity has now been replicated in Japanese (Ozeki *et al.*, 2011), South Korean (Kim *et al.*, 2011), and Canadian (Amstutz *et al.*, 2013) populations. Although the drug label for CBZ has been changed, the association with HLA-A\*31:01 is for information only. Prospective studies are likely to be needed before HLA-A\*31:01 testing can be implemented into routine clinical care.

## CONCLUSION

The importance of adverse drug reactions is often underestimated. They are common, can be

life threatening, and are unnecessarily expensive. Because of the wide range of drugs available, the manifestations of toxicity can be variable and affect any organ system. In fact, adverse drug reactions have taken over from syphilis and tuberculosis as the great mimics of other diseases. It is also likely that the pattern of toxicity is going to change with the introduction of new biotechnology products. It is therefore important for the prescribing clinician to be aware of the toxic profile of drugs they prescribe and to be ever vigilant for the occurrence of unexpected adverse reactions.

Both type A and type B adverse reactions are complex, and their prevention for future populations will depend on an understanding of their pathogenesis and exactly how a foreign chemical (i.e., drug) interacts with macromolecules within the body. Pharmacogenomic strategies have been proposed for the prevention of these reactions in the future by prediction of susceptible individuals (Roses, 2000). However, despite the hype surrounding the area, this is likely to be a long-term goal and will crucially depend on (a) the availability of accurately phenotyped patients, which for the rare reactions will necessitate multicenter international collaborations, (b) the demonstration that genotyping is clinically and cost effective, (c) an understanding of the mechanisms of the adverse reactions so that more targeted single nucleotide polymorphism profiling can be undertaken, and (d) most crucially, education of the end-users (i.e., clinicians), so that they understand the rationale for performing the tests and how to interpret the results.

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# 31

## Fatal Medication Errors and Adverse Drug Reactions

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### INTRODUCTION

The harms from the therapeutic use of drugs include adverse consequences from reactions to drugs, adverse interactions between drugs, and the harm that comes from medication errors.

A widely accepted definition of an adverse drug reaction (ADR) is (WHO, 1972)

a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.

Some difficulties with this are overcome by the following definition (Aronson and Ferner, 2005):

an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product; adverse effects usually predict

hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.

Medication errors (i.e., errors in prescribing, drawing up, and administering drugs) are a particularly important cause of drug-related harm, because they are potentially preventable. There are several suggested definitions. We have proposed the following:

a medication error is a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient (Ferner and Aronson, 1999, 2006).

“Failure” in this context signifies that the process has fallen below some attainable standard. This definition carries the important implication that such failures could be avoided if the attainable standard were in fact attained. A corollary is that

those ADRs that are categorized as “preventable” represent medication errors. When four proposed definitions of medication error were tested against scenarios of drug-related harm, only this definition exactly fitted the four test cases (Yu *et al.*, 2005).

## THE HARMS FROM ERRORS AND ADVERSE DRUG REACTIONS

ADRs and errors can cause serious harm and even death. However, fatal adverse events are relatively rare, and the proportion of fatal cases in most spontaneous reporting schemes is low. There is considerable uncertainty about both the incidence of fatal reactions and their likely causes.

Deaths that result from drug treatment have implications for patients, healthcare providers, and the healthcare system. There is a major focus, both in the literature and in the media, on deaths due to medication error, because they could, in an ideal world, have been avoided. The report from the Institute of Medicine in the USA, which extrapolated from information obtained in two relatively restricted hospital surveys, suggested that as many as 98 000 deaths a year in the USA were the result of “medical error” (Kohn *et al.*, 1999). Cases such as those in which patients died after the erroneous administration of intrathecal vincristine in place of intrathecal methotrexate have received wide press coverage and stimulated careful enquiry (Woods, 2001). The number of cases where criminal proceedings are brought against doctors when their patients die because of a medical error has also increased in England (Ferner, 2000; Ferner and McDowell, 2006). Paradoxically, this censoriousness has come at the same time as a realization that error is an inevitable part of the human condition, and that for processes to be safe, they have to be designed (“engineered”) to be robust in the face of human error (Reason, 2000). The most recent figures suggest that in England fewer doctors are being charged, but those convicted have received longer sentences (McDowell and Ferner, 2013). Ireland is unusual among common law countries in never having criminally prosecuted a healthcare professional for a fatal error which occurred in the course of their duty (Lyons, 2013).

Safety in aviation and healthcare have similarities; the realization that errors usually represent a combination of systems and human factors led to a call for a “no blame” culture in medicine as in aviation. This has gradually given way to calls for a “just blame” culture: “there is a need to acknowledge that individual accountability is not removed from a general no blame culture” (Donaldson, 2006).

A large study of medical records from 51 hospitals in New York state for patients treated in the year 1984, part of the classic Harvard Medical Practice Study, estimated that nearly 1% of patients suffered adverse events (not just medication errors) that were the result of negligence, as judged by a panel of physicians. By their assessment, negligence caused half of all deaths from iatrogenic harm; and of those who suffered negligent harm, a quarter died as a result (Brennan *et al.*, 1991).

## THE LITERATURE RELATING TO FATAL HARM FROM DRUGS

### STUDIES INVESTIGATING ADVERSE DRUG REACTIONS

Determining the frequency of ADRs is challenging, and the United States General Accounting Office (2000) has reported that “the magnitude of health risk [from drug-induced harm] is uncertain, because of limited incidence data”. A wide variety of study designs has been used by researchers to determine the nature and incidence of ADRs, and studies that have focused on deaths resulting from ADRs are described below.

#### Meta-Analyses

The widely cited meta-analysis by Lazarou *et al.* (1998) examined the evidence from 16 studies published between 1964 and 1995 and concluded that ADRs accounted for over 100 000 deaths in the USA in one year. This would mean that doctors and their treatments caused about 4% of all deaths. This study has, however, been criticized because there was a high risk of publication bias and a large

degree of heterogeneity between the studies, and the results were extrapolated from just 78 fatal ADRs.

Chyka (2000) examined two sources of data on the number of deaths attributed to ADRs in the USA. He compared death certificates and the Food and Drug Administration's (FDA's) spontaneous postmarketing surveillance system (MedWatch), using International Classification of Disease 9th Revision (ICD-9) codes to identify relevant death certificates, for the year 1995. The number of deaths recorded under appropriate ICD-9 codes resulting from ADRs was 206, whereas MedWatch tabulated 6894 fatalities. The proportions of men and women were similar, and the majority of deaths involved persons 60 years of age and older in both data sets. He noted that numbers of deaths reported in these data sets varied 34-fold and were up to several hundred-fold less than values based on extrapolations of data from surveillance programs. His conclusion was that better and more comprehensive data are needed to develop appropriate healthcare policies to improve drug safety. We strongly agree with this view.

#### Data from Spontaneous Adverse Drug Reaction Reporting Databases

Several authors have examined data from spontaneous ADR reporting schemes. For example, Clarkson and Choonara (2002) examined deaths reported to the Yellow Card scheme in the UK from 1964 to 2000 to establish the number and nature of fatal ADR reports regarding children under the age of 17 years. The number of reports of a fatal reaction, expressed as a percentage of all adverse reaction reports in children, fell from 8.9% in 1964–1965, and 1% in 1981–1985, to 0.37% in 1996–2000, suggesting major changes in reporting habits. A Yellow Card was submitted for 390 children who died throughout the entire period, and anticonvulsant medicines were recorded in 65 cases. As there are few details of concomitant disease, rates of prescribing, or the underlying fatality rate in pediatric patients with epilepsy, the data are hard to interpret.

In Canada, Liu *et al.* (2001) reviewed the reports of fatal ADRs submitted to the Ontario Medical

Association Adverse Drug Reactions Monitoring Program from 1990 to 1994. In this period, 7120 reports were submitted, of which 97 (1.4%) were fatal. The study by Bottiger *et al.* (1979) scrutinized the 11 596 ADR reports submitted to the Swedish Adverse Drug Reaction Committee over a 10-year period. From 1966 to 1975, 274 fatal ADRs were reported, with approximately 25–30 cases annually. The majority of the ADRs were associated with anti-inflammatory drugs, antibiotics and sulfonamides.

Leone *et al.* (2008) examined 38 507 cases in the Italian ADR database for spontaneous reports of drugs that caused or contributed to death, and examined records of 450 fatal ADRs, of which 159 were reported to be directly caused by the drug. Curiously, the commonest fatal ADR was anaphylaxis to ceftriaxone; the authors attributed this to the Italian penchant for administering antibacterial agents parenterally. As the authors acknowledge, spontaneous reporting schemes cannot accurately define either numerator or denominator. They comment on the relative absence of reports of deaths from gastrointestinal hemorrhage, which strongly suggests reporting bias.

One unusual aspect of the UK Yellow Card scheme is that, even before relaxation of the rules governing the status of the reporter, Coroners (medical examiners) have been permitted to report cases where ADRs are suspected to have caused or contributed to death. Over the 5 years 2006–2011, the Medicines and Healthcare Products Regulatory Agency (MHRA) received 35 reports from Coroners of suspected fatal ADRs. These reports seem considerably more detailed than the average spontaneous ADR report, as they are informed by evidence from Coronial inquests. Only five drugs figured more than once: varenicline (four); citalopram (three); amitriptyline (two); chloroquine (two); and methotrexate (two). Of these 13 deaths, nine were determined by Coroners to be due to suicide, sometimes because a suspicion remained that drug treatment may have led to suicidal thoughts. Where post-mortem concentrations of drug had been measured, these were sometimes interpreted in the light of known therapeutic concentrations, although there are pitfalls in such extrapolation (Ferner, 2008).

Data from spontaneous reporting schemes do, however, have manifold disadvantages when used to assess rates of fatal incidents – a task they are not designed to perform. Usually, the diagnostic criteria for an ADR or an error are at the discretion of the reporter, who will rarely have assessed causality or preventability in a formal way. A small but variable proportion of incidents are reported. These factors make the numerator uncertain. Prescribing data are usually not available, so the number of persons at risk is unknown, and so the denominators are also unknown. These problems are compounded when data are sought for a specific age group.

#### Data from Hospital Admissions

A study in Liverpool, one of the largest prospective surveys of its kind, examined over 18 000 acute admissions and classified 6.5% of them as consequences of ADRs. Of the total cohort, 0.15% were adjudged to be admitted with an ADR from which they died (Pirmohamed *et al.*, 2004). In France, a multicenter study by the French pharmacovigilance centers established, on the basis of a survey of over 3000 hospital admissions, that over 3% were the result of ADRs. The ADR was fatal in 0.12% of the admissions (Pouyanne *et al.*, 2000).

A computerized pharmaco-epidemiological surveillance system in Zurich was used to record adverse drug events prospectively and to categorize them as because of ADRs or errors. Of 6383 patients admitted between 1996 and 2000, 4.4% presented with an adverse drug event; and of these, one-third were the result of error. Two patients died from these errors (Hardmeier *et al.*, 2004).

These studies are of considerable interest but suffer from several general disadvantages. They do not refer to a defined population, so that the burden of ill health due to ADRs cannot be accurately estimated. Diagnosis of drug-induced disease is inevitably subjective and relies quite heavily on past experience. This in turn means that adverse events are ascribed too frequently to well-known ADRs and too rarely to reactions that are not well publicized. They also suffer from bias in attribution: simply because an event occurs in a patient taking a particular drug, and the event is known to be associated with the drug, is insufficient to prove a causal association in the specific instance. This is under-

lined by the fact that treatment with low-dose aspirin doubles the rate of gastrointestinal hemorrhage (Derry and Loke, 2000; Sørensen *et al.*, 2000). Put inversely, half of the episodes of gastrointestinal hemorrhage occurring in patients taking aspirin would not have been caused by the drug treatment.

#### Data from Surveillance Schemes

A surveillance study of children who died from ADRs identified only seven suspected cases in 13 months; an “expert panel” considered five of the deaths unlikely to be associated with the reported drug (Cheng *et al.*, 2007).

#### Fatal Cases of Adverse Drug Reactions

The examination of fatal cases can help to understand the incidence and nature of the most serious ADRs. Several other studies are now available in addition to our own previous studies of cases reported to the Coroner (Ferner and Whittington, 1994, 2002).

Juntti-Patinen and Neuvonen (2002) examined records from 1511 of 1546 fatal cases occurring during the year 2000 at the university hospital in Helsinki. They classified 75 deaths as probably or certainly because of drugs, of which cytotoxic drugs accounted for 23 cases and anticoagulants accounted for 20 cases (warfarin, 15). There were an additional 12 cases where death had possibly been related to cytotoxic or anticoagulant treatment.

An important prospective study from a department of medicine in a Norwegian hospital (Ebbesen *et al.*, 2001) classified the 732 deaths (of 13 992 admissions) over 2 years as directly or indirectly associated with drug therapy. Almost all the patients were admitted as acute medical emergencies. The authors adjudged 64 cases (9% of deaths, 0.5% of admissions) to be directly caused by drug therapy and a further 69 (9.5% of deaths, 0.5% of admissions) to be indirectly caused by drug therapy. The hospital served a population of about 300 000 people. A remarkable aspect of this study was that nearly 80% of all patients who died underwent post-mortem examination. The autopsy and post-mortem measurements of drug concentrations allowed a much clearer decision to be made on the potential involvement of drug therapy in the patient's decease. The authors believed that post-

mortem results pointed decisively towards a contribution from drug therapy in 75 of 133 cases where drug therapy was involved and decisively excluded drug therapy as a cause of death in 62 of the remaining 595 patients. The rate of adverse drug events, 9.5 per 1000 admissions, was high, whereas the overall mortality rate of 5.2% was in keeping with data from similar institutions. The authors concluded that post-mortem data are often decisive in the analysis of fatal ADRs, even though they are not part of standard causality assessment.

Of course, the examination of fatal cases does not necessarily overcome the problem of estimating the denominator (i.e., the size of population at risk). While hospital cases from a defined catchment area do allow some estimate to be made, many of the series of fatal cases fail to provide evidence that could estimate incidence.

### Population Studies

Studies in a defined population have the advantage that they allow the burden of disease to be assessed. A study based on the entire population of three counties in south-east Sweden examined 1574 deaths (of a total 11015 deaths) in 1 year using a register of causes of death, medical records, and medico-legal files. Only eight death certificates recorded an ADR, while the study identified 49 patients who had died of an ADR. Eighteen of them died from gastrointestinal hemorrhage and 14 from brain hemorrhage (Wester *et al.*, 2008). An analysis of all fatal ADRs reported to the Swedish Drug Information system over 10 years had found similar results, with hemorrhage causing over 60% of deaths, although warfarin was a more important cause than in the later series (Wester *et al.*, 2007). Of the 49 fatal ADRs in the population study, clinical experts evaluated seven (14%) as "preventable" – a figure corresponding to nearly 1% of all deaths in Sweden (Jönsson *et al.*, 2010). There are, however, difficulties with the concept of "preventability" of ADRs (Ferner and Aronson, 2010).

### STUDIES INVESTIGATING HARM FROM DRUGS AND MEDICATION ERRORS

Studies investigating ADRs differ in design, and so too do those investigating harm from drugs and

medication errors. The contribution of medication errors to the overall figure for deaths from "medical error" is not clearly established, but surveys of hospital in-patients (Bates *et al.*, 1995) and of nursing home residents (Barker *et al.*, 1982) have shown that medication errors are extremely common. Anecdotal reports from several sources, including Coroners' inquests (Whittington and Thompson, 1983; Ayers *et al.*, 1987; Whittington, 1991), and the medical defense societies (Ferner, 1995) have alerted doctors to some of the dangers.

In the UK, the National Patient Safety Agency (NPSA) was until 2013 responsible for collecting anonymous reports of harm to patients. Between 1997 and 2005, the NPSA received 596 138 incident reports, of which 2275 (0.4%) concerned fatal incidents. Only 37 of these fatal incidents were due to medication errors (Parliamentary Questions, 2010).

More recent systematic studies of medication errors have examined the incidence in various settings. MEDMARX, an anonymous self-reporting scheme for medication errors in the United States, detected 839 553 errors from 537 hospitals over 6 years. One hundred patients died. Errors arising on intensive care units were most likely to have fatal consequences: adjusted odds ratio 2.48 [95% confidence interval 1.18–5.19] (Latif *et al.*, 2013). Some studies have examined the overall incidence of drug-induced harm and determined how many might have been prevented by judicious prescribing or administration of medicines. A systematic review of 10 studies of drug-induced harm in hospital estimated that about one-third were preventable (median 35%, range 19–73%) (Kanjanarat *et al.*, 2003).

An Australian study examining national statistics and data from the literature showed that up to 4% of all hospital admissions, and as many as 30% of hospital admissions in the elderly, resulted from drug-induced harm (Runciman *et al.*, 2003). Estimates of the proportion that were preventable varied from 32% to 77%. The drugs most commonly implicated in adverse events requiring admission were anticoagulants and opioids. Among hospital patients in Canada, the adverse event rate was 7.5 per 100 hospital admissions, of which more than one-quarter were related to drug or fluid therapy, and 1.6 per 100 were fatal (Baker *et al.*, 2004). Some 6.5% of acute medical admissions in

Nottingham were judged to be related to drugs, and the investigators adjudged two-thirds to be preventable (Howard *et al.*, 2003).

In the specific context of parenteral cytotoxic chemotherapy, a Swedish national error reporting service collected over a period of 12 years some 60 cases, of which six were fatal (Fyhr and Akselsson, 2012).

In a 9-month study of 1247 residents of two long-term care facilities, Gurwitz *et al.* (2005) identified 815 episodes of drug-induced harm, of which 338 (41%) were judged to have been preventable. Four residents who suffered drug-induced harm died as a result. An examination of 447 fatal episodes of drug-induced harm published in the pharmacy journal *ClinAlert* defined 58% as ADRs and 17% as medication errors (Kelly, 2001). The American study by Gurwitz *et al.* (2003) investigated the incidence of drug-induced harm in the wider community, outside the hospital. Among approximately 30 000 people over the age of 65 years who were attending a group practice in the community, 4% experienced an episode of drug-induced harm and 0.022% died because of drug-induced harm over the course of 1 year.

A study of fatal medication errors – deaths in which medication errors are recorded as the primary cause of death – based on death certificate data for 62 338 584 deaths in the USA showed a small but significant increase in hospital deaths from medication errors in the month after new junior doctors started work (Phillips and Barker, 2010). Perhaps new doctors report more scrupulously. Underreporting is certainly important in assessing data from Coronial inquests, as it is in assessing data from spontaneous ADR reports. By way of example, a Taiwanese study estimated that only 1 in 300 deaths related to complications (or misadventure) in medical and surgical care was reported to the Coroner (Lu *et al.*, 2008).

Numerous studies of different design and length, and in various different populations, have reported very different values for the incidence of fatal harm from medicines. One additional source of information that is potentially useful for investigating the epidemiology of drug-induced harm is the records kept by coroners in England and Wales. In other jurisdictions, those responsible for inquiring into

the cause of death (procurators fiscal, medical examiners, and so on) may provide similar data.

## INFORMATION FROM CORONERS' INQUESTS

Coroners in England and Wales have to determine how a person dies if death is from a violent, unnatural, or unknown cause. Deaths due to errors in prescribing, dispensing, or giving drugs, and those caused by ADRs, fall within these categories. Coroners have extensive powers of investigation.

There are some caveats. The facts are not always clear, and so some deaths may be regarded as natural that in fact are because of therapy. Even if the facts are clear, the decision to report a death to the Coroner is not always straightforward, so some deaths may be reported by one doctor but not another. The extent of underreporting is unknown. Each Coroner's Court covers deaths occurring in a defined area, so that, broadly speaking, the size of the population served by the Court is known. Local circumstances, such as the presence of a regional referral center for some condition that is often fatal (such as liver failure), can, however, inflate the apparent incidence of deaths due to that cause.

We have previously described the findings in cases of death due to ADRs or to medication errors in one Coroner's district, Birmingham and Solihull, between 1986 and 1991 (Ferner and Whittington, 1994). We then extended those data to cover the period January 1986 to June 2000 (Ferner and Whittington, 2002) and then to November 2001–June 2005 (Ferner *et al.*, 2007). Details of the search strategies are given in Ferner *et al.* (2007).

There were significant differences in the collection and analysis of the data, most notably because a medically qualified Coroner presided over the first two periods, and was after retirement replaced by a lawyer. Moreover, some of the processes have changed. It is also possible that two Coroners might differ in their verdicts on the same set of facts, so that one might categorize a case as because of drug-induced harm, whereas the other would not. We have not been able to investigate this aspect of Coronial decision-making.

The population in 1991 was 1.21 million people, and the number of deaths was approximately

13 000 per year, of which approximately 4% were reported to the Coroner. In 2004, the population was 1.32 million, with approximately 11 000 deaths per year.

### 1986–1991

There were 46 drug-related deaths identified in this 6-year period, of which 10 cases were attributed to medication errors and 36 attributed to ADRs. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common drug class to be associated with death, accounting for 14/46 (30%) of the cases.

### 1992–2000

A further 40 cases of drug-related deaths were identified from January 1992 to June 2000. There were 24 cases of clear-cut ADRs, 3 cases that were because of medication error alone, and 13 cases where there were elements of both. Once more, NSAIDs accounted for the greatest number of cases, being associated with 14/40 (35%) of all cases. Warfarin was responsible for seven deaths, three because of error, and heparin for two, one because of error.

### 2001–2005

Hand searching of all the determinations of the Coroner's inquests from November 2001 to June 2005 identified 43 cases of death due to harm from drugs in 3366 inquests. Thirty-six deaths were a result of an ADR, and seven were directly related to either a medical error or both a medical error and an ADR. One death because of an ADR was compounded by a diagnostic error.

Warfarin accounted for the greatest number of adverse events, with 11/43 (26%) of the deaths, in contrast to the previous two series, where the majority of adverse events were related to NSAIDs.

The details of seven of the cases in which error played some part are as follows.

#### *Case 1*

A 14-year-old boy who was taking fluoxetine 20 mg daily and diazepam 3 mg twice daily was admitted

for detoxification to a specialist center for the treatment of drug and alcohol addiction. The patient was prescribed 20 mg of methadone and 50 mg of thioridazine, and the dose of diazepam was increased to 10 mg twice daily upon admission. At 36 h after admission, the patient was found in bed blue and not breathing. Cardio-pulmonary resuscitation was unsuccessful. The pathologist considered the death to be because of the inhalation of gastric contents and asphyxia secondary to potentially toxic blood concentration of methadone, in the presence of significant therapeutic concentrations of diazepam and thioridazine and high therapeutic concentrations of fluoxetine.

*Comment:* No analysis for drugs of abuse was taken upon admission to the center, so the treating doctors did not know whether the patient was actually abusing heroin or other drugs. Methadone is an extremely dangerous drug, which is absorbed only slowly after oral administration, so that maximum blood concentrations, and hence maximum respiratory depression, can occur many hours after ingestion. Pharmacodynamic interactions with other respiratory sedatives, including diazepam, are to be expected.

#### *Case 2*

A 58-year-old man with a grade 1 subarachnoid hemorrhage underwent carotid angiography. Staff failed to recognize that no contrast medium (a clear, colorless liquid) had been loaded into the syringe, and therefore a bolus of air, instead of contrast, was injected into the right carotid artery. The patient died in spite of appropriate emergency treatment of air embolism.

*Comment:* A rare example of an ADR because of the (unobserved) absence of drug.

#### *Case 3*

A 31-year-old woman with suspected tuberculosis was injected with 100 000 units of tuberculin purified protein derivative (PPD) intradermally, a 1000-fold overdose. She became unwell with increased temperature and rigors, developed pulmonary fibrosis, and died. The junior doctor who had administered the drug had used the appropriate dosage for the multiple puncture Heaf test and

assumed the single injection was simply an alternative means of delivering the tuberculin PPD when a Heaf gun was not available.

*Comment:* Errors of this type are predictable when there are two formulations of the same product that differ enormously in concentration.

#### Case 4

A 64-year-old man who was taking diclofenac for chronic joint pain underwent arthroplasty of the left hip and insertion of a spacer. During the operation, he developed atrial fibrillation and was treated with warfarin; postoperatively, his heart rhythm returned to normal. Six days later he passed large amounts of melena and was presumed to have had acute gastrointestinal bleeding. Intravenous vitamin K was given because his international normalized ratio (INR) was increased. (The INR is a measure of blood clotting, a value of 1.3 or less is normal and the therapeutic target is usually 2.5.) He had a cardiac arrest and died in spite of resuscitation.

*Comment:* This case highlights the risks of prescribing warfarin with diclofenac, especially if the INR is not carefully monitored.

#### Case 5

An 80-year-old woman with long history of heart trouble and osteoarthritis was admitted to hospital suffering from urinary retention. She had episodes consistent with transient ischemic attacks. There was no history of peptic ulcer. Her warfarin (1 mg daily) was continued, and 1 month after admission treatment was started with aspirin, 75 mg daily. A chest radiograph showed right basal consolidation due to pneumonia, which was treated with amoxicillin and clarithromycin. Her condition deteriorated, and she suffered from severe rectal bleeding. The INR was 5.7. She died shortly afterwards.

*Comment:* The risk of gastrointestinal hemorrhage is doubled by low-dose aspirin, and so combination of warfarin and low-dose aspirin is potentially hazardous. As clarithromycin can inhibit the metabolism of warfarin and increase INR, and as the risk of bleeding rises steeply as INR increases, this patient was at risk from two potentially lethal adverse drug interactions simultaneously.

#### Case 6

A 72-year-old woman who took warfarin 1 mg daily was admitted to hospital complaining of right-sided weakness and slurred speech after falling out of bed. She had become jaundiced a few days before the admission, and when visited by her general practitioner (GP), her INR had not been checked or warfarin treatment stopped. Her INR on admission was 5.5, and a computerized tomography (CT) scan showed an acute hemorrhage in the left parietal white matter. She was prescribed 10 mg of intravenous vitamin K to reverse the effects of warfarin, but this was not administered until 7 h later. She suddenly became deeply unconscious and subsequently died.

*Comment:* Liver impairment during warfarin treatment is especially dangerous, because it can have the dual effect of increasing the concentration and action of warfarin, which is no longer effectively metabolized, and reducing the production of vitamin K-dependent clotting factors, which are synthesized in the liver.

#### Case 7

A 69-year-old woman with past history of hypertension, gout, and arthritis presented to the accident and emergency department with shortness of breath and dizziness. She was prescribed enoxaparin 130 mg daily subcutaneously. Two days after admission, it was noted by staff that she had not been given two previous doses of enoxaparin. She was given a single dose but suffered a cardiac arrest caused by a pulmonary embolus later that afternoon, and resuscitation was unsuccessful. The Coroner's verdict was: "Died from a naturally occurring pulmonary embolism following the failure to administer two doses of a prescribed medication".

*Comment:* This case illustrates the danger of omitting potentially life-saving treatment.

### OVERALL SUMMARY OF THE THREE SERIES

Table 31.1 presents a general summary of the three series. Overall, the number of deaths per year has decreased, whereas the number of Coroner's inquests being undertaken has increased. The

Table 31.1 General summary of the three series.

	1986–91	1992 to June 2000	November 2001 to June 2005
Population	1 190 000 (in 1986)	1 210 000 (in 1991)	1 320 000 (in 2004)
Deaths			
n	86 235	105 900	41 648
per year	14 373	12 459	11 359
Coroner's inquests			
n	3 277	4 502	3 366
per year	546	530	918
Drug-related deaths			
n	46	40	43
per year	8	5	12
which were because of error or error related	10	16	7

number of drug-related deaths per year also appears to have increased in the third series, but it is difficult to make comparisons between the three series due to different methods in identifying drug-related deaths.

The drugs associated with fatal events over the course of the three series are presented in Table 31.2. The most startling difference between the three series of reports is that NSAIDs no longer account for the majority of the deaths and that there is a significant increase in the number of deaths that are associated with warfarin. Table 31.3 demonstrates the increase in warfarin-associated deaths identified in the Coroner's inquests since 1986. Over the course of a 10-year period (1986–1995), only two cases were found to be associated with warfarin compared with 17 cases from 1996 to June 2005. A similar trend over the same period is evident in the number of fatal suspected ADRs to warfarin spontaneously reported to the UK MHRA and the Committee on Human Medicines through the Yellow Card scheme.

The increase in the number of fatal suspected ADRs due to warfarin may be explained by the increased use of warfarin in drug therapy. Data obtained from the Department of Health indicate an increasing trend in the number of warfarin prescriptions in the community in England from 1991 to 2004 (Figure 31.1). When the data from the Yellow Card scheme are plotted alongside the number of warfarin prescriptions, a strong positive correlation is observed between the increasing number of

reports of deaths suspected to be associated with warfarin and increasing medication use (Spearman  $\rho = 0.839$ ,  $P < 0.0005$ ). This association, however, is constrained by the inherent limitations of a spontaneous reporting scheme, as the incidence of deaths due to warfarin treatment cannot be determined through the Yellow Card scheme.

## THE GENESIS OF MEDICATION ERRORS

Errors can be classified into two broad categories: "mistakes" and "slips or lapses" (Ferner and Aronson, 2006). The former occur when something is wrong with the premise on which an action is based. For example, the action in case 3, when the patient was given a dose of tuberculin PPD intradermally that was appropriate for a multiple puncture, represents a mistake. This was an error in the planning of an action as the junior doctor was not aware of the different dosage requirements needed for the two methods of conducting a tuberculosis test. By contrast, case 2, in which a momentary lapse of attention led to air, instead of contrast medium, being injected into a patient's carotid artery illustrates a slip, which is an error of the second sort, occurring during the execution of a planned action (Reason, 1990). To some extent, training and education will help to overcome mistakes, but it is difficult to prevent slips and lapses by training, because they represent defects in tasks that are not under conscious control.

Table 31.2 Drugs associated with fatal events identified by the Birmingham and Solihull Coroner 1986 to June 2005.

1986–91	1992 to June 2000	November 2001 to June 2005
Psychotropics (5)	Psychotropics (7)	Psychotropics (3)
Fluoxetine	Amitriptyline	Amitriptyline
Lithium (2)	Chlorpromazine	Olanzapine and quetiapine
Haloperidol	Dosulepin+chlorpromazine	Flupentixol
Chlorpromazine	Pipotiazine	
	Lithium (2)	
	Clozapine	
Antibiotics (8)	Antibiotics (4)	Antibiotics (5)
Co-trimoxazole (3)	Ciprofloxacin	Cefuroxime
Isoniazid and others (4)	Isoniazid	Flucloxacillin
Oxytetracycline	Levofloxacin	Isoniazid
	Penicillins	Antibiotics (2)
Endocrine drugs (1)	Endocrine drugs (2)	Endocrine drugs (0)
Cyproterone acetate	Dexamethasone	
	Anabolic steroids	
NSAIDs (14)	NSAIDs (14)	NSAIDs (5)
Aspirin	Aspirin	NSAID (2)
Azapropazone+warfarin	Diclofenac (5)	Diclofenac
Diclofenac (2)	Flurbiprofen	Aspirin (2)
Ibuprofen (3)	Ibuprofen	
Indometacin+prednisolone	Indometacin (3)	
Ketoprofen	Mefenamic acid	
Naproxen (4)	Naproxen	
Piroxicam	Piroxicam	
Other antirheumatic (2)	Other antirheumatic (1)	Other antirheumatic (1)
Methotrexate	Methotrexate	Leflunomide
Penicillamine		
Opioids (2)	Opioids (0)	Opioids (2)
Diamorphine		Methadone
Dihydrocodeine, pethidine and diamorphine		Morphine+amitriptyline
Anticoagulants (3)	Anticoagulants (9)	Anticoagulants (12)
Warfarin (3)	Warfarin (7)	Warfarin (10)
	Heparin (2)	Warfarin+diclofenac
		Enoxaparin
Miscellaneous (11)	Miscellaneous (3)	Miscellaneous (15)
Captopril	Theophylline+prednisolone	Chemotherapy (4)
Contrast media	Phenytoin	Phenytoin
Dantrolene (2)	Ethanol+various drugs	Air instead of contrast medium
Oxygen (2)		Neostigmine
Potassium chloride slow release		Tuberculin PPD
Potassium chloride solution		Anesthesia
Spironolactone		Sildenafil
Suxamethonium		Carbamazepine
Unknown		Methyldopa
		Imatinib
		Streptokinase
		Spironolactone

Table 31.3 Number of deaths associated with warfarin identified by the Birmingham and Solihull Coroner and reported to the MHRA and Committee on Human Medicines (CHM) through the Yellow Card scheme from 1986 to June 2005.

Time period	Deaths identified by Birmingham and Solihull Coroner's inquests	Suspected deaths due to warfarin reported to the MHRA and CHM through the UK Yellow Card scheme
1986–90	1	13
1991–95	1	19
1996–2000	6	49
2001 to June 2005	11	74

## THE LESSONS FROM DEATHS RELATED TO MEDICATION

Previous studies have highlighted slips as a major cause of medication errors (Koren *et al.*, 1986). The ten-fold dosing errors they reported still occur (Doherty and McDonnell, 2012). The drama of patients dying from overdoses of drugs because of a misplaced decimal point, or because the names of two drugs were confused, only emphasizes the difficulties. However, in this data set, we found that slips were much rarer than mistakes and that medication errors were themselves a rare cause of death as determined at a Coroner's inquest. The "system" in which drugs are used needs to be improved, and that system includes both prescribers and patients. Better education, and more relevant information at the point when doctors prescribe, will help.

Some drugs, notably warfarin, lithium, opioids, and potassium chloride, are difficult to use safely

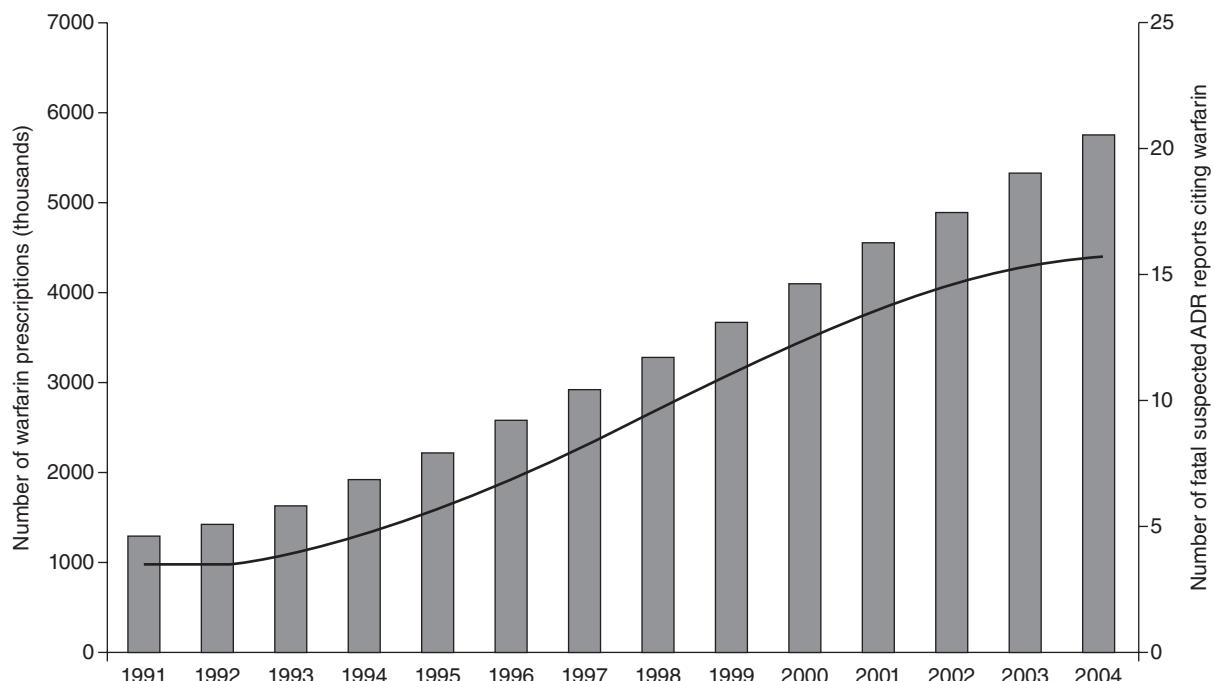


Figure 31.1 Trends in fatal suspected ADR reports to the MHRA and Committee on Human Medicines citing warfarin (black line) and warfarin prescriptions (gray bars).

and require especially careful prescribing and monitoring. This reality is underlined by the increased number of deaths due to warfarin demonstrated in the third series. The number of deaths due to warfarin treatment will only fall through improved education and emphasis on the need for vigilant monitoring of patients being treated with this drug. Nonetheless, however safe systems for prescribing, dispensing, and administering drugs become, patients will continue to die from ADRs. That problem can only be mitigated by a more careful assessment of risks and benefits in prescribing for each patient and every drug and by the development of safer drugs.

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# Dermatological Adverse Drug Reactions

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## INTRODUCTION

Skin is one of the most common targets of adverse drug reactions (ADRs) (Arndt and Hershel, 1976). Eruptions are observed in 0.1–1% of treated patients in premarketing trials of most drugs, and also in the placebo groups. A number of drugs of current utilization are associated with higher rates of skin eruptions: 5–7% for aminopenicillins, 3–4% for antibacterial sulfonamides, and 5–10% for many antiepileptics. In a reported prospective survey, 90% of these drug eruptions were benign (Hunziker *et al.*, 1997). Because underreporting is expected to be more frequent for benign reactions, one may assume that severe cutaneous ADRs account for about 2% of all skin reactions.

The Council for International Organization of Medical Sciences (CIOMS) considers as serious ADRs that “are fatal or life-threatening, or require prolonged hospitalization, or result in persistent or significant disability or incapacity” (CIOMS, 1997).

Because hospitalization may depend on the socio-economic status of the patient and on access to healthcare, we prefer to consider as severe those drug eruptions that are associated with a definite risk of increased mortality, even if the risk is low, and whether the risk of death is related to “acute skin failure,” to associated visceral lesions, or to both factors. Not all severe skin ADRs develop rapidly. Many well-defined clinical entities, like drug-induced pemphigus, psoriasis, or lupus, usually occur after prolonged exposure.

Not all skin ADRs are “allergic” (i.e., mediated by a specific response of the immune system against the drug itself or a metabolite).

Many medications are capable of inducing skin lesions by direct toxicity or interaction with skin functions. Such direct mechanisms include toxic alterations of skin, hair, nails (many anticancer agents), sebaceous glands (acneiform lesions of epidermal growth factor antagonists). These reactions will not be further addressed in this chapter because

they are predictable, detected in premarketing studies, and often preventable. The benefits–risks balance can be appropriately evaluated before release of the medication on the market, and such effects are therefore not a major concern for pharmacovigilance.

We will mainly focus on “idiosyncratic” acute reactions. Most were demonstrated in the past 10 years to be related to specific immune responses, usually of “delayed” type, and therefore qualify as “drug hypersensitivity reactions” (Pichler *et al.*, 2011).

It is our opinion anyhow that the different clinical patterns of drug eruptions should be distinguished, rather than all mixed under the denomination of “hypersensitivity reactions” (Knowles *et al.*, 2000). That is based on mechanistic considerations, since more and more recent pieces of evidence suggest that the different phenotypes of “drug eruptions” are mediated by different genetic background and a variety of effector and regulatory immune mechanisms (Nassif *et al.*, 2004; Takahashi *et al.*, 2009; Pichler *et al.*, 2011). Further attempts in deciphering the mechanisms of “drug eruptions” should include a stringent description of the phenotypes that are investigated.

## PATTERNS OF CUTANEOUS ADVERSE DRUG REACTIONS

### EXANTHEMATOUS DRUG ERUPTION

Exanthematous or maculopapular eruptions, often reported as “drug rashes” or “drug eruptions,” are the most common type of ADR affecting the skin. The main mechanism is probably immunologic, and may correspond to type IV delayed cell-mediated hypersensitivity reaction.

The eruption usually occurs between 4 and 14 days after beginning a new therapy, and even a few hours after it has ceased (“eruption of the ninth day”). However, it can develop sooner, especially in the case of rechallenge. The eruption consists of erythematous macules, papules, often symmetric. They begin on the trunk, upper extremities, and progressively become confluent (Plate 32.1). The eruption is typically polymorphous: morbilliform

or sometimes urticarial on the limbs, confluent on the thorax, purpuric on the feet. Mucous membranes are usually not involved. Pruritus and low-grade fever are often associated with the eruption, which frequently lasts less than 2 weeks.

Cutaneous pathological slides exhibit a very mild lymphocytic infiltrate around vessels of the dermis and a few necrotic keratinocytes within the epidermis. This pattern, often difficult to differentiate from normal skin, is not specific and cannot help to distinguish a drug eruption from an eruption of another cause.

The differential diagnosis of exanthematous drug reactions includes viral eruptions (Epstein–Barr virus (EBV), cytomegalovirus, human herpesvirus 6 (HHV6), parvovirus B19, etc.), toxic eruptions, acute graft-versus-host reaction, Kawasaki syndrome, Still’s disease, and so on. Dermatologists usually consider that viral infections are the cause of most drug eruptions in children, while drugs are more frequently responsible in adults.

Treatment is largely supportive, usually after the removal of the offending agent, using topical corticosteroids, emollients, and systemic antipruritic agents. When the suspected drug is of paramount importance for the patient, treating “through the eruption” can be considered as an option. In most instances, the eruption will disappear in about the same time as if the drug had been withdrawn. Because a few patients may experience a progressive worsening of the eruption leading to one of the severe reactions described below, the benefit–risk balance of this attitude should be considered and the evolution of the rash strictly monitored.

Most drugs can induce an erythematous eruption in about 1% of users. The following drugs have higher risks (more than 3% of users): allopurinol, aminopenicillins, cephalosporins, antibacterial sulfonamides, most antiepileptic agents, anti-HIV medications.

### URTICARIA AND ANGIOEDEMA

Urticaria is a common, transient eruption of erythematous and edematous papules and plaques, nearly always associated with pruritus. When dermis and subcutaneous tissues are involved, this

reaction is known as angioedema. Most cases of angioedema are associated to urticaria. They can be complicated by a life-threatening anaphylactic reaction. Urticaria, angioedema, and anaphylaxis may be a type I hypersensitivity reaction mediated by immunoglobulin E (IgE) antibodies (penicillin allergy). But other "pseudo-allergic" mechanisms, leading to direct and nonspecific liberation of histamine or other mediators of inflammation, are also common for drug reactions (contrast media, nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, angiotensin-converting-enzyme (ACE) inhibitors).

Clinically, itchy erythematous, edematous papules and plaques develop in variable numbers and size (Plate 32.2). They are localized anywhere on the body, including the palms, soles, and scalp. They frequently last a few hours and disappear within 24 h, leaving the skin with a normal appearance. Angioedema is often associated with urticaria, consisting of pale or pink swellings which affect the face (eyelids, lips, ears, etc.), but also oral mucosa, the tongue, larynx, pharynx, and so on. More severe reaction, such as anaphylaxis, can involve other systems and lead to respiratory collapse, shock, and eventually death.

Urticaria is histologically nonspecific with a superficial and deep scarce infiltrate of mononuclear cells accompanied by eosinophils and neutrophils, edematous reticular dermis, vascular and lymphatic dilatation. The epidermis is uninvolved.

Urticaria has been classified into acute, when the eruption lasts less than 6 weeks, or chronic when it persists much longer.

It usually occurs within a few hours of drug administration, but may also occur within a few minutes.

Withdrawal of the causative agent is the main treatment. It can sometimes be associated with histamine H<sub>1</sub> receptor blockers. Systemic steroids and an intramuscular injection of epinephrine are necessary in an emergency if severe angioedema and anaphylaxis occur.

Many drugs can induce urticaria (most often of the acute type), but more than 80% of cases of urticaria are related to other causes (insect stings, food allergy, etc.). Antibiotics, especially penicillin, and general anesthetics are classic causes of

IgE-mediated hypersensitivity reaction. A radioallergosorbent test (RAST) or enzyme-linked immunosorbent assay (ELISA) and skin tests (prick-tests) can be useful to confirm the diagnosis. Because they may rarely induce an anaphylactic reaction, prick-tests must be performed only by experienced physicians.

The two most frequent causes of drug-induced non-IgE-mediated urticaria and angioedema are NSAIDs and ACE inhibitors. Angioedema occurs in 2–10 per 10 000 new users of ACE inhibitors (Hedner *et al.*, 1992), a rate that is probably higher than the risk associated with penicillins (about 1 per 10 000 courses). The reaction begins much later than IgE-mediated urticaria, usually in the first weeks of treatment. Up to one-third of patients with angioedema related to ACE inhibitors have a recurrence when using angiotensin 2 receptor antagonists (van Rijnsoever *et al.*, 1998). This strongly suggests a pharmacologic or "pseudo-allergic" mechanism.

## PHOTOSENSITIVITY

Cutaneous photosensitivity diseases may be idiopathic, produced by endogenous photosensitizers (e.g., porphyrins) or associated with exogenous photosensitizers like drugs. The association of light and a drug can be responsible for acute inflammation of the skin. The photosensitivity reactions are divided into two types: phototoxicity and photoallergy (Gould *et al.*, 1995).

## PHOTOTOXICITY

Phototoxic disorders are not rare and always predictable. Phototoxicity can occur in any person who receives sufficient quantities of a phototoxic drug, together with the proper light exposure. The reaction results directly from photochemistry involving the skin. The association of light with a photosensitizing chemical in the skin creates an unstable singlet or triplet state within the electrons. This leads to the generation of reactive oxygen, which is responsible for cell damage.

Clinical manifestations usually present as an exaggerated sunburn occurring in sun-exposed

areas only (Plate 32.3). This is followed by hyperpigmentation. Photo-onycholysis and pseudoporphyria (blisters on sun-exposed parts of the limbs) are less common clinical forms.

Phototoxicity is histologically characterized by epidermal cell degeneration with necrotic keratinocytes, edema, sparse dermal lymphocytic infiltrate, and vasodilatation. Phototoxicity is easily documented *in vitro* or *in vivo*. A photopatch test will be positive in all individuals and will therefore not be a discriminator for causality assessment. The minimal dose of ultraviolet (UV) radiation (UVA more often than UVB) inducing an erythema will be decreased in all subjects during treatment.

### PHOTOALLERGY

A photoallergic reaction is considered as a result of cell-mediated hypersensitivity. UV radiation is required to convert a drug into an immunopathologically active compound (photo-antigen) that induces the immune response.

Photoallergic eruption is more chronic than phototoxicity and is mainly eczematous and pruritic. A lichen planus-like reaction has also been reported. It is usually more marked in sun-exposed sites, but may often progress outside these areas. In the chronic phase, erythema, scaling, and lichenification predominate. Photoallergic reactions are usually transient and resolve after a variable length of time when the offending agent has been removed. Rarely, an extreme sensitivity to sun may persist for months or years ("persistent light reactors"). Photopatch testing is valuable when photoallergy is suspected.

A multitude of drugs induce photosensitivity reactions, including antiinfectious agents (sulfonamides, pyrimethamine, fluoroquinolones, cyclines, voriconazole), fragrances, NSAIDs, phenothiazine, thiazide diuretics, amiodarone, and others.

In phototoxic reactions, the treatment requires removal of the offending agent and/or avoidance of sun exposure. For a drug with a short elimination half-life, administration in the evening may be enough to decrease the risk below the clinical threshold. In photoallergy, drug withdrawal is always recommended, because of the risk of worse reactions even with low UV doses. Topical corticosteroid or systemic antipruritic agents may be useful.

### VASCULITIS

Vasculitis corresponds to immune-mediated inflammation and damage to a blood vessel's wall. It may be caused by a variety of agents, especially infections and collagen vascular diseases. Many cases remain idiopathic. Drug-induced vasculitis is believed to result from antibodies directed against drug-related haptens (Roujeau and Stern, 1994). Direct drug toxicity against a vessel's wall, autoantibodies reacting with endothelial cells, and cell-mediated cytotoxic reactions against vessels were also proposed as explanations. The precise mechanism is still unknown.

This drug-induced eruption consists of palpable purpuric papules which predominate on the lower extremities (Plate 32.4). Urticaria-like lesions, ulcers, nodules, hemorrhagic blisters, Raynaud's disease, and digital necrosis may also occur. The vasculitis may involve other organs, with fever, arthralgias, myalgias, headache, dyspnea, neurological involvement, and renal abnormalities, sometimes life-threatening. The histology of small blood vessels exhibits necrotizing and/or leukocytoclastic vasculitis. The direct immunofluorescence is often positive, with immunoglobulin and C3 deposits on capillary walls.

Vasculitis occurs 7 to 21 days after drug administration, and less than 3 days after rechallenge. Withdrawing the drug usually leads to a rapid resolution. A systemic corticosteroid may benefit some patients. Drug-induced cases are a minority of cases of vasculitis (no more than 10% in a large series) and have to be differentiated from other causes of cutaneous vasculitis: infection, autoimmune diseases (polyarteritis nodosa, Wegener's granulomatosis, etc.), Schönlein-Henoch purpura, and cancer.

The main drugs implicated are propylthiouracil, allopurinol, NSAIDs, cimetidine, penicillin, hydantoin, and sulfonamides.

### ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Beylot *et al.* (1980) described an acute pustular dermatosis named "acute generalized exanthematic pustulosis" (AGEP). Of these eruptions, at

least 80% could be drug induced. Hypersensitivity to mercury and infection with enteroviruses may also be responsible. The incidence of AGEP has been underestimated, and many cases have been confused with pustular psoriasis. Synonyms are pustular drug rash, pustular eruption, and pustuloderma (Staughton *et al.*, 1984). Proposed diagnosis criteria (Sidoroff *et al.*, 2001) include:

- 1 an acute pustular eruption;
- 2 fever above 38°C;
- 3 neutrophilia with or without a mild eosinophilia;
- 4 subcorneal or intraepidermal pustules on skin biopsy;
- 5 spontaneous resolution in less than 15 days.

AGEP is characterized by fever, which generally begins the same day as the pustular rash. Numerous, small, mostly nonfollicular pustules arise on a widespread edematous erythema, burning, pruritic, or both (Plate 32.5). Edema of the face and the hands, purpura, vesicles, blisters, erythema multiforme-like lesions, and mild involvement of mucous membrane have also been associated. Pustules are mainly localized on the main folds (neck, axillae, groins, etc.), trunk, and upper extremities.

The histopathology shows spongiform pustules located under the stratum corneum, the most superficial layer of the epidermis. Papillary dermal edema and perivascular polymorphous infiltrate are usually present. Leukocytoclastic vasculitis and focal necrotic keratinocytes have also been reported.

Hyperleukocytosis with elevated neutrophils count, transient renal failure, and hypocalcemia are frequently seen.

There are two different times between the drug administration and the skin eruption. For antibiotics it is usually very short, less than 2 days. A more classical delay of 1–2 weeks is observed with diltiazem, another classical inducer. The eruption lasts 1–2 weeks and is followed by a superficial desquamation. The withdrawal of the responsible drug is the main treatment, associated with a topical corticosteroid and sometimes a systemic antipruritic agent.

AGEP must be differentiated from acute pustular psoriasis of the von Zumbusch type. The pus-

tules in both diseases are clinically indistinguishable; the histopathology can be helpful.

Antibiotics (aminopenicillins, cephalosporins, some macrolides, and quinolones), diltiazem, hydroxychloroquine, and terbinafine are the main drugs implicated in AGEP (Sidoroff *et al.*, 2007).

#### DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS/HYPERSENSITIVITY

“Hypersensitivity syndrome” refers to a specific severe skin reaction. The acronym DRESS, for drug reaction with eosinophilia and systemic symptoms, has been proposed as more specific than “hypersensitivity,” which would be appropriate for most types of drug reaction. It has been estimated to occur in between 1 in 1000 and 1 in 10 000 exposures with drugs such as antiepileptics and sulfonamides. This syndrome is typically characterized in its complete form by a severe eruption, lymphadenopathy, fever, hepatitis, interstitial nephritis, pulmonary infiltrates, and sometimes arthralgias. The clinical lesions are associated with hematological alterations: eosinophilia and lymphocytosis with basophil “atypical” lymphocytes (Shear and Spielberg, 1988; Roujeau and Stern, 1994; Callot *et al.*, 1996). Multivisceral involvement differentiates hypersensitivity syndrome from common exanthematous eruption.

These reactions are more frequent among persons of African ancestry. They begin 2–6 weeks after the first drug use, later than most other skin reactions. This long latency period may be related to insidious onset of some manifestations. Fever and skin rash are the most common symptoms. Cutaneous manifestations initially consist of a morbilliform rash, which later becomes infiltrated with an edematous follicular accentuation (Plate 32.6). Erythroderma, vesicles, tight blisters induced by dermal edema, and follicular as well as nonfollicular pustules can also occur. Face, upper trunk, and extremities are initially involved. Edema of the face is frequent and evocative of diagnosis.

Prominent eosinophilia (70% of cases) and atypical lymphocytosis (50–60%) are the most characteristic biological features of this reaction. Liver abnormalities with raised aminotransferase, alkaline phosphatase, bilirubin levels, and abnormal

prothrombin time are present in about 50% of patients.

Histopathology of skin lesions exhibits a rather dense lymphocytic infiltrate in the superficial dermis and/or perivascular, associated with dermal edema.

Rash and hepatitis may persist for several weeks after drug withdrawal, and some of the manifestations may be life threatening.

The differential diagnosis includes other cutaneous drug reactions, acute viral infection, idiopathic hypereosinophilic syndrome, lymphoma, and "pseudolymphoma."

A diagnosis score for DRESS has been proposed by the RegiSCAR group (Kardaun *et al.*, 2007).

Special attention should be paid to viral infection, and especially to HHV6, since several publications suggest a possible interaction between DRESS and reactivation of HHV6 or other lymphotropic viruses (Descamps *et al.*, 2001; Kano *et al.*, 2004).

Topical high-potency corticosteroids can be helpful in skin manifestations. Systemic corticosteroids are often proposed when internal organ involvement exists.

The aromatic antiepileptic agents (phenobarbital, carbamazepine, phenytoin), lamotrigine, allopurinol, minocycline, and sulfonamides are the most frequent causes of DRESS/hypersensitivity syndrome; gold salts, dapsone, strontium ranelate, and telaprevir can also induce this syndrome.

## FIXED DRUG ERUPTION

A fixed drug eruption is considered to be an exclusively drug-induced cutaneous reaction. The lesions develop usually less than 2 days after the drug intake. Clinically, they are characterized by a solitary or few, round, sharply demarcated erythematous and edematous plaques, sometimes with a central blister (Plate 32.7). The eruption can be located on every site of the body and may involve mucous membranes, principally the lips and genitalia. The eruption progressively fades in a few days, to leave a post-inflammatory brown pigmentation. With rechallenge with the causative drug, the lesions recur at exactly the same sites. After several relapses the eruption may involve large areas of the body. This generalized bullous fixed

drug eruption may be difficult to distinguish from toxic epidermal necrolysis (TEN).

Histopathology reveals a superficial and deep dermal and perivascular infiltrate (composed of lymphocytes, eosinophils, and sometimes neutrophils) associated with necrotic keratinocytes. Dermal macrophages pigmented by melanin (melanophages) when present are considered an important clue to the diagnosis.

The drugs most frequently associated with fixed drug eruption are phenazone derivates, barbiturates, tetracycline, sulfonamides, and carbamazepine (Kauppinen and Stubb, 1984).

## DRUG-INDUCED PEMPHIGUS

Pemphigus is a chronic autoimmune blistering disease provoked by autoantibodies reacting with normal constituents of desmosomes, the structures that provide attachment between epidermal cells. It presents clinically with flaccid intraepidermal blisters and erosions of the skin and mucous membranes (Plate 32.8). Nikolsky's sign is found.

The histology exhibits detachment of epidermal cells (acantholysis), responsible for intraepidermal blisters located subcorneally (pemphigus foliaceus) or in the lower epidermis (pemphigus vulgaris).

Direct immunofluorescence performed to a perilesional skin biopsy specimen reveals immunoglobulin deposits around keratinocytes in the epidermis in all "spontaneous" cases but in only 50% of drug-induced cases. The presence in the serum of autoantibodies reacting against the epidermis is detected by indirect immunofluorescence, Western blot, or ELISA tests.

In Western countries it was estimated that up to 10% of cases of pemphigus could be drug induced. It begins several weeks or months after drug therapy is initiated. It presents as pemphigus foliaceus or as pemphigus vulgaris with mucosal involvement. The main drugs incriminated were D-penicillamine and other drugs containing a thiol radical, like captopril and piroxicam. With decreasing usage of D-penicillamine, drug-induced pemphigus is rarer. The remission after drug withdrawal is not always spontaneous, particularly in cases of pemphigus attributed to drugs that do not have a thiol part.

## STEVENS—JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens—Johnson syndrome (SJS) and TEN are rare, life-threatening, drug-induced skin reactions. The incidence of SJS and TEN is evaluated to two cases per million person-years (Rzany *et al.*, 1996). The immunopathologic pattern of early lesions suggests a cell-mediated cytotoxic reaction against epidermal cells. Widespread apoptosis of epidermal cells is provoked by drug-specific cytotoxic T cells and natural killer cells that release large amounts of granulysin, a highly cytoxic cytokine (Chung *et al.*, 2008). Genetic predisposition was demonstrated for SJS or TEN induced by carbamazepine in Asia (Chung *et al.*, 2004), but not in Europe (Lonjou *et al.*, 2008) or induced by allopurinol (Hung *et al.*, 2006; Lonjou *et al.*, 2008).

It is now considered that SJS and TEN are severity variants of the same drug-induced disease. SJS should be distinguished from erythema multiforme major (Bastuji-Garin *et al.*, 1993), the latter being mostly related to infections, especially with herpes (Auquier-Dunant *et al.*, 2002).

Erythema multiforme (major when mucous membranes are involved) is characterized by typical concentric “target” lesions acrally distributed, with limited blisters (detachment rarely involves more than 2–3% of the body surface area). The pathology shows an interface dermatitis with moderate to marked lymphocyte infiltrate in the dermis, exocytosis, and mild necrosis of epidermal cells. In our experience, erythema multiforme is rarely if ever drug induced. Most of the cases that are reported or published as drug-induced “erythema multiforme” are either cases that we would label as SJS or cases of erythematous drug eruptions, because of confusion between “multiforme” and the polymorphous patterns of many erythematous eruptions.

SJS is characterized by atypical targets and more often by small blisters arising on purple macules. Lesions are widespread and usually predominate on the trunk. Confluence of blisters on limited areas leads to detachment below 10% of the body surface area. The pathology can be separated from that of erythema multiforme by less lymphocyte

infiltrate and more epidermal necrosis (Côté *et al.*, 1995).

TEN is characterized by the same lesions as SJS, but with a confluence of blisters leading to a positive Nikolsky sign and to the detachment of large epidermal sheets on more than 30% of the body surface area (cases with detachment of between 10 and 30% are labeled overlap SJS-TEN) (Plate 32.9). Skin pathology shows necrosis of full-thickness epidermis and negative immunofluorescence. This is important for distinguishing TEN from exfoliative dermatitis, staphylococcal scalded skin syndrome, acute exanthematous pustulosis, and paraneoplastic pemphigus, which may be misdiagnosed as SJS or TEN.

Patients with SJS or TEN have high fever. Severe erosions of mucous membranes are nearly constant.

Systemic manifestations include mild elevation of hepatic enzymes (overt hepatitis in 10% of cases) and intestinal and pulmonary manifestations (with sloughing of epithelia similar to what happens to the skin). Leucopenia is frequent and eosinophilia unusual. Death occurs in 10% of patients with SJS and more than 30% of patients with TEN, principally from sepsis or pulmonary involvement (Roujeau and Stern, 1994).

The treatment is mainly symptomatic, consisting of nursing care, maintenance of fluid and electrolyte balance and nutritional support. Early withdrawal of all potentially responsible drugs is essential. Short courses of corticosteroids early in the disease have been advocated, but their effectiveness has never been demonstrated in controlled trials. Thalidomide has been shown to be detrimental in TEN, possibly because of a paradoxical enhancement of TNF $\alpha$  production (Wolkenstein *et al.*, 1998). High-dose intravenous immunoglobulins were disappointing.

Drug reactions are responsible for at least 70% of cases of both SJS and TEN (Knowles *et al.*, 2000), but not for all cases. At least 15% of cases are unlikely drug induced (unpublished results from study of a large cohort of patients using an SJS/TEN-specific causality algorithm – ALDEN (Sassolas *et al.*, 2010)). Allopurinol, lamotrigine, carbamazepine, phenytoine, sulfamethoxazole, and

other antibacterial sulfonamides, nevirapine, and oxicam NSAIDs are the drugs associated with the higher risks. Two international case-control studies of SJS and TEN found elevated relative risks for new users (treatment duration of less than 2 months) of the above-mentioned drugs (Roujeau *et al.*, 1995; Mockenhaupt *et al.*, 2008). Excess risks for associated drugs were in the range of 1 to 4.5 cases for 1 million users per week (Roujeau *et al.*, 1995).

SJS and TEN typically begin within 4 weeks of initiating therapy, usually 7–21 days after the first drug exposure and sometimes a few days after the drug has been withdrawn. It occurs more rapidly with rechallenge.

## OTHER DRUG-INDUCED CUTANEOUS REACTIONS

### SERUM SICKNESS-LIKE ERUPTION

This syndrome is principally reported in children and typically includes fever, arthralgias, rash (morbilloform, urticaria), and lymphadenopathy (Roujeau and Stern, 1994; Knowles *et al.*, 2000).

It occurs 1–3 weeks after drug exposure. Unlike “true” serum sickness reaction, hypocomplementemia, immune complexes, vasculitis, and renal lesions are absent. This reaction occurs in about 1 in 2000 children given cefaclor, which along with minocycline, penicillins, and propranolol are the main drugs responsible for this eruption.

### ANTICOAGULANT-INDUCED SKIN NECROSIS

This reaction is a rare, but life-threatening, effect of warfarin, which typically begins 3–5 days after therapy is initiated. Clinically, red, painful plaques evolve to necrosis, hemorrhagic blisters, ulcers, and so on as a consequence of occlusive thrombi in vessels of the skin and subcutaneous tissue (Roujeau and Stern, 1994). Of the individuals who receive warfarin, 1 in 10 000 will develop skin necrosis. People with a hereditary deficiency of protein C are at the highest risk. Therapy includes discontinuing warfarin, administering vitamin K, giving heparin as an anticoagulant, and purified protein C concen-

trate. Heparin also induces thrombosis and necrosis in the skin and other organs. In this case, the discontinuation of the drug and treatment with warfarin or an antiplatelet drug is useful.

## PSEUDOLYMPHOMA

Drug-induced pseudolymphoma corresponds to a very rare and insidious disease, which simulates lymphoma clinically and histologically. It develops months or years after the beginning of the incriminated drug. Cutaneous lesions may be solitary or numerous, localized or widespread red papules, plaques, or nodules. Lymphadenopathy is often associated, but can also be isolated (Callot *et al.*, 1996).

Histologically, dense lymphocytic infiltrate mimics T-cell lymphoma and B-cell lymphoma, but the lymphocytes are polyclonal. Complete recovery occurs a few weeks after withdrawal of the responsible drug. The majority of drug-induced pseudolymphomas have been reported with hydantoin, butobarbital, carbamazepine, ACE inhibitors, amiloride, and D-penicillamine..

Erythema nodosum, acneiform eruptions, lupus erythematosus, psoriasis, oral erosions, alopecia, lipodystrophy, and many other skin manifestations may also be induced by drugs. These are usually well-defined clinical entities, which we will not discuss here.

## ASSESSMENT AND REPORTING OF CUTANEOUS ADVERSE DRUG REACTIONS

Case assessment should begin with an accurate description of the skin lesions. If a specific diagnosis is proposed, then it is important to know if it has been made or confirmed by a dermatologist. The use of lay words is often more informative than the use of “specific” terms when the accuracy of these terms is not certain.

Relevant clinical information includes:

### 1 Distribution of lesions

- Face, hands, feet versus thorax and abdomen
- Photoexposed versus covered areas

### 2 Number of lesions

- 3 Pattern of individual lesions (macules, purpura, blisters, pustules, etc.)
- 4 Mucous membrane involvement.
 

*It is important to distinguish whether the cutaneous part of an orifice of the body is involved or if there are lesions of mucous membranes (e.g., lips versus mouth, scrotum versus glans on genitalia). Only "true" mucous membrane lesions indicate a severe reaction.*
- 5 Duration of the eruption
- 6 Associated symptoms/signs
  - Fever
  - Pruritus
  - Lymph node enlargement.

The documentation of cases should be completed by photographic pictures. Digital cameras or even mobile phones can provide both easy and adequate documentation. This will be of major help for the retrospective assessment of cases by experts.

A skin biopsy is not useful in mild eruptions, but is mandatory for all severe reactions. It will allow a retrospective validation of the diagnosis and in some cases may help to exclude nondrug causes of a reaction pattern.

Information should be obtained on the presence of factors that increase the risk of drug eruptions: HIV infection, acute EBV infection, collagen vascular disease.

The attribution to a newly released drug of a few cases of severe cutaneous reactions may lead to restrictions in the use of this drug, with important medical and economic impacts. This underlines the importance of a good assessment of cases, which should be proportional to the seriousness of the reaction.

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# Gastrointestinal Adverse Drug Reactions

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## INTRODUCTION

There are a wide range of drug classes that can produce disturbances on gastrointestinal (GI) function. In the 1970s, it was reported that between 20 and 40% of adverse drug reactions (ADRs) in at hospital monitoring were GI in origin (Hurwitz and Wade, 1969). More recent information about the actual incidence of ADRs of subjects admitted to hospital due to an ADR (Col *et al.*, 1990; Einarson, 1993; Nelson and Talbert, 1996; Lazarou *et al.*, 1998; Roughead *et al.*, 1998; Pouyanne *et al.*, 2000) or of in-hospitalized patients (Bates *et al.*, 1993, 1995a,b; Bowman *et al.*, 1994; Lazarou *et al.*, 1998) provided limited information specifically about GI events.

In an observational study of 1024 patients in an internal medicine ward in the USA (Bowman *et al.*, 1994), the GI system was the organ system affected in 17.8% of drug-related adverse events. Similar results were obtained from a study in over 4000 hospitalized patients in the USA where they found

247 ADRs among 207 admissions (Bates *et al.*, 1997). The specific by organ system affected sub-analysis showed that 18% of events were of GI origin, predominantly nausea, vomiting, and antibiotic-associated diarrhea.

A prospective study from France showed that GI events were the most frequent cause for admission to hospital for an ADR (Pouyanne *et al.*, 2000). Of 100 admissions, 27 were GI, including 13 cases of GI hemorrhage caused by anticoagulant drugs and 9 caused by the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs).

The extent of drug-related hospital admissions in Australia was reviewed from Australian studies published between 1988 and 1996 (Roughead *et al.*, 1998). Fourteen studies were included in the analysis, although the diagnosis associated with the drug-related admissions was available from only five reports. Among the conditions commonly identified was GI bleeding, which was usually associated with either warfarin or NSAID therapy.

Many drugs causing GI disorders have been recognized (Bateman and Aziz, 1998).

Well-established deleterious effects of drugs include changes in GI motility, altered gastric emptying, disturbances of nutrient absorption, antimicrobial-associated colitis, and pseudomembranous colitis. Furthermore, drug-induced lesions are documented for the whole GI tract. These encompass a wide range of pathophysiological processes, including inflammation, the formation of strictures, hemorrhage, ulceration, and perforation. Others consist of symptoms such as nausea and vomiting (Quigley *et al.*, 2001), diarrhea (Fine and Schiller, 1999), or constipation (Locke *et al.*, 2000) in the absence of underlying pathology.

The actual evidence on GI ADRs is dominated by reports concerning the NSAIDs. Effects have been documented over many years, but it was during the 1990s that the risk factors for upper GI problems were systematically examined. Over the same period, the small and large bowel toxicities of the NSAIDs also became clearly identified.

In this chapter, we summarize some of the more important evidence and reviews from 30 years ago concerning the adverse effects of NSAIDs on the GI tract. We also review the medical literature to identify adverse GI effects with other medications detected using a variety of pharmacovigilance techniques.

The oesophagus, despite its physiological defense mechanisms, is prone to suffer injury induced by a wide variety of agents. Drug-induced esophageal injury or "pill esophagitis" was first described in the 1970s (Pemberton, 1970). In most cases, direct esophageal toxicity is the underlying cause, and the condition is generally fully reversible on the withdrawal of treatment (Doman and Ginsberg, 1981; Kikendall, 1999a). Pill esophagitis is often under-diagnosed; in many instances, it is incorrectly believed to be gastro-esophageal reflux disease (Doman and Ginsberg, 1981; Bonavina *et al.*, 1987). Almost 1000 reports in the medical literature of pill esophagitis attributable to about 100 different medications have been extensively reviewed (Kikendall, 1999a,b). Drugs most frequently implicated in pill esophagitis (reports of  $\geq 10$  cases) include antibiotics (doxycycline, tetracycline hydrochloride and other unspecified tetracyclines, oxytet-

racycline, and pivmecillinam), potassium chloride, alendronate, ferrous sulfate and ferrous succinate, quinidine, naproxen, aspirin (ASA), emeproprium bromide, pinaverium bromide, and alprenolol (Bott *et al.*, 1987; Baehr and McDonald, 1998; Kikendall, 1999a,b; Graham, 2000).

In the upper GI tract, NSAIDs are strongly associated with peptic ulceration, along with associated complications such as bleeding and perforation. NSAIDs also cause upper GI hemorrhage, as may the selective serotonin re-uptake inhibitors. Studies in volunteers have shown that alendronate, one of the bisphosphonate class of drugs, may cause acute gastric mucosal damage and gastric ulceration.

NSAIDs can also cause a low-grade enteropathy in the small intestine. Additionally, in both small and large intestine, they have been associated with the formation of strictures, bleeding, and perforation.

In addition, association between a rotavirus vaccine and intussusception in children has been reported, and fibrosing colonopathy has been linked with the use of pancreatic supplements in children and adults with cystic fibrosis. The possibility that measles-mumps-rubella vaccination may be a causal factor in the development of inflammatory bowel disease is currently a matter of some controversy.

Numerous drugs have been reported to have caused obstruction of the GI tract (Iredale, 1993). Acute colonic pseudo-obstruction is characterized by massive colonic dilation with a clinical and radiological appearance of mechanical obstruction but in the absence of primary colonic pathology. Although the underlying pathogenetic mechanisms are unknown, it is commonly associated with surgery, trauma, metabolic imbalance, neurological disease, and serious systemic illness. Anecdotal case reports in the 1980s and 1990s have associated various drugs with colonic pseudo-obstruction, including clonidine (Maganini and Pollitt, 1983; Steiger *et al.*, 1997), imipramine (Sood and Kumar, 1996), amitriptyline (McMahon, 1989), amitriptyline with concomitant lithium (Fava and Galizia, 1995), nimodipine (Fahy, 1996), tocolytic therapy comprising intravenous magnesium and nifedipine (Pecha and Danilewitz, 1996), interleukin-2 (Post *et al.*, 1991), diltiazem (Mantzoros *et al.*, 1994; Fauville *et al.*, 1995), morphine (Murthy *et al.*, 1998),

fludarabine (Campbell *et al.*, 2000), and enteral activated charcoal alone (Brubacher *et al.*, 1996) and together with sorbitol and papaveretum (Longdon and Henderson, 1992) when given for the management of theophylline overdose.

## NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Today, NSAIDs are among the most commonly used drugs in the world (including ASA). In Europe, NSAIDs represent more than 7.7% of all prescriptions, and it is probable that these figures are under-estimated because over-the-counter use is not included (Jones, 2001). More than 20 million prescriptions per year are written in the UK alone (Langman, 1988). In absolute terms, in the year 2004, a total of 111 million NSAID prescriptions were written in the USA (Shaheen *et al.*, 2006), and it is expected that the use of NSAIDs will increase because the incidence of rheumatic diseases is also increasing. Their use is more frequent among women and increases with age, as does the incidence of rheumatic diseases. Indeed, more than 90% of prescriptions for NSAIDs are made to patients aged >65 years.

Their main benefit derives from their anti-inflammatory and analgesic effect that can improve the quality of life for patients with inflammatory disorders, but the use of these drugs is not innocuous since the major problem with the use of these drugs is that adverse events are common, especially GI morbidities, including complications in both upper and lower GI tract. In the upper GI tract, this may range from clinically insignificant blood loss and minor erosive changes to deep ulceration with the associated risk of hemorrhage or perforation. Adverse events of NSAIDs in the small and large intestine range from asymptomatic enteropathy to severe complications such as ulceration, bleeding, perforation, and stricture (Bjarnason *et al.*, 1993; Aabakken, 1999; Faucheron, 1999).

### UPPER GASTROINTESTINAL DAMAGE

NSAIDs can adversely affect both the upper and lower GI tract. The clinical significance and fre-

quency of adverse events with NSAIDs in the lower GI tract have been increasingly reported, but are less characterized than those from the upper GI tract. A study by Lanas *et al.* (2009) showed that the frequency of hospitalizations due to upper GI complications decreased over 10 years, whereas those from the lower GI tract increased.

Because of the broad and nonspecific definitions of GI disorders caused by the use of NSAIDs, as well as differences in patient populations, drugs, dosages, and periods of use, estimates of the prevalence of adverse effects vary greatly. In general, at least 10–20% of patients have dyspepsia while taking an NSAID, although the prevalence may range from 5 to 50% (Larkai *et al.*, 1987; Singh *et al.*, 1996).

Within a 6-month period of treatment, 5–15% of patients with rheumatoid arthritis can be expected to discontinue NSAID therapy because of dyspepsia (Singh *et al.*, 1996). According to prospective data from the Arthritis, Rheumatism, and Aging Medical Information System, 13 of every 1000 patients with rheumatoid arthritis who take NSAIDs for 1 year have a serious GI complication. The risk in patients with osteoarthritis is somewhat lower (7.3 per 1000 patients per year) (Singh and Triadafilopoulos, 1999).

From a clinical point of view, upper GI adverse events of NSAIDs can be categorized in different types:

- *Symptoms like dyspepsia, nausea, vomiting, abdominal pain, and heartburn.* They are the most usual adverse GI effects linked to NSAID use, and can be present in up to 40% of NSAID users (Brun and Jones, 2001). Sadly, the occurrence of these symptoms is not clearly predictive of the appearance of GI complications; about 50–60% of patients with complications will not have warning signs or symptoms (Armstrong and Blower, 1987). Conversely, as many as 50% of patients with dyspepsia have normal-appearing mucosa (Larkai *et al.*, 1987). About 10% of long-term NSAID users stop NSAID treatment because of these adverse GI effects (Brun and Jones, 2001).
- *NSAID-related gastroduodenal injury with unclear clinical significance.* This injury includes

a combination of subepithelial hemorrhages, erosions, and ulcerations. This damage happens in 30–50% of patients taking NSAIDs, but most lesions are asymptomatic, trifling, and disappear or reduce in number with continued use thanks probably due to the mucosal adaptation process (Lanas and Hunt, 2006). Only 15–30% of NSAIDs users have endoscopically confirmed GI ulcers (Larkai *et al.*, 1987; Lanas and Hunt, 2006). The gastric antrum is the most frequently affected location, but the rest of the GI tract can also be affected.

- **Symptomatic ulcers and GI complications (GI bleeding, ulcer perforation and obstruction).** GI complications occur in approximately 1–1.5% of patients in the first year of treatment with traditional NSAIDs (tNSAIDs) (Silverstein *et al.*, 1995, 2000; Bombardier *et al.*, 2000; Schnitzer *et al.*, 2004), and when symptomatic ulcers are included this figure rises to 4–5% (Tannenbaum *et al.*, 2006). The average relative risk (RR) of developing a serious GI complications is three- to five-fold greater among NSAID users than among nonusers. In one study by Lanas *et al.* (2006) among non-ASA NSAIDs, aceclofenac (adjusted (adj) RR 3.1; 95% confidence interval (CI) 2.3–4.2) was associated with the lowest RR of upper GI bleeding, whereas ketorolac (adj RR 14.4; 95% CI 5.2–39.9) had the highest (Table 33.1). Some studies have suggested that the first 2 months of treatment is the period of greater risk for complications, with an RR of 4.5% (95% CI 2.9–7) (de Abajo and García-Rodríguez, 2001; Lanas *et al.*, 2006), but the risk remains constant after that and for the period of NSAID treatment. The most important risk factor among patients with bleeding ulcers was NSAIDs or ASA use, that was found in 53% of bleeding patients, overcoming bleeding ulcers due to *Helicobacter pylori* infection (Ramsoekh *et al.*, 2005).
- **Mortality.** The worst outcome of GI complications is death, but mortality data associated with NSAID treatment are scant (Lanas *et al.*, 2005). In the USA, a report from the early 1990s estimated deaths at 16 500 per year. However, this may represent an overestimate because these data were extrapolated from a relatively small

Table 33.1 Relative risk and 95% confidence interval of upper GI bleeding associated with individual NSAID.

Individual NSAID	Age-adjusted RR (95% CI)
Ibuprofen	2.5 (2–3.1)
Diclofenac	2.1 (1.6–2.7)
Aceclofenac	1.4 (0.9–2.2)
Naproxen	4.0 (2.8–5.8)
Piroxicam	7.2 (4.8–10.7)
Indomethacin	3.3 (1.7–6.6)
Meloxicam	3.6 (1.8–7.2)
Ketorolac	8.0 (3.4–18.5)
Lomoxicam	3.5 (1.2–9.8)
Ketoprofen	6.5 (2.3–18.2)
Other NSAID	6.7 (2.6–16.9)

rheumatoid arthritis population to the general population (Singh and Ramey, 1998). In Spain, in the year 2001, 50 114 GI bleeding events were reported, with 18 191 GI complications and 1022 deaths attributed to ASA or other NSAID use. The mortality rate in this study was estimated as 15.3 deaths/100 000 NSAID/ASA users. Up to one-third of all NSAID/ASA deaths can be attributed to low-dose ASA use. However, this lower rate estimate could be due to fact that both NSAID-associated GI complications and death have been decreasing in recent years. It is important to highlight that recent data indicate that most peptic ulcer bleeding-linked deaths are not direct sequelae of the bleeding ulcer itself. Instead, mortality derives from multiorgan failure, cardiopulmonary conditions, or terminal malignancy, suggesting that improving treatments of the bleeding ulcer may affect mortality very little (Lanas, 2010).

In addition, it is very important to identify factors that increase the risk of GI events in NSAID users. Several studies have demonstrated what the major risk factors for GI events associated with NSAID therapy are (Langman *et al.*, 1994; Laine *et al.*, 2002; Lanas *et al.*, 2002; Fries *et al.*, 2004). Among them, the two main ones are prior history of complicated ulcers, the most important one, and age. Older age is the most common in NSAID users, and those aged >70 years are considered to carry a risk similar to those with history of peptic

ulcer. Advancing age increases risk by about 4% per year, probably because of the presence of other associated risk factors (Laine *et al.*, 2002).

Higher doses of NSAIDs increase the risk of gastroduodenal ulceration and upper GI complications (Carson *et al.*, 1987b; Gabriel *et al.*, 1991; Griffin *et al.*, 1991; Henry *et al.*, 1993; Garcia-Rodriguez and Jick, 1994; Langman *et al.*, 1994). The RR of developing peptic ulcer disease as a function of the dose of NSAID was investigated in a nested case-control study of 1400 patients over 65 years old enrolled in a Medicaid program in the USA (Griffin *et al.*, 1991). Patients had been hospitalized for confirmed peptic ulcer, and RRs were compared with over 7000 controls. For NSAIDs users, the risk increased with increasing dose, from an RR of 2.8 for the lowest to an RR of 8.0 for the highest dose category. Similar findings were reported from a study in the UK (Langman *et al.*, 1994). The previous use of NSAIDs in 1144 patients aged 60 years or older and admitted to hospital with peptic ulcer bleeding was compared with matched hospital and community controls. Among subjects who took a non-ASA NSAID during the previous month, the risk of ulcer complications increased with dose. NSAID users with a prior history of GI disease are more likely to experience adverse GI events when taking NSAIDs (Gabriel *et al.*, 1991; Garcia-Rodriguez and Jick, 1994; Weil *et al.*, 2000). Patients with a past history of peptic ulcer disease who are receiving NSAIDs are at a three- to four-fold higher risk of another episode of upper GI bleeding than are NSAID users with no past history of ulcer (Garcia-Rodriguez and Jick, 1994; Weil *et al.*, 2000).

The combined use of NSAIDs and corticosteroids is associated with approximately two to three times the risk of GI toxicity than is the use of NSAIDs alone (Carson *et al.*, 1987a; Gabriel *et al.*, 1991; Piper *et al.*, 1991; Garcia-Rodriguez and Jick, 1994; Weil *et al.*, 2000). Concomitant treatment with NSAIDs and corticosteroids increased the risk of hospitalization due to gastroduodenal events in elderly patients (Piper *et al.*, 1991). Relative risk of hospitalization was 1.1 with corticosteroids alone and 4.1 with NSAIDs alone, but was increased 15-fold when both were combined. It should be noted that peptic ulcer is a rare complication of

corticosteroid therapy alone (Conn and Poynard, 1994). The concurrent use of selective serotonin re-uptake inhibitors with NSAIDs has also been shown to potentiate the risk of upper GI bleeding (de Abajo *et al.*, 1999), as has the concomitant use of NSAIDs and anticoagulants (Shorr *et al.*, 1993; Weil *et al.*, 2000).

The role of *H. pylori* in patients taking NSAIDs and the potential effect of its eradication on the risk of upper GI events in infected NSAID users has been controversial. A meta-analysis of case-control studies showed synergy for the development of complicated and uncomplicated ulcer between *H. pylori* infection and NSAIDs (Chan *et al.*, 2001). *H. pylori* is also a risk factor in low-dose ASA users (Huang *et al.*, 2002; Lanas *et al.*, 2002), and even a post hoc analysis of the VIGOR trial suggested that the GI benefits of coxib are lower in coxib users with the infection than in those without the infection (Laine *et al.*, 2002).

Concomitant ASA use is another factor that increases the GI risk. It is important to note that more than 20% of patients who need NSAIDs also take low-dose ASA (LD-ASA). The addition of LD-ASA to tNSAIDs or coxibs increases the risk of GI events (estimated annual GI risk is 5.6–7.5% GI events/year) (Abraham *et al.*, 2008). Because of that, patients who combine an NSAID with LD-ASA are another high-risk group. Evidence from observational studies and randomized trials showed that the risk of coxib plus ASA is lower than NSAIDs plus ASA, but both were increased by ASA (Fries *et al.*, 2004; Johnson, 2005).

The identification of the cyclooxygenase (COX)-2 isoenzyme opened the door to development of NSAIDs that selectively inhibit COX-2. The main goal of this was to decrease the GI toxicity. Coxibs spare COX-1 and primarily inhibit COX-2 function, therefore decreasing but not eliminating NSAID-associated GI toxicity, and they are as efficacious as tNSAIDs in relieving pain (Silverstein *et al.*, 2000).

Data from large GI outcomes studies have characterized the GI effects of coxibs. The Celecoxib Long-term Arthritis Safety Study (CLASS) that compared high-dose celecoxib (400 mg bid), diclofenac (75 mg bid), and ibuprofen (800 mg three times daily) showed that symptomatic ulcers were

significantly less common among celecoxib users than among tNSAIDs users; however, ulcer complication rates were not significantly different (which was probably due to the confounding factor of concomitant LD-ASA use that was present in 22% of patients) (Silverstein *et al.*, 2000). However, a recent meta-analysis of available trials of the Cochrane Collaboration confirms that celecoxib at any dose was associated with statistically less GI events (Moore *et al.*, 2005). Moreover, the results of another large outcomes study, celecoxib versus naproxen and diclofenac in osteoarthritis patients (SUCCESS I Study), confirmed the significantly better safety profile of celecoxib compared with tNSAIDs (Singh *et al.*, 2006). The Vioxx Gastrointestinal Safety of Rofecoxib (VIGOR) study concluded that rofecoxib users had 50% fewer GI events than naproxen users did (Bombardier *et al.*, 2000). Later, in the comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), there was a 75% decrease in adverse GI events with the coxib (Schnitzer *et al.*, 2004). It is important to emphasize that although the incidence of adverse GI events increased in relation to the presence of GI risk factors, the differences from NSAIDs were maintained in subgroups of patients with and without risk factors (Skelly and Hawkey, 2003). Notwithstanding, it is important to note that three of the above commented outcome studies (CLASS, TARGET, and SUCCESS), one endoscopy study (Solomon *et al.*, 2005) and several epidemiological studies (Rahme *et al.*, 2004; Lanas *et al.*, 2005) have shown that the concomitant use of LD-ASA and coxib or tNSAIDs increases further the risk of upper GI bleeding in NSAID users and attenuates the GI advantage of a coxib over a tNSAID. A recent meta-analysis of randomized controlled trials has shown that coxib plus LD-ASA use was associated with a lower risk of upper GI complications when compared with non-selective NSAID plus LD-ASA (Rostom *et al.*, 2009). These GI benefits have to be balanced against the known cardiovascular risks, particularly with long-term use. The VIGOR and Adenomatous Polyp Prevention on Vioxx Trial Investigators (APPROVe) studies showed that rofecoxib was

associated with increased risk of cardiovascular events after 12 and 36 months of treatment when compared with naproxen (VIGOR) or placebo (APPROVe) (Bombardier *et al.*, 2000; Bresalier *et al.*, 2005). Other outcome studies have also shown that celecoxib at doses of 400 mg bid or 200 mg bid (Laine *et al.*, 2004), but not 400 mg once a day (Arber *et al.*, 2006), is associated with increased risk of cardiovascular events. Observational studies have shown, however, that celecoxib at 200 mg/day dose was not associated with increased risk of cardiovascular events (Bombardier *et al.*, 2000; Silverstein *et al.*, 2000). Recent observational studies have also shown that most NSAIDs (including nonselective) may be associated with increased cardiovascular risk, and this may be different for the different compounds, dose, and length of treatment (Hippisley-Cox and Coupland, 2005; Lanas *et al.*, 2005; Chan *et al.*, 2006). Of all traditional NSAIDs, diclofenac has been found to be the one increasing the cardiovascular risk the most (McGettigan and Henry, 2006). In the MEDAL program, etoricoxib at a dose of 60–90 mg/day was found to be not different to diclofenac in the incidence of cardiovascular events (Cannon *et al.*, 2006). The study also showed no differences in the incidence of upper GI complications between these two compounds, although the total number of events (symptomatic ulcers and complications) was statistically lower in etoricoxib users (Laine *et al.*, 2007). Lastly, both tNSAIDs and coxib may also increase blood pressure and reduce kidney function. A new class of drugs, the COX-inhibiting nitric oxide donators, have been shown to have reduced upper GI toxicity and a better profile on blood pressure than tNSAIDs (Hawkey *et al.*, 2003; Lanas, 2008; Mackenzie *et al.*, 2008) and could be a therapeutic option in patients with increased blood pressure that need NSAIDs, when they were available in the market (White *et al.*, 2009).

## LOWER GASTROINTESTINAL INJURY

In the last few years, it is becoming clear that NSAIDs can damage the small bowel and the colon, and that the magnitude of the damage may be greater than that of NSAID-associated gastropathy

(Adebayo and Bjarnason, 2006). There are several reasons for the low appreciation of NSAID enteropathy, which include among others that patients are usually asymptomatic and that diagnosis has, until recently, only been possible with the use of tests that are not available in clinical practice.

NSAID-induced damage to the intestinal epithelium is the consequence of a local effect after oral administration, a recurrent local effect due to the enterohepatic recirculation of the drug, and the systemic effects of the drug after absorption. The increased intestinal permeability is primarily a local intestinal event, but COX-1 and/or dual COX-1 and COX-2 inhibition plays a role in this initial event. Once intestinal permeability is increased, a cascade of events, driven by toxin and bacteria, induce inflammation and mucosal ulceration that could eventually progress to bleeding, perforation, or gut stricture due to fibrosis involved in the healing repair process (Lanas *et al.*, 2003; Adebayo and Bjarnason, 2006).

Subclinical mucosal damage is very frequent in the distal GI tract, since at least 60–70% of patients taking NSAIDs develop enteropathy (Adebayo and Bjarnason, 2006). Video capsule endoscopic studies have now shown that NSAIDs induce intestinal edema, petechias, erosions, and even ulceration in the small bowel, confirming previous autopsy data. Some reports suggest that these types of lesions are very frequent and can be seen in up to 40% of rheumatic patients taking NSAIDs (Graham *et al.*, 2005). The clinical significance of these findings is not yet clear; however, it may be possible that these lesions could explain why some patients on NSAIDs or LD-ASA develop bleeding of unknown source, iron-deficiency anemia, hypoalbuminemia, or even abdominal symptoms, particularly if the upper and lower endoscopy studies are normal. GI bleeding and perforation are the most clinically relevant side effects, since they contribute significantly to the increased risk of morbidity and mortality associated with these drugs. Current evidence suggests that NSAIDs increase the risk of lower GI bleeding and perforation to a similar extent to that seen in the upper GI tract. In a nationwide study on the mortality associated with NSAID use in 2001 in Spain (Lanas *et al.*, 2005), the case fatality rate was

almost identical for both upper and lower GI complications. A new study of this group has shown that the time trends of hospitalization due to GI complications is decreasing for upper GI complications and increasing for lower GI complications. Extensive validation of cases also showed that hospitalizations due to lower GI events were associated with increased mortality and consuming more resources than upper GI complications (Lanas, 2008).

Current data with COX-2-selective NSAIDs cannot conclude that all available coxibs have shown a safer profile in clinically relevant endpoints over tNSAIDS when considering the whole GI tract.

## LOW-DOSE ASPIRIN

ASA is an NSAID that inhibits COX, a key enzyme in the biosynthesis of prostaglandins (Simmons *et al.*, 2004). As with other NSAIDs, this property makes ASA an effective pain reliever at doses >325 mg daily. At low doses (75–325 mg daily), ASA predominantly inhibits the COX1 isoform, thereby inhibiting the synthesis of platelet thromboxane A2, a substance that promotes platelet aggregation. By irreversibly inhibiting COX1, aspirin has unique antiplatelet activity (Loll *et al.*, 1995), as COX1 inhibition with other nonselective NSAIDs is reversible (Oullet *et al.*, 2001). Today, nearly 36% of the population of the USA (>50 million people) take ASA for prevention (primary or secondary) of cardiovascular disease (Esmatjes *et al.*, 2003). This widespread use of ASA for vascular protection, together with its use as an analgesic and antipyretic drug in patients with osteoarticular pain and fever, makes this compound one of the most prescribed and used worldwide.

## UPPER GASTROINTESTINAL DAMAGE

LD-ASA administration has been associated with a wide variety of adverse events in the upper GI tract, from minor complications (petechiae or erosions) to more serious toxicity, including ulcers, complications, and even death (Figure 33.1). Most

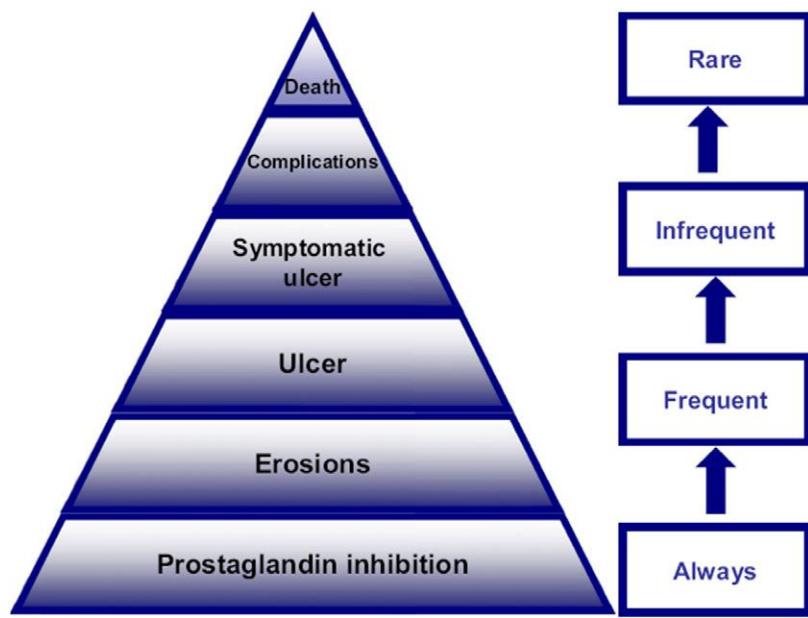


Figure 33.1 Biologic progression of gastrointestinal damage associated with low-dose aspirin.

patients who take ASA develop acute mucosal lesions, particularly relating to damage of the gastroduodenal mucosa, such as petechiae and erosions. Some erosions might progress into ulcers and/or associated complications; in some patients these complications can be fatal. In this way, a small minority of patients who take LD-ASA subsequently develop symptomatic ulceration.

The most frequent adverse events associated with LD-ASA that are clinically relevant include esophagitis and gastroduodenal ulcers or related complications (Lanas *et al.*, 2009). A meta-analysis published in 2006 of 14 randomized, placebo-controlled trials showed an RR of 2.07 (95% CI 1.61–2.66) and an attributable rate of 0.12% per year of major GI bleeding attributable to LD-ASA when compared with placebo (McQuaid and Laine, 2006). A nationwide study in Spain of mortality associated with hospital admission because of GI complication events found an NSAID-associated or ASA-associated death rates of 21.0 and 24.8 cases per 1 000 000 people, respectively, or 15.3 deaths per 100 000 patients who used NSAIDs or ASA (Lanas *et al.*, 2005). LD-ASA use was respon-

sible for between 8.2% and 12.2% of all complications and deaths.

#### LOWER GASTROINTESTINAL INJURY

Growing evidence indicates that aspirin can damage the GI tract below the angle of Treitz. Long-term ASA users can suffer small bowel bleeding and protein loss that might contribute to iron-deficiency anemia and hypoalbuminemia (Fortun and Hawkey, 2005). The mechanisms of damage and the real clinical impact of most observations are, however, far from being understood (Fortun and Hawkey, 2005). Prostaglandin inhibition attributable to inhibition of COX by aspirin use is present in all segments of the digestive tract. A study in healthy volunteers has shown that even low-dose enteric-coated aspirin was associated with damage in 50% of volunteers, and some developed ulcers in their small bowel (Smecuol *et al.*, 2009). The clinical significance of these findings is not yet clear. However, it might be possible that these small bowel lesions could explain why some patients on LD-ASA develop bleeding of “unknown”

source, iron-deficiency anemia, or even abdominal symptoms.

## CLOPIDOGREL

Cardiology guidelines recommend the antithrombotic agent clopidogrel for patients who are unable to take ASA because of previous GI intolerance. (Bhatt *et al.*, 2008; Harrington *et al.*, 2008) The findings of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study (clopidogrel at 75 mg daily, compared with ASA at 325 mg daily) showed that clopidogrel resulted in a lower incidence of dyspepsia than ASA (15.01% versus 17.06%), less bleeding within the GI tract, with the site not stated (1.99% versus 2.66%), and a lower incidence of severe GI bleeding (0.49% versus 0.71%). Although the differences between the two treatments were statistically significant (all  $P < 0.05$ ), the clinical relevance of these findings is unclear (CAPRIE Steering Committee, 1996). In clinical practice, two case-control studies have found clopidogrel to be associated with a similar RR of ulcer bleeding to LD-ASA (Ibáñez *et al.*, 2006, Lanas and Hunt, 2006). A clinical outcome trial found recurrent bleeding rates of 8.6% in patients receiving clopidogrel alone versus 0.7% of similar patients taking ASA plus esomeprazole for 12 months (Chan *et al.*, 2005).

## BIPHOSPHONATES

Bisphosphonates are inhibitors of bone resorption. Decreasing bone resorption is advantageous in patients with osteoporosis and in patients with high turnover diseases of bone (bone metastases, Paget's disease of bone), but there are concerns that these benefits may be lost in the long term by accumulation of old, less mechanically competent bone.

Upper GI discomfort is the most commonly reported adverse event with oral nitrogen-containing bisphosphonates and often leads to cessation of treatment. These events are beyond dispute, but controversies surround the exact mechanism underlying the mucosal lesions and whether there is a higher risk of lesions with alendronate than with

risedronate. The latter was recently addressed by Cadarette *et al.* (2009), who analyzed GI events in 10416 bisphosphonate users from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) claims database. The analysis covered 10420 new recipients of weekly alendronate and risedronate (35 mg). In the study population, 35% of patients had a history of GI events, 13.5% were exposed to glucocorticoids, and 14% received NSAIDs. On treatment, upper GI symptoms were recorded in 662 of 5818 alendronate users and 516 of 4602 risedronate users, adjusted incidence rate ratio 0.96 (95% CI 0.85–1.07) for risedronate versus alendronate,  $P < 0.45$ . A significant difference was observed, however, in the likelihood of changing therapy, favoring risedronate. Also, a borderline lower incidence of upper GI endoscopy was also observed with risedronate (0.82 (0.62–1.07),  $P = 0.14$ ). This may mean that risedronate is somewhat better tolerated or possibly that physicians are more likely to act on upper GI complaints in alendronate-treated patients. Recently, the US Food and Drug Administration reported on 23 patients in the USA who had developed esophageal cancer while taking alendronate (Wysowski, 2009). The number of expected cases is unknown as the size of the alendronate-treated population for the USA has not been made public. Two subsequent rapid reports from health databases found that the risk of esophageal cancer is decreased in users of oral bisphosphonates, compared with a background population with the same comorbidity and fracture history (Abrahamsen *et al.*, 2009) and compared with patients treated with other antiosteoporotic drugs (Abrahamsen *et al.*, 2009). This may not simply represent channeling of bisphosphonates to patients with a low likelihood of upper GI symptoms; patients who begin antiosteoporotic therapy can be shown to be at increased risk of gastroduodenal and esophageal events even before therapy is begun (Vestergaard *et al.*, 2010). Compared with the reduction in the risk of classical osteoporotic fractures, the risk of harm caused by bisphosphonates is relatively low, at least based on information presently available from clinical trials and from large administrative health databases. Physicians should target bisphosphonates only to patients who can be shown to be at clearly elevated

risk of fracture, and it would be prudent to reassess bone mass density and risk profile after 3–5 years of therapy to avoid continuing treatment in patients at low fracture risk.

## SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

It has recently been suggested that the ingestion of selective serotonin re-uptake inhibitors is associated with upper GI bleeding (de Abajo *et al.*, 1999). From a general practice research database, 1651 cases of GI bleeding were identified along with 10 000 controls matched for age, gender, and year of identification. Current use of selective serotonin re-uptake inhibitors or other antidepressants within 30 days before GI bleeding was assessed. The use of selective serotonin re-uptake inhibitors was identified in 3.1% of patients with upper GI bleeding compared with 1% of controls. The RR was unaffected by gender, age, dose, or duration of treatment. The absolute risk of upper GI bleeding was estimated as one case per 8000 prescriptions or one case per 1300 users. The authors also reported that the risk of upper GI bleeding was greatly potentiated by the concomitant use of NSAIDs and, to a lesser extent, LD-ASA (de Abajo *et al.*, 1999). Further studies using alternative methods to confirm these observations have been recommended (Po, 1999).

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# Hematological Adverse Drug Reactions

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## INTRODUCTION

The scope of hematology for our purposes in this chapter is the consideration of effects on (a) the different cell types that circulate in the peripheral blood; (b) the bone marrow that generates and replenishes those cells, many of which have a short lifespan; and (c) the mechanisms involved in plasma coagulation that maintain hemostasis.

One of the adverse drug reactions (ADRs) most feared by both prescribers and manufacturers alike is the unpredictable, idiosyncratic, and unexpected occurrence of peripheral blood cytopenias due to myelosuppression. These are type B reactions according to the classification of Rawlins and Thompson (1977). The demonstration of an association with this type of reaction has been responsible for the withdrawal of licensing of many drugs over the years by the relevant authorities.

It is salutary to reflect that, in the industrialized world, serious life-threatening hematological ADRs

are also a regular, deliberate and accepted part of everyday medical practice. Predictable dose-dependent, reversible, "type A" cytopenias are the anticipated counterpart of effective cytotoxic therapy for malignant disease. Strategies and facilities for monitoring and detection followed by appropriate supportive intervention with antimicrobial agents, blood product, and growth factor therapy are integral to the practice of physicians prescribing these drugs. Whilst this chapter will concentrate on the rarer type B reactions, it is important to note that the advances in supportive care and expertise developed in relation to cytotoxic therapy that have led to improved outcomes and the safe intensification of many chemotherapy regimes are equally applicable to idiosyncratic reactions. It is critically important that affected patients are recognized early and referred to appropriate expertise and facilities.

Myelosuppression is the principal dose-limiting effect for most cytotoxic agents, but in the context

of the treatment of malignant disease it is often appropriate to accept a narrow therapeutic index for effective agents. Although rare, there are examples where this can also be justified for type B reactions in nonmalignant disease. Clozapine is an example of a uniquely effective drug in a difficult therapeutic field (refractory schizophrenia). Despite an established association with the potentially dangerous ADR of agranulocytosis, the drug is specially licensed for use under strictly specified monitoring conditions.

Genetic risk factors are being identified, which may predispose patients to reactions with particular drugs. As marker tests become available, previously apparently idiosyncratic reactions may be anticipated for certain individuals, allowing dose adjustment or alternative treatment choices to prevent ADRs.

This chapter will review the types of reactions by which drugs may cause cytopenias or affect plasma coagulation. By considering examples of documented ADRs, strategies for predicting, detecting, and preventing reactions, as well as managing those that do occur, are discussed.

## MECHANISMS OF ADVERSE DRUG REACTION-CAUSING CYTOPENIAS

A reduction, below the recognized reference range, in the numbers of any cell type in the peripheral blood must be because of either a reduction in the production of that particular cell type by the marrow (myelosuppression) or a shortened survival of the cell type in the peripheral blood.

### MYELOSUPPRESSION

Reduction in marrow output as an ADR may be caused by a reduction in marrow cellularity (hypoplasia or aplasia, depending on severity). This may globally affect all cell lines, as in aplastic anemia (AA), or may selectively affect only one lineage (e.g., pure red cell aplasia (PRCA)). It may also be caused by interference with normal maturation in a cellular marrow (dysplasia), as in megaloblastic or sideroblastic anemia.

### CYTOTOXIC DRUGS

Most cytotoxic drugs cause “type A” myelosuppressive ADRs by interfering with DNA synthesis or producing chemical damage to DNA that interferes with its replication. Others attack the mitotic spindle, inhibit protein synthesis, or induce cell differentiation (Chabner and Wilson, 1995). Normal cells recover, but it is not surprising that dose-limiting toxicity is seen in the marrow that contains the most mitotically active normal cells in the body.

A rare indirect cause of drug-induced myelosuppression is the late development of myelodysplasia or leukemia because of genetic damage from previous exposure to cytotoxic and other drugs (Le Beau *et al.*, 1986), but this is not considered further here.

### OTHER DRUGS

Non-cytotoxic drug effects causing acquired marrow failure are more difficult to establish. Theoretical mechanisms include the induction of defects in the hemopoietic stem cells, damage to the stromal microenvironment of the marrow, inhibition of the production or release of hemopoietic growth factors, or induction of humoral or cellular immunosuppression of marrow cells (Young and Maciejewski, 1997).

### CONSTITUTIONAL RISK FACTORS

Susceptibility to type A reactions varies between individuals because of differences in absorption and metabolism of the drug (pharmacokinetic changes) or differences in target organ sensitivity (Rawlins and Thomas, 1998). Some apparently idiosyncratic type B reactions may actually become more appropriately classified as predictable type A reactions for particular individuals with constitutional risk factors, once mechanisms are elucidated and tests to identify those at risk become available.

The antibiotic chloramphenicol was one of the first drugs for which epidemiological evidence indicated a causal association with apparently idiosyncratic AA. An early report of the coincidence of this very rare reaction in a pair of identical twins suggested the possibility of genetic susceptibility (Nagao and Mauer, 1969).

The antipsychotic agent clozapine has an epidemiologically established association with agranulocytosis (Amsler *et al.*, 1977), which is considered further later in this chapter. An apparently increased risk of this complication correlated with human leukocyte antigen (HLA) phenotype (Dettling *et al.*, 2001). Analysis of a cohort of patients from the Long Island Jewish Medical Center in New York (Lieberman *et al.*, 1990) found that the HLA-B38 phenotype had an incidence of 83% in patients with agranulocytosis and 20% in clozapine-treated patients who did not develop the complication. The B38 phenotype was part of a haplotype more common in the Ashkenazi Jewish population, and the subsequent work identified two different haplotype associations with clozapine-induced agranulocytosis: one in Ashkenazi Jewish patients and one in non-Jewish patients (Corzo *et al.*, 1994). The association of both haplotypes with variants of the heat-shock protein-70 (HSP-70), encoded by loci within the major histocompatibility complex (MHC) region, suggests linkage rather than direct association of the HLA in genetic susceptibility (Corzo *et al.*, 1995).

6-Mercaptopurine (6-MP) is a thiopurine used extensively in the treatment of childhood acute lymphoblastic leukemia. Azathioprine is a pro-drug of 6-MP in widespread use as an immunosuppressive agent in a variety of autoimmune conditions.

6-MP is inactivated by the enzyme thiopurine methyltransferase (TPMT). Genetically determined variations in TPMT activity were found to be associated with occasional unexpectedly severe myelosuppression associated with 6-MP (Evans *et al.*, 1991) and azathioprine (Lennard *et al.*, 1989). The determination of TPMT activity, either by the measurement of enzyme activity or by the molecular detection of the polymorphisms associated with reduced activity, is feasible and could allow avoidance of drug in deficient patients and logical dose stratification in heterozygotes. A pharmacoeconomic case has been made for this approach before the use of azathioprine in dermatological practice (Jackson *et al.*, 1997). Polymerase chain reaction (PCR)-based techniques for relevant genotypic analysis offer an attractive alternative to the performance of radiochemical activity assays in pharmacogenetic screening (Coulthard *et al.*, 2000).

Methotrexate (MTX) is a dihydrofolate reductase inhibitor used extensively as a cytotoxic agent in lymphoid and other malignancies and as an immunosuppressive agent particularly in inflammatory arthritis. Polymorphisms in the methylenetetrahydrofolate (*MTHFR*) gene have been associated with variation in efficacy and toxicity of MTX in rheumatoid arthritis patients (Urano *et al.*, 2002).

These examples suggest that technologies for predicting the risk of previously apparently completely idiosyncratic reactions may become available for at least some drugs that may help to reduce the incidence of these dangerous complications.

### SHORTENED PERIPHERAL BLOOD CELL SURVIVAL

Shortened survival of cells in the peripheral blood by ADR is most commonly mediated by immune destruction. Antibodies to the drug itself, alone or as a hapten in association with cell surface antigens or in immune complexes, may initiate effector mechanisms that damage cells. Alternatively, autoantibodies may occur because of altered immune regulation. Peripherally destructive immune mechanisms in ADRs more commonly only affect one cell type but may involve red cells, granulocytes, or platelets. A shortened red cell survival (hemolysis) may also be mediated by oxidant stress, particularly in more susceptible individuals (e.g., those with inherited glucose-6-phosphate dehydrogenase (G6PD) deficiency). Red cell and platelet survival may both be shortened by endothelial damage, causing inappropriate intravascular plasma coagulation or platelet aggregation in disseminated intravascular coagulation (DIC) and thrombotic thrombocytopenic purpura (TTP), respectively.

Table 34.1 lists mechanisms of cytopenias in ADRs together with examples of implicated agents.

### MECHANISMS OF ADVERSE DRUG REACTION-AFFECTING HEMOSTASIS

Clearly, antithrombotic drugs such as oral and parenteral anticoagulants, thrombolytic, and antiplatelet agents compromise hemostatic mechanisms at therapeutic doses as well as in overdose, in

Table 34.1 Mechanisms of ADR-causing peripheral blood cytopenia: types of reaction, clinical features, examples of implicated agents, etc. (some of which are further discussed in the text).

### **Myelosuppression**

#### **AA**

<i>Clinical findings</i>	Pancytopenia, hypocellular marrow
<i>Example drugs</i>	
Antimicrobials	Chloramphenicol, cotrimoxazole, sulfonamides, nitrofurantoin, zidovudine, quinacrine, amodiaquine, mepacrine, pyrimethamine, chloroquine, mebendazole
Antirheumatics	Gold, penicillamine, indomethacin, oxyphenbutazone, phenylbutazone, piroxicam, sulfasalazine, diclofenac, sulindac, allopurinol
Anticonvulsants	Phenytoin, carbamazepine, felbamate
Psychotropic agents	Phenothiazines, dothiepin, mianserin
Cardiovascular drugs	Captopril, lisinopril
Other drugs	Tolbutamide, acetazolamide, alpha-interferon
<b>PRCA</b>	
<i>Clinical findings</i>	Anemia, reticulocytopenia, absent marrow red cell precursors
<i>Example drugs</i>	Azathioprine, maloprim, sodium valproate, erythropoietin
<b>Megaloblastic anemia</b>	
<i>Clinical findings</i>	Anemia, macrocytosis, megaloblastic erythropoiesis in marrow
<i>Example drugs</i>	Methotrexate, trimethoprim, phenytoin, azathioprine, hydroxycarbamide, fluorouracil, cytarabine, zidovudine
<b>Sideroblastic anemia</b>	
<i>Clinical findings</i>	Anemia, ring sideroblasts in marrow
<i>Example drugs</i>	Isoniazid, pyridoxine, chloramphenicol, cycloserine, penicillamine, phenacetin, linezolid

### **Myelosuppression±peripheral cell destruction**

#### **Agranulocytosis**

<i>Clinical findings</i>	Severe neutropenia, sudden onset. Reduced marrow granulopoiesis or "maturation arrest"
<i>Example drugs</i>	Propylthiouracil, carbimazole, methimazole, clozapine, sulfasalazine

### **Peripheral cell destruction**

#### **AIHA**

<i>Clinical findings</i>	Anemia, reticulocytosis, unconjugated hyperbilirubinemia, positive direct antiglobulin (Coombs) test
<i>Example drugs</i>	Methyldopa, mefenamic acid, nomifensine

#### **ITP**

<i>Clinical findings</i>	Thrombocytopenia, normal plasma coagulation, normal marrow
<i>Example drugs</i>	Procainamide, quinidine, quinine, NSAIDs, heparin

#### **Non-immune hemolysis**

<i>Clinical findings</i>	Anemia, reticulocytosis, unconjugated hyperbilirubinaemia, negative Coombs test
<i>Example drugs</i>	Dapsone, primaquine, nitrofurantoin, oxidant drugs in G6PD deficiency

#### **TTP**

<i>Clinical findings</i>	Thrombocytopenia, anemia, reticulocytosis, jaundice. Normal plasma coagulation.
<i>Example drugs</i>	Microangiopathic picture (blood film)

#### **Ticlopidine**

a manner analogous to the "type A" occurrence of cytopenias with cytotoxic agents. Interactions of drugs disrupting the therapeutic control of oral anticoagulant treatment are another important cause of ADR. These reactions will not, however, be considered here.

Hemostasis is obviously affected by ADRs causing thrombocytopenia, as discussed in the previous section.

Other drugs may predispose to hemorrhage by unintended effects on platelet function, by affecting the production of plasma coagulation factors, or

Table 34.2 Mechanisms of ADR causing abnormal plasma coagulation.

<b>Thrombocytopenia (Table 34.1)</b>	
<b>Impaired platelet function</b>	
<i>Clinical features</i>	Bruising, mucosal bleeding, normal platelet count, normal plasma coagulation
<i>Example drugs</i>	Aspirin, NSAIDs, dipyridamole, prostacyclin, theophylline, caffeine, dextran, high-dose penicillin
<b>Hypoprothrombinemia</b>	
<i>Clinical features</i>	Bruising, prolonged prothrombin time
<i>Example drugs</i>	Cephalosporins
<b>Disseminated intravascular coagulation</b>	
<i>Clinical features</i>	Bleeding, prolonged coagulation times, reduced fibrinogen, thrombocytopenia
<i>Example drugs</i>	Asparaginase
<b>Increased activated protein C resistance</b>	
<i>Clinical features</i>	Increased risk of venous thromboembolic (VTE) disease
<i>Example drugs</i>	Estrogen-containing medications: oral contraceptives, hormone replacement therapy
<b>Lupus anticoagulant</b>	
<i>Clinical features</i>	Prolonged activated partial thromboplastin time, increased risk of VTE
<i>Example drugs</i>	Procainamide, quinidine, alpha-interferon

by causing the consumption of coagulation factors (as in DIC). A predisposition to thrombosis may be caused by acquired resistance to the anticoagulant effect of activated protein C (e.g., estrogen-containing medications) or by the stimulation of acquired antibodies to phospholipid (the “lupus anticoagulant” phenomenon).

Table 34.2 lists mechanisms of hemostatic ADRs (for non-antithrombotic drugs) together with examples of implicated agents.

## SOME EXAMPLES OF INDIVIDUAL ADVERSE DRUG REACTION: PHARMACOVIGILANCE IN ACTION

### MYELOSUPPRESSIVE ADVERSE DRUG REACTION

#### Aplastic Anaemia

##### *Quinacrine (Atabrine)*

This antimalarial was perhaps the first drug for which a robust statistical association with AA was established (Caster, 1946). It was widely administered as prophylaxis to US troops in malarial areas in 1943–1944, and an incidence of AA of 7–28 cases per 100 000 per year was compared with 1–2 cases per 100 000 in personnel stationed in non-malarial areas not receiving the drug. A character-

istic skin rash often preceded the hematological complication.

#### *Chloramphenicol*

This broad-spectrum antibiotic was introduced in 1948. Even before its clinical use, the theoretical possibility of hematological toxicity had been raised because of its chemical similarity to the anti-pyretic amidopyrine that has an association with neutropenia (Smadel and Jackson, 1944). Reversible changes affecting hemopoiesis are relatively common with prolonged use of the drug and may be because of mitochondrial effects principally altering iron metabolism (Osaki, 1979). Case reports and subsequent epidemiological studies established a causative link with apparently idiosyncratic AA (Modan *et al.*, 1975), the occurrence of which is not related to the dose or duration of drug exposure. Chloramphenicol is also used topically for the treatment of conjunctival infection, and there was controversy about whether chloramphenicol eye drops may cause AA (Rayner and Buckley, 1996). Cases of AA in patients receiving chloramphenicol eye drops have been reported, but the incidence of AA does not appear to be above the background level to be expected in the absence of any drug exposure. A study in the UK, where chloramphenicol eye drops are still widely prescribed, failed to

demonstrate detectable serum levels of chloramphenicol after 1–2 weeks of topical ocular treatment (Walker *et al.*, 1998). The authors felt that this was theoretical evidence against a potential mechanism for toxicity with this route of administration, which together with the absence of epidemiological evidence failed to support calls for the abolition of topical chloramphenicol use. Indeed, in the UK, it is now obtainable “over the counter” without medical prescription.

#### *Gold and Penicillamine*

AA is a rare complication with these second-line agents for the treatment of inflammatory arthritis. Neutropenia and/or thrombocytopenia often precede the development of AA, and regular monitoring allows the cessation of drug before this complication arises (Willame *et al.*, 1987).

#### *Phenylbutazone*

This potent nonsteroidal anti-inflammatory drug (NSAID) was associated with a significant incidence of AA and its use is now restricted in the UK to the management of severe refractory ankylosing spondylitis under hospital supervision.

#### **SELECTIVE MARROW HYPOPLASIA**

##### **Pure Red Cell Aplasia**

This is characterized by isolated anemia and reticulo-cytopenia and the absence of nucleated red cell precursors in an otherwise normal marrow. This reaction is rare, but there is overlap with AA as with agranulocytosis in the implicated causative agents (Ammus and Unis, 1987).

#### *Erythropoietin*

Between 1993 and 1998, there were sporadic reports of PRCA associated with neutralizing antibodies to erythropoietin presenting with resistance to therapy in patients receiving the agent subcutaneously for

renal anemia. Between 1998 and 2000, an increased number of cases were reported in France, and 12 of 13 patients had received one particular subcutaneous formulation (Eprex) (Casadevall *et al.*, 2002). In 2002, several European regulatory authorities mandated intravenous rather than subcutaneous administration of the Eprex product as a consequence. A detailed analysis of reports of this ADR for all preparations of erythropoietin from the US Food and Drug Administration and from the manufacturers between January 1998 and April 2004 was reported in the *New England Journal of Medicine* (Bennett *et al.*, 2004). Subcutaneous administration of proteins is known to be associated with an increased potential to induce antibody formation (Porter, 2001). In the case of subcutaneous Eprex, it seems that stabilizers and lubricating oil in the plungers of the prefilled syringe preparations were responsible for the increased immunogenicity rather than the erythropoietin itself (Locatelli *et al.*, 2004).

#### **Drug-Induced Agranulocytosis**

Neutropenia is defined by the lower limit of the reference range, which will vary between laboratories but becomes progressively significant in terms of infection risk below  $1.5 \times 10^9/\text{L}$ . Agranulocytosis refers to severe neutropenia  $<0.5 \times 10^9/\text{L}$ . The principal mechanism in drug-induced agranulocytosis is immune, and a degree of peripheral neutrophil destruction is involved as well as myelosuppression. The cellularity of the marrow, and the degree of representation of early myeloid cells, may help to predict recovery time and response to colony-stimulating factor (CSF) therapy (Julia *et al.*, 1991; Sprikkelman *et al.*, 1994). There is considerable overlap with drugs implicated in the etiology of idiosyncratic AA. Some drugs merit further individual consideration.

#### *Clozapine*

This antipsychotic agent clozapine was introduced in the late 1960s as an effective therapy for schizophrenia without the extrapyramidal side effects associated with other major tranquilizers. In

Finland in 1975, 16 patients taking clozapine developed neutropenia, an estimated incidence of 2% (Amsler *et al.*, 1977). Half of them died of infective complications. Because of its unique therapeutic advantages, the drug has not been withdrawn, but mechanisms for ensuring careful monitoring were established. The use was restricted to patients registered with the Clozaril Patient Monitoring Service run by the original drug manufacturer, Novartis Pharmaceuticals. With subsequent generic availability, similar monitoring systems have been set up by generic manufacturers. Regular blood count specimens are required to be sent to the central laboratory of the monitoring service, which requires to confirm that the total white cell count is  $>3.0 \times 10^9/\text{L}$  and the neutrophil count  $>1.5 \times 10^9/\text{L}$  and that significant downward trends in values above these levels are not occurring before drug supply is issued just to last until the next count is due. All instances of agranulocytosis are therefore reported, and large epidemiological studies (Alvir *et al.*, 1993; Munro *et al.*, 1999) have subsequently accurately confirmed an incidence of approximately 1% for this complication and have helped to identify potential risk factors, as described above. Early discontinuation and prompt recognition enabling immediate appropriate supportive care have markedly reduced the incidence and morbidity of this severe reaction to acceptable levels.

#### *Antithyroid Drugs*

Propylthiouracil, carbimazole, and methimazole (the active ingredient to which carbimazole is metabolized) are associated with an incidence of agranulocytosis of 3/100 000 per year. The highest incidence is in the first 3 months of treatment, perhaps as susceptible individuals identify themselves (Cooper *et al.*, 1983).

#### *Sulfasalazine*

Agranulocytosis was found to have an incidence in 1/700 patients within the first 3 months of treatment, following which the risk was low (Keisu and Ekman, 1992).

### SHORTENED PERIPHERAL BLOOD CELL SURVIVAL ADVERSE DRUG REACTION

#### Nomifensine and Autoimmune Hemolytic Anaemia

Nomifensine was introduced in Europe in 1976 as a new tricyclic antidepressant with fewer anti-cholinergic and sedative effects than its older counterparts. The problematic toxicity of standard tricyclics in overdosage made it an attractive alternative. Autoimmune hemolytic anaemia (AIHA) had not been observed during pre-licensing studies. Four cases were reported in the UK in 1978–1979 (Stonier, 1992), but the incidence was thought to be very rare. An increase in reports between 1983 and 1986, including a fatal case, led to the withdrawal of the drug from the market by the manufacturer.

#### Heparin-Induced Thrombocytopenia

Many patients receiving anticoagulation with heparin will demonstrate mild, transient, clinically insignificant and non-immune minor thrombocytopenia. The rarer immune-mediated heparin-induced thrombocytopenia is caused by an immunoglobulin G (IgG) autoantibody directed against a complex of heparin and platelet factor 4 (PF4), a platelet surface protein, which may appear after 7–10 days of heparin therapy (or earlier if the patient has been exposed previously). Although more frequent with unfractionated heparin, it can also occur with low molecular weight heparin preparations (Warkentin *et al.*, 1995). Unlike with other drug-induced immune thrombocytopenias (ITPs), numerically severe thrombocytopenia is not usual, and the platelet nadir is typically around  $50 \times 10^9/\text{L}$ . However, it induces a highly prothrombotic state because of immune-mediated platelet activation. New venous or arterial thrombosis occurs in some 50% of cases, and there is a high morbidity/mortality. Patients receiving heparins should have regular platelet count monitoring. If significant thrombocytopenia and/or new thromboembolic events occur in heparinized patients, then heparin should be discontinued and tests for platelet/PF4 antibodies undertaken. If continuing anticoagulant treatment is required, then a direct thrombin

inhibitor such as hirudin or argatroban is appropriate (Schiele *et al.*, 1995).

## MANAGEMENT OF HEMATOLOGICAL ADVERSE DRUG REACTION

Once a hematological ADR is suspected, the two principal components of appropriate management are first the identification and withdrawal of any potentially implicated agent and second the provision of necessary expert supportive care of the patient pending recovery.

### IDENTIFICATION AND WITHDRAWAL OF CAUSATIVE AGENT

This may be readily apparent in the case of cytotoxic chemotherapy. Idiosyncratic reactions may be suspected by exposure to a drug having an established association with myelosuppression. Newly licensed preparations in the drug history of patients presenting with otherwise unexplained marrow failure should be regarded with suspicion.

It is critically important that all potentially implicated drugs are discontinued at the first sign of idiopathic myelosuppression. Unlike with some allergic reactions, cross-reactivity between different drugs of the same class for these reactions is not problematical. It is safer to stop or switch all potentially implicated medication if there is any doubt that it may be involved.

### SUPPORTIVE CARE

Hematological cytopenias (especially neutropenia) are potentially life threatening, and it is critically important that patients are referred to specialists with appropriate expertise and facilities for management (Carey, 2003). Strategies for the logical empirical antimicrobial treatment of presumed infection in febrile neutropenic patients are well developed. Red cell and platelet transfusion support may be appropriate for anemia and thrombocytopenia, respectively. Recombinant growth factors such as granulocyte CSF and erythropoietin can help to reduce the severity and duration of neutropenia and anemia, respectively.

Specific therapy for prolonged drug-induced marrow failure that does not improve after causative drug withdrawal involves the consideration of immunosuppressive therapy or allogeneic stem cell transplantation, as for idiopathic AA (Bacigalupo *et al.*, 2000).

## STRATEGIES FOR THE DETECTION AND PREVENTION OF IDIOSYNCRATIC HEMATOLOGICAL ADVERSE DRUG REACTIONS

### INDIVIDUAL MONITORING

Regular full blood count (FBC) monitoring is clearly indicated when drugs associated with type A hematological ADR, such as cytotoxic agents, are prescribed. For idiosyncratic reactions, early warning rather than prevention is the main goal. For a small number of drugs with a significant risk of myelosuppression, regular monitoring, as for cytotoxic therapy, is required or desirable (Table 34.3). Patient and carer education in the significance of symptoms suggestive of infection, bleeding, and anemia are again important. Monitoring may prevent a minor cytopenia developing into a more severe aplasia by indicating the discontinuation of gold or penicillamine therapy where a pro-

Table 34.3 Some non-cytotoxic drugs for which routine blood count monitoring is justifiable.

Drug	Incidence of idiopathic myelo-suppression (where assessed)
Gold salts	1 in 700 patients in first 3 months; thereafter risk is low
Penicillamine	7–8/1000 in first year; 7/10 000 thereafter
Azathioprine	
Sulfasalazine	
Clozapine	
Carbamazole, methimazole, thiouracils	3/10 000 per year, mainly in first 3 months of treatment
Azidothymidine	
Alpha-interferon	

dromal gradual count reduction may precede a severe reaction. Monitoring itself will clearly not prevent a suddenly precipitate agranulocytosis with, for example, antithyroid drugs, which may occur in between even quite frequent monitoring visits. It does, however, reinforce patient education in the potential complication, and their access to FBC increasing the likelihood of early detection.

The case for routine surveillance monitoring with antithyroid drugs is controversial (*Drug and Therapeutics Bulletin*, 1997a,b). A prospective study in Japan found a 0.4% incidence of agranulocytosis occurring within the first 3 months of treatment with methimazole or propylthiouracil, and 43 of 55 the affected patients were detected by routine monitoring before the onset of symptoms (Tajiri *et al.*, 1990). Counts recovered in all the patients, and 29 did not develop any infection. Monitoring clearly allowed the prevention of a potentially dangerous complication for a significant group of patients in this study, but the pharmacoeconomic justification for routine monitoring in this situation is not universally accepted.

#### INDIVIDUAL RISK-FACTOR IDENTIFICATION

In addition to FBC monitoring, pretreatment assessment of TPMT either by enzyme activity or by genetic markers before azathioprine or 6-MP treatment and MTHFR status before MTX therapy, as discussed above, may assist prevention. It is likely that additional predictive tests will become applicable as pharmacogenetic knowledge increases.

#### SPONTANEOUS REPORTING

The notification of suspected occurrences of drug-induced myelosuppression to national licensing authorities is an important contribution to prevention, and particularly important for idiosyncratic reactions to new agents. The UK "Yellow Card" scheme informs an ADRs On-line Information Tracking database that captures all reports for separate drugs and categorizes hematological reactions into nonserious, serious, and fatal categories. Whilst such data, which have no reliable numerator, cannot define incidences of reactions, they can highlight suspicions of new potentially significant

reactions and follow trends in frequency and severity of established reactions.

#### CONCLUSION

Though relatively rare, idiosyncratic hematological ADRs are potentially life threatening. Any patient receiving drug therapy who presents with symptoms of anemia, unusual infection, or bleeding should have simple screening tests, including an FBC performed. Significant cytopenias or coagulation derangement should prompt the consideration of the possibility of ADRs and discontinuation or substitution of potentially implicated agents. Patients should be investigated and managed by staff with appropriate expertise and facilities for relevant supportive care.

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# Hepatic Adverse Drug Reactions

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## INTRODUCTION

Because the liver is central to the biotransformation of virtually all drugs and foreign substances, drug-induced liver injury (DILI) is a potential complication of nearly every medication that is prescribed. The liver is the most common target organ for toxicity encountered during the course of drug development (Ballet, 1997). Despite considerable progress in toxicological studies, the concordance between liver toxicity in animals and humans remains at about 55% (Olsson *et al.*, 2000), which is clearly too low to be relied upon. This was highlighted by the tragic fialuridine trial, wherein potential mitochondrial injury leading to hepatic failure (resulting in five deaths and two liver transplants among 15 treated patients) was not detected during preclinical testing in rats, dogs, monkeys, and woodchucks (infected with the woodchuck hepatitis virus) treated with the drug for a month (McKenzie *et al.*, 1995; Josephson, 1996).

Between 1998 and 2005, reported serious and fatal adverse events increased nearly threefold, four times faster than the increase in the total number of outpatient prescriptions during the same period (Moore *et al.*, 2007). Hepatotoxicity accounted for suspension or withdrawal of 47 drugs in the USA or Europe (Suzuki *et al.*, 2010). Furthermore, the number of prescription drugs, including the new molecular entities, on the market increased dramatically from 5% in 1980 to 75% in 1998 (Friedman *et al.*, 1999). Hence, a larger number of agents now appear to contribute to the total burden of drug-induced liver disease. Physician awareness of this constantly changing pattern of drug-induced hepatotoxicity is essential for early recognition. The apparent rise in the burden of hepatotoxicity may in part be due to ever-widening access to "complementary and alternative medicine," which allows self-medication as patients do not consider these as "true drugs." Promotion of the "herbal" products through the internet and inadequate regulatory

controls does not even ensure quality control of the product, let alone pharmacovigilance (Stickel *et al.*, 2003; Larrey 2007; Larrey and Faure, 2011).

## DEFINITIONS

An adverse drug reaction (ADR) is defined as any response to a drug that is noxious, is unintended, and occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease. Idiosyncratic DILI is best described as an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered. This is the focus of this chapter, and is distinct and different from liver injury secondary to drug overdoses. The problems of case definition and standardized phenotyping of DILI have recently been addressed by an international group of experts, and their recommendations have provided a framework for the evaluation of drug-induced hepatotoxicity (Aithal *et al.*, 2011). In the context of DILI, an elevation in the serum concentration of alanine aminotransferase (ALT), conjugated bilirubin, or alkaline phosphatase (ALP) are used to identify liver injury. Considering that transient unexplained asymptomatic ALT elevation two to three times above the upper limit of normal (ULN) range is seen even in those where underlying liver disease has been excluded, case definitions for DILI (Aithal *et al.*, 2011) include: (1) more than or equal to fivefold elevation above the ULN for ALT, (2) more than or equal to twofold elevation above the ULN for ALP (particularly with accompanying elevations in concentrations of 5'-nucleotidase or  $\gamma$ -glutamyl transpeptidase in the absence of known bone pathology driving the rise in ALP level), or (3) more than or equal to threefold elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding  $2 \times$  ULN. Liver injury is designated "hepatocellular" when there is a fivefold (or more) increase in ALT alone or when the ratio of serum activity (activity is expressed as a multiple of ULN) of ALT to ALP is 5 or more. Liver injury is designated "cholestatic" when there is a twofold or more increase in ALP alone or when the ratio of serum activity of ALT to ALP is 2 or less. Liver injury is termed "mixed" when the ratio

of the serum activity of ALT to ALP is between 2 and 5. Persistent DILI is defined by evidence of continued liver injury  $>3$  months after hepatocellular or mixed liver injury, and  $>6$  months after cholestatic liver injury. The term "chronic DILI" should be reserved for cases in which there is evidence of persistent liver injury at  $>1$  year after the onset of DILI (Aithal *et al.*, 2011).

## METHODS OF ESTIMATING THE FREQUENCY OF ADVERSE HEPATIC REACTIONS

### RANDOMIZED CONTROLLED TRIALS

The epidemiology of adverse hepatic reaction remains poorly documented. Randomized controlled trials (RCTs) have the advantages of close and prospective surveillance as well as a control group. Data from an RCT demonstrated that tamoxifen was associated with the development of fatty liver disease; an RCT also allowed its incidence to be estimated accurately and the role of pre-existing metabolic syndrome as a risk factor increasing the susceptibility to this drug-associated chronic liver disease to be established (Bruno *et al.*, 2005). Similarly, an RCT confirmed that fluctuating liver enzymes on statin therapy were not associated with clinically significant DILI and established the safety of the drug in people with pre-existent fatty liver (Athyras *et al.*, 2010). However, the incidence of most forms of DILI is generally too low to assess accurately in clinical trials (Laine *et al.*, 2009). When a group of drugs withdrawn were taken as an example, the median number of subjects exposed to the drug at the time of marketing was 1800, while 2.4 million people were exposed to the drug at the time of withdrawal (Friedman *et al.*, 1999). This is put in perspective by the fact that around 30 000 treated subjects need to be observed to identify, with a power 0.95, at least one with drug hepatotoxicity when the incidence is 1 in 10 000 patient years (Stricher, 1992). The debate surrounding the initial approval and the withdrawal from the market of troglitazone highlights the realities of drug development and the need for postmarketing surveillance. In the clinical trials of troglitazone, 1.9%

of patients receiving the drug had elevated liver enzymes, two of which developed reversible jaundice (Watkins and Whitcomb, 1998). It took more than 3 years and 90 deaths or liver transplants (in over a million patients treated) before the drug was withdrawn from the market (Lumpkin, 2000). Furthermore, clinical trials usually include selected patients, and the findings may therefore not be generalized to a wider population. This is also compounded by trial rules that mandate discontinuation of the medication at a point when “self-resolving liver enzyme elevations” cannot be distinguished from DILI (Aithal, 2011).

#### SPONTANEOUS REPORTING

Hence, in the UK and many other countries, post-marketing surveillance relies largely on spontaneous reporting (Rawlins, 1995), and data on adverse hepatic reactions have come often from this source. Spontaneous reporting allows the surveillance to continue throughout the life of the marketed drug when a large number of individuals have been exposed to the drug, and hence relatively rare adverse reactions have been recognized. However, underreporting is common, leading to substantial underestimates; in a prospective study, only 1 in 16 of clinically significant DILIs that occurred were reported formally by the clinicians (Sgro *et al.*, 2002). In a variation to entirely voluntary reporting, it has been mandatory in Sweden to report fatal, serious or new/unknown drug reactions to the Swedish Adverse Drug Reactions Advisory Committee since 1975, and the reporting rate appears to be higher (Olsson *et al.*, 2003). However, a high rate of reporting may result from a high frequency of adverse reactions or may simply be due to the publicity or novelty of a new agent. One such “apparent epidemic” of flucloxacillin-induced jaundice in Australia (reporting 357 ADRs and 17 deaths) has been considered to be a reporting artifact (Devereaux *et al.*, 1995; Roughead *et al.*, 1999). In addition to the variability of reporting, the identification of cases in a nonsystemic way introduces significant inaccuracy to the data. In a survey from the UK, about half of the reported adverse hepatic reactions were classified as “unrelated” to the drugs under systemic evaluation (Aithal *et al.*, 1999). A

further difficulty with spontaneous reporting is that the denominator is usually unknown, although drug sales figures could be used to estimate the frequency of adverse reactions.

#### RECORD LINKAGE STUDIES

Recording linkage studies connect information on drug exposure from prescription data with outcome and have the advantages of prospective design and comprehensive identification of cases. The General Practice Research Database is an electronic database consisting of information on the world’s largest longitudinal cohort, representing 5% of the population of England and Wales; this has been successfully used to assess the incidence of DILI in the general population as well as incidence of DILI in association with certain medications that are considered to have contributed significantly to the burden of DILI (de Abajo *et al.*, 2004). Similarly, record linkage studies based on the Group Health Cooperative of Puget Sound in the USA have also contributed valuable epidemiological information regarding DILI (Derby *et al.*, 1993; Jick *et al.*, 1999). However, record linkage studies rely upon outcomes such as deaths, hospital admissions, and discharge diagnoses, which are generally more serious reactions or those which occur during in-patient stay. In a study reporting the incidence of DILI among in-patients, in more than half the cases the diagnosis of DILI did not appear in the physicians’ discharge letters (Meier *et al.*, 2005). All of these account for an underestimation of the frequency of adverse hepatic reactions in record linkage studies.

#### HEPATOTOXICITY REGISTRIES AND NETWORKS

During the last decade, several networks and registries have been set up with a view to prospectively identify, evaluate, and collect information, including biological samples from patients suspected to have DILI. These registries have the advantages of prospective evaluation, and hence have better characterized cohorts. However, the rate of enrolment is dependent upon the willingness of clinicians and participants; hence, variable degree of capture does not allow estimation of prevalence or incidence of

DILI. The Registry of Hepatotoxicity in southern Spain that was established in 1994 is one such registry (Andrade *et al.*, 2005); and in the USA the National Institutes of Health funded the Acute Liver Failure Study Group, a 24-center consortium to prospectively enroll adult patients with ALF of all etiology in 1996 (Ostapowicz *et al.*, 2002), and the Drug-Induced Liver Injury Network, a multi-center network to evaluate and enroll patients with a suspicion of DILI in 2003 (Fontana *et al.*, 2009). Data from these sources have been useful to assess the burden of DILI, especially those which account for a proportion of acute liver failures (Ostapowicz *et al.*, 2002), as well as to study the natural history and outcomes of acute DILI (Andrade *et al.*, 2006; Chalasani *et al.*, 2008).

### CASE–CONTROL STUDIES

These are particularly useful when the outcome is rare yet distinct. In the field of drug-induced liver disease, they may be applied to hepatic tumors, industrial hepatotoxicity, and the role of aspirin in Reye's syndrome (Farrell, 1994).

### BURDEN OF DRUG-INDUCED LIVER INJURY

Despite increasing awareness of hepatotoxicity and the availability of less-toxic alternatives, the incidence of DILI has not decreased. DILI accounts for 3.5–9.5% of all ADR reports and up to 14.7% of fatal adverse reactions (Friis and Andreasen, 1992; Aithal *et al.*, 1999). A retrospective population-based study involving 1.64 million people in the UK (de Abajo *et al.*, 2004) estimated the rate of incidence of DILI leading to hospital referral as 2.4 per 100 000 person-years. Another prospective population-based study estimated a global crude annual incidence rate of 14 per 100 000 population with a standardized annual incidence rate of 8.1 per 100 000 population (Sgro *et al.*, 2002). Acute serious liver injury requiring hospitalization has been estimated to be 7–10 per 1 000 000 population per year (Ibanez *et al.*, 2002; Sgro *et al.*, 2002).

DILI accounts for 0.04–0.05% of all hospital admissions and 1.4–3.8% of gastroenterology ward

admissions (Carey *et al.*, 2008; Devarbhavi *et al.*, 2010; M'Kada *et al.*, 2012). Drugs are responsible for between 2% and 6% of jaundice and about 10% of “acute hepatitis” cases (Lewis and Zimmerman, 1989; Whitehead *et al.*, 2001). In Western countries DILI accounts for 10–20% of cases of acute hepatic failure (Larrey and Pageaux, 2005; Reuben *et al.*, 2010, Suzuki *et al.*, 2010); in tropical countries such as India, DILI underlies 7% of acute liver failures (Kumar *et al.*, 2010). Drug-induced chronic hepatitis has been considered rare, even though it accounts for up to 6% of all chronic hepatitis (Aithal and Day, 1999). Drug hepatotoxicity almost certainly remains an important and often neglected cause of cholestasis, although its relative frequency among other cholestatic syndromes has not been reported. Drugs probably contribute to the etiology of less than 1% of all liver tumors (Farrell, 1994).

Finally, the recent review of publications regarding DILI by the HEPATOX data bank system (which contains 1322 drugs and 16 996 references) collected 674 new bibliographic references within the period from September 2010 to August 2011. Neuropsychiatric compounds represented 16% of bibliographic data. The top 15 drugs (16.5%) included carbamazepine, phenytoin, and valproic acid. These findings were consistent with data collected in the VigiBase™ (Suzuki *et al.*, 2010).

### RELATIVE FREQUENCIES OF DRUGS IMPLICATED

Over the last few decades, with heightened awareness of impact of hepatotoxicity, relatively “high-risk” agents have been replaced. Hence, relatively rare reactions to commonly prescribed “low-risk” agents have become the most important cause of DILI. The most frequently incriminated drugs among the DILI registries include antimicrobials such as co-amoxiclav, flucloxacillin, erythromycin, co-trimoxazole, and nitrofurantoin, nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, ibuprofen, and naproxen, and neuropsychiatric medications such as carbamazepine, phenytoin, and valproate (Suzuki *et al.*, 2010). DILI secondary to anti-tuberculosis drugs, such as isoniazid and rifampicin, continues to be reported

Table 35.1 Drugs causing adverse hepatic reactions.

**Acute hepatocellular pattern of liver injury**

*NSAIDs:* diclofenac, ibuprofen, naproxen, nimesulide, piroxicam, sulindac

*Anesthetics:* enflurane, halothane, isoflurane

*Antimicrobials:* ketoconazole, ofloxacin, sulfamides, sulphones, terbinafine, tetracyclines; antimycobacterials such as isoniazid, pyrazinamide, rifampicin; anti-HIV agents such as didanosine, indinavir, zidovudine

*Neuropsychotropics:* tricyclics (most), fluoxetine, paroxetine, pemoline, sertraline, tacrine, riluzole; illegal compounds such as cocaine and ecstasy

*Antiepileptics:* carbamazepine, phenytoin, valproate

*Cardiovascular drugs:* bezafibrate, captopril, diltiazem, enalapril, lisinopril, lovastatin, simvastatin, ticlopidine

*Antineoplastic and immunomodulatory agents:* cyclophosphamide, cis-platinum, doxorubicin, granulocyte colony stimulating factor, IL-2

*Others:* etretinate, glipizide, herbal remedies, ranitidine

**Acute cholestatic pattern of liver injury**

*Hormonal preparations:* androgens, oral contraceptives, tamoxifen

*Antimicrobials:* clindamycin, co-amoxiclav, co-trimoxazole, erythromycin, flucloxacillin, troleandomycin

*Analgesics/anti-inflammatory drugs:* gold salts, propoxyphene, sulindac

*Neuropsychiatric drugs:* carbamazepine, chlorpromazine, tricyclic antidepressants

*Antineoplastic and immunomodulatory agents:* asparaginase, azathioprine, cyclosporin

*Cardiovascular drugs:* ajmaline, captopril, propafenone, ticlopidine

*Others:* allopurinol, chlorpropamide

**Auto-immune hepatitis**

Minocycline, nitrofurantoin, diclofenac, indomethacin, statins, infliximab, halothane, herbal medicine (germander), methyldopa

**Chronic drug-associated liver disease and/or cirrhosis**

Methotrexate, tamoxifen, vitamin A

**Chronic cholestasis and ductopenia**

Ajmaline, carbamazepine, chlorpromazine, co-amoxiclav, co-trimoxazole, erythromycin, flucloxacillin, methyltestosterone, phenytoin

**Granulomatous hepatitis**

Allopurinol, carbamazepine, cephalexin, diltiazem, gold salts, hydralazine, isoniazid, methyldopa, nitrofurantoin, penicillin, penicillamine, phenytoin, procainamide, quinidine, sulfonamides, sulfonylureas

**Macro- and microvesicular steatosis**

Amiodarone, asparaginase, buprenorphine, corticosteroids, flutamide, female sex hormone, methotrexate, perhexiline, salicylate, tacrine, tetracycline, valproate, zidovudine

**Hepatic vascular lesion**

*Hepatic vein thrombosis/veno-occlusive disease:* azathioprine, dacarbazine, combination chemotherapy (carmustine, cytarabine, mitomycin, thioguanine, urethane), oral contraceptives

*Sinusoidal dilation/peliosis:* anabolic steroids, azathioprine, hydroxyurea, oral contraceptives

*Perisinusoidal fibrosis:* azathioprine, methotrexate, vitamin A

**Tumors**

Anabolic steroids, oral contraceptives

worldwide (Devarbhavi *et al.*, 2010; Kumar *et al.*, 2010; Suzuki *et al.*, 2010). In addition, hepatotoxicity due to substances that were previously thought to have little toxicity, such as herbal remedies, are being increasingly recognized (Aithal, 2005; Larrey, 2007). A brief list of the drugs that are important causes of hepatotoxicity and the pattern of the liver injury is shown in Table 35.1.

**DIAGNOSIS OF ADVERSE HEPATIC REACTION**

The importance of drugs as a cause of liver injury lies not just in the overall number of cases, but also in the severity of some reactions and their potential reversibility provided the drug etiology is promptly recognized. Adverse hepatic reactions can mimic a

wide spectrum of hepatobiliary diseases. Early recognition and prompt withdrawal of the drug is essential in preventing serious hepatic failure and is the critical step in the management of adverse reactions (Nolan *et al.*, 1999). Failure to detect hepatotoxicity at an early stage has led to mortality in many reported cases of hepatotoxicity (Moulding, 1999). Inaccurate diagnosis may lead to inappropriate withdrawal of medication that is effective (such as antimicrobials or anticonvulsants) in an individual or a missed alternative diagnosis (such as autoimmune hepatitis or biliary obstruction) that merits prompt treatment.

Sadly, delayed, missed, or incorrect diagnoses of DILI are not infrequent in clinical practice. When diagnosis was systematically reviewed, 43% of all suspected hepatic adverse reactions reported through the pharmacovigilance system in the UK were classified as incorrect diagnosis (Aithal *et al.*, 1999). In those where initial diagnosis was incorrect, there was substantial delay in reaching the correct diagnosis; the median delay was 72 days and 120 days in secondary and primary care cases, respectively. In a recent study where all cases of DILI (defined as more than three times the ULN elevation of ALT) among in-patients were prospectively identified, primary physicians failed recognize the adverse reaction in more than 90% of cases (M'Kada *et al.*, 2012).

## CAUSALITY ASSESSMENT METHODS

The lack of specific tests for diagnosing drug hepatotoxicity poses particular problems for definitively attributing a liver reaction to an implicated drug. The approach to the diagnosis of a drug-induced liver disease involves physician awareness, the exclusion of other causes of the reaction, and an objective weighing of the circumstantial evidence. These considerations have been termed "causality assessment" and form the cornerstone to the diagnosis of drug-induced hepatotoxicity.

### DECISION-TREE MODEL

An algorithm-based model developed by Stricher (1992) considers three factors:

- 1 specificity of the clinico-pathological pattern and its course;
- 2 temporal relationship between intake/discontinuation of the suspected drug and onset/disappearance of hepatic injury; and
- 3 exclusion of other possible causes for the observed pattern.

The model assesses the degree of certainty of a causal relationship between hepatic injury and drug intake; however, it has several major disadvantages. First, all the factors are given equal weight; second, the quantitative data are reduced to qualitative "yes" or "no" answers. Finally, categories such as "probable" and "possible" lead to a semantic cause of inter-observer variation.

### BAYESIAN MODEL

A logical approach to the problem of causality assessment is based on Bayes' theorem. This model uses the background incidence of an event, the individual clinical features of a particular case, and the probability of other potential causes. The model estimates the probability of a specific reaction in a particular individual in a given situation being related to the drug therapy. However, the Bayesian model is time consuming, and hence impracticable to use in the evaluation of a large number of adverse hepatotoxic reactions. In addition, the background incidence of a given reaction may not be known, thus further limiting its use. In a large survey, the Bayesian model had an accuracy of 62% in the diagnosis of drug-induced liver disease when compared with the final diagnosis after investigations (Lavelle and Kavanagh, 1995).

### ROUSSEL UCLAF CAUSALITY ASSESSMENT METHOD

In 1990, under the auspices of the Council for International Organizations of Medical Sciences, an international group of "experts" proposed criteria for assessing causality of drug-induced liver disease to standardize the evaluation of drug hepatotoxicity by physicians, health authorities of different countries, and pharmaceutical manufacturers (Benichou *et al.*, 1993). A detailed scoring

Table 35.2 RUCAM hepatocellular injury scale. Source: Danan and Benichou (1993). Reproduced with permission of Elsevier.

Subject information	Score
<b>1. Temporal relationship of start of drug to ALT &gt; 2 × ULN</b>	
Initial treatment 5–90 days; subsequent treatment course: 1–15 days	2
Initial treatment <5 or >90 days; subsequent treatment course: >15 days	1
From cessation of drug: ≤15 days, or ≤15 days after subsequent treatment	1
Otherwise	0
<b>2. After drug cessation – difference between peak ALT and upper limits normal</b>	
Decreases >50% within 8 days	3
Decreases >50% within 30 days	2
No information or decrease >50% after >30 days, or inconclusive	0
Decrease <50% after 30 days or recurrent increase	-2
<b>3. Risk factors</b>	
No alcohol use	0
Alcohol use	1
Age ≤55 years	0
Age >55 years	1
<b>4. Concomitant drug</b>	
No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive rechallenge or validated diagnostic test	-3
<b>5. Nondrug causes</b>	
<i>Six are primary:</i> recent hepatitis A, B, or C, biliary obstruction, acute alcoholic hepatitis (AST > 2 × ALT), recent hypotension	
<i>Secondary group:</i> underlying other disease; possible CMV, EBV or HSV infection	
All primary and secondary causes reasonably ruled out	2
All 6 primary causes ruled out	1
4 or 5 primary causes ruled out	0
<4 primary causes ruled out ( <i>max. negative score for items 4 and 5: -4</i> )	-2
Nondrug cause highly probable	-3
<b>6. Previous information on hepatotoxicity of the drug in question</b>	
Package insert or labelling mention	2
Published case reports but not in label	1
Reaction unknown	0
<b>7. Rechallenge</b>	
Positive (ALT doubles with drug in question alone)	3
Compatible (ALT doubles with same drugs as given before initial reaction) +1	1
Negative (increase in ALT but <2 × ULN, same conditions as when reaction occurred)	-2
Not done, or indeterminate result	0
Total (range of algebraic sum: -8 to +14)	
Score interpretation: Highly probable >8; Probable 6–8; Possible 3–5; Unlikely 1–2; Excluded <0	

system called the Roussel Uclaf Causality Assessment Method (RUCAM, after the host pharmaceutical company Roussel Uclaf) was developed to determine the probability of the reaction being related to the drug and validated using cases of DILI with known positive rechallenge (Danan and Benichou, 1993). When compared with the

clinical diagnostic scale, another causality assessment method, the RUCAM scale was more reliable and correlated better with expert reviews (Aithal *et al.*, 2000; Lucena *et al.*, 2001; Rockey *et al.*, 2010). The categories included in RUCAM and the scoring scale are summarized in Tables 35.2 and 35.3.

Table 35.3 RUCAM cholestatic or mixed liver injury scale. Source: Danan and Benichou (1993). Reproduced with permission of Elsevier.

Subject information	Score
<b>1. Temporal relationship of start of drug to ALP &gt; 2 × ULN</b>	
Initial treatment 5–90 days; subsequent treatment course: 1–90 days	2
Initial treatment <5 or >90 days; subsequent treatment course: >90 days	1
From cessation of drug: ≤30 days, or ≤30 days after subsequent treatment	1
Otherwise	0
<b>2. After drug cessation – difference between peak ALP or total bilirubin and ULN</b>	
Decreases ≥50% within 180 days	2
Decreases <50% within 180 days	1
Persistence or increase or no information	0
If drug is continued – inconclusive	0
<b>3. Risk factors</b>	
No alcohol use	0
Alcohol use	1
Age <55 years	0
Age >55 years	1
<b>4. Concomitant drug</b>	
No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive rechallenge or validated diagnostic test	-3
<b>5. Nondrug causes</b>	
<i>Six are primary:</i> recent hepatitis A, B, or C, biliary obstruction, acute alcoholic hepatitis (AST > 2 × ALT), recent hypotension	
<i>Secondary group:</i> underlying other disease; possible CMV, EBV or HSV infection	
All primary and secondary causes reasonably ruled out	2
All 6 primary causes ruled out	1
4 or 5 primary causes ruled out	0
<4 primary causes ruled out (max. negative score for items 4 and 5: -4)	-2
Nondrug cause highly probable	-3
<b>6. Previous information on hepatotoxicity of the drug in question</b>	
Package insert or labelling mention	2
Published case reports but not in label	1
Reaction unknown	0
<b>7. Rechallenge</b>	
Positive (ALT doubles with drug in question alone)	3
Compatible (ALT doubles with same drugs as given before initial reaction) +1	1
Negative (increase in ALT but <2 × ULN, same conditions as when reaction occurred)	-2
Not done, or indeterminate result	0
Total (range of algebraic sum: -8 to +14)	
Score interpretation: Highly probable >8; Probable 6–8; Possible 3–5; Unlikely 1–2; Excluded <0	

Even though RUCAM is widely used as a method of choice, it cannot be used rigidly in all circumstances, especially to exclude a drug as a cause of a given reaction. For example, the classification of a causal relationship between a drug and cholestatic injury as “incompatible” if the onset occurs more than a month after the last drug intake would

unduly refute such cases attributable to co-amoxiclav intake (Larrey *et al.*, 1992). Similarly, flucloxacillin-induced cholestasis, which in one-third of patients may take up to 18 months after the drug withdrawal to resolve (Turner *et al.*, 1989), may be classified as “inconclusive” according to the RUCAM criteria. RUCAM specifies alcohol, pregnancy, and

age over 55 years as risk factors, which would reduce the flexibility to weigh other risk factors relevant to the clinical setting.

### CLINICAL DIAGNOSTIC SCALE

The “Clinical Diagnostic Scale” (CDS) (otherwise called the Maria & Victorino scale) is a relatively simpler scoring system (Maria and Victorino, 1997). Scores are attributed in seven different components of a given reaction, and the causality is graded according to the final score. The original validation of CDS used real and fictitious cases and the opinion of the panel of experts as the gold standard. A detailed comparison of RUCAM and CDS concluded that the latter performed poorly while evaluating reactions with long latency periods and evolution to chronicity after withdrawal (e.g., cholestasis due to amoxiclav) (Lucena *et al.*, 2001).

The CDS generally underscores the reactions. Even in the initial study, only four (all of which had positive rechallenge) were classified as definite adverse hepatic reaction (Maria and Victorino, 1997). The reason for low scoring is because of the emphasis given to positive rechallenge as well as extra-hepatic manifestations (maximum of three scores each). Deliberate rechallenge of an incriminated drug is ethically unjustifiable, and inadvertent re-exposure is reported in a minority (8.8%) of hepatic ADRs. Extra-hepatic manifestations, considered to represent immuno-allergic reaction, are infrequent with hepatotoxicity due to many of the currently used drugs (Banks *et al.*, 1995; Hautekeete *et al.*, 1999). None of the 180 patients in a large series of diclofenac hepatotoxicity cases would have scored maximum points for this component on the CDS (Banks *et al.*, 1995).

Systemic evaluation using causality assessment methods such as RUCAM or CDS provides objectivity and consistency to the assessment of suspected adverse hepatic drug reactions. Their more widespread adoption should enhance the accuracy of case definition for epidemiological studies.

### RECHALLENGE

The recurrence of liver injury after re-administration (often inadvertent) of a suspected drug is the

most persuasive evidence for drug-induced liver disease and may outweigh other considerations in causality assessment. The biochemical criteria for a positive rechallenge have been outlined by the consensus group (Benichou *et al.*, 1993). However, negative rechallenge cannot be used to exclude the diagnosis of DILI. Only 11–24% of patients develop recurrent DILI on reintroduction of the medications once the initial DILI has resolved (Hunt, 2010). Considering that first-line anti-tuberculosis drugs are highly effective and relatively inexpensive, benefits of rechallenge must outweigh its risks; it is unwise to discard these drugs from the regimen. Therefore, it is acceptable to attempt reintroduction of these medications in particular. However, more than half the cases of halothane-induced DILI recur on rechallenge, often inadvertently (Mushin *et al.*, 1971). Rechallenge of an incriminated drug can be dangerous and may even be fatal (Ransohoff and Jacobs, 1981; Lo *et al.*, 1998). Therefore, deliberate rechallenge may only be justified when continued treatment with the implicated agent is highly desirable.

### ROLE OF LIVER BIOPSY

DILI can cause any known pattern of liver pathology (Kleiner, 2009), although certain histological features are particularly suggestive of drug-induced etiology. Hence, benefits of performing a liver biopsy should be weighed against the disadvantages and its limitations. Liver biopsy is worthwhile (1) when autoimmune hepatitis is one of the differential diagnoses in consideration (Suzuki *et al.*, 2011), (2) when the event does not resolve on drug discontinuation, and (3) in circumstances where the clinical/laboratory features are atypical or the patient appears to suffer an as yet unrecognized form of DILI.

### PATHOGENESIS

The vast majority of hepatotoxicity cases that are detected during clinical trials or encountered in clinical practice are unrelated to the known pharmacology of the drug (Olsson *et al.*, 2000); this,

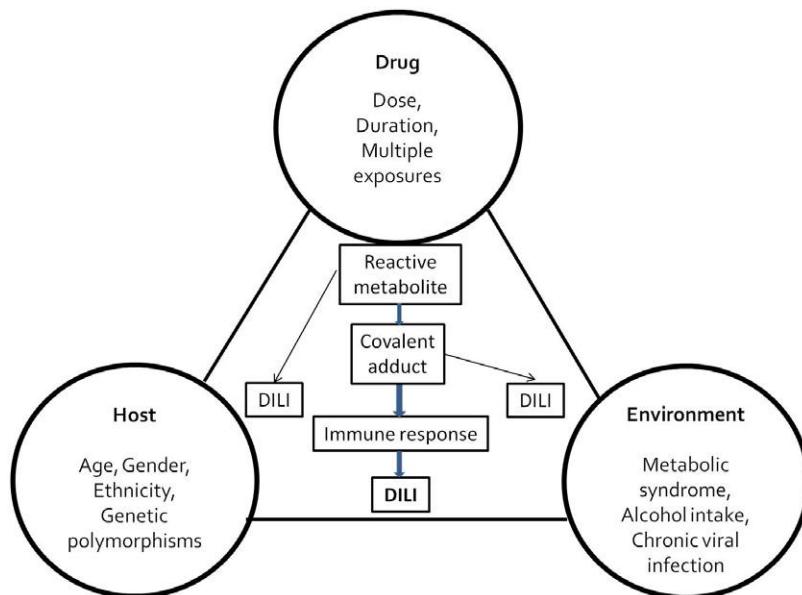


Figure 35.1 Drug, host and environmental factors influence the metabolic and immunological processes leading to DILI.

coupled with the fact that idiosyncratic DILI is a rare event considering the large number of people exposed to the medication, means that the pathogenesis of hepatic ADRs remains poorly understood. Over the past decade, investigations, especially those involving well-characterized DILI cohorts, have identified a number of important drug-related, host genetic, and environmental factors associated with susceptibility to hepatotoxicity. These indicate that DILI develops as a consequence of multiple interactions involving both metabolic and immunologic processes (Figure 35.1). Therefore, classification of DILI into metabolic idiosyncrasy and immune-allergic reactions is too simplistic, incomplete, and often inaccurate.

#### DRUG-RELATED FACTORS ASSOCIATED WITH DRUG-INDUCED LIVER INJURY

The preclinical phase of drug development includes toxicity studies in animals; the use of high doses in a group of animals should reveal a toxicity that would occur with a low frequency in a population receiving therapeutic doses. This means that hepatotoxicity inherent to the compound is detected at this stage and those associated with unacceptable

risk are eliminated. Therefore, "dose dependence" is the hallmark of hepatotoxicity that is predominantly due to "drug-related" factors. Only 9% of serious DILI cases reported to the Swedish Adverse Drug Reactions Advisory Committee (1970–2004) were due to drugs with a daily dose of 10 mg or less, compared with 14% due to those with a daily dose 11–49 mg and 77% caused by medications given at a dose of 50 mg or more (Lammert *et al.*, 2008). There was also a significant relationship between daily dose reports of liver failure, liver transplantation, and death caused by DILI. In addition, consistent with the hypothesis that reactive metabolites generated by hepatic metabolism are likely to be a common upstream event in the pathogenesis, compounds with >50% hepatic metabolism are more likely to be associated with ALT greater than three times the ULN, liver failure, and fatal DILI (Lammert *et al.*, 2010).

There are other examples of idiosyncratic DILI where association with dose has been demonstrated: diclofenac-induced liver injury occurs five times more often in association with a daily dose of 150 mg or higher when compared with a lower dose (de Abajo *et al.* 2004; Aithal and Day, 2007). With regard to flucloxacillin, patients who receive more

than 14 days of treatment have a sevenfold risk of developing DILI compared with those who received a shorter course of therapy (Fairley *et al.*, 1993; Russmann *et al.*, 2005). Risk of developing acute liver injury from co-amoxiclav is three times greater after two or more courses than after a single course of therapy (Rodríguez *et al.*, 1996).

#### HOST FACTORS ASSOCIATED WITH RISK OF DRUG-INDUCED LIVER INJURY

Older age is associated with decreased liver blood flow, changes in the drug distribution, and metabolism, thus potentially reducing the effective clearance of the drugs. Age has been shown to be a risk factor for DILI due to anti-tuberculosis medications in a number of studies; however, these studies have used empirical age cut-offs ranging from 35 to 60 years for stratification (Ramappa and Aithal, 2013). In contrast, DILI secondary to valproate is significantly more common under the age of 2 years compared with adults (Dealberto, 2007; Murray *et al.*, 2008). While women are at higher risk of DILI due to nitrofurantoin (Pugh *et al.*, 2009), diclofenac (Aithal and Day, 2007), and isoniazid (Ramappa and Aithal, 2013), hepatotoxicity due to azathioprine has been reported in predominantly male cohorts (Romagnuolo *et al.*, 1998).

Malnutrition and recent weight loss have both been associated with higher incidence of anti-tuberculosis drug-induced hepatotoxicity (Singla *et al.*, 2010; Warmelink *et al.*, 2011). On the other hand, obesity is a risk factor for the development of chronic drug-associated liver diseases; non-alcoholic fatty liver disease associated with tamoxifen occurs only in people with metabolic syndrome (Bruno *et al.*, 2005).

The observation that drug hypersensitivity is more common in patients with concomitant viral infection has led to the suggestion that a mild co-existent injurious signal can often act as a “danger signal” that permits the development of initial events in the pathophysiological process into a full blown hepatotoxic reaction (Aithal, 2004). The risk of DILI on anti-tuberculosis therapy is increased in association with chronic hepatitis B and C and human immunodeficiency virus infection (Wong *et al.*, 2000; Ramappa and Aithal,

2013). Observational studies have also demonstrated that risk factors such as diabetes, alcohol excess, obesity, and chronic viral hepatitis increase the risk of advanced hepatic fibrosis at a lower cumulative dose of methotrexate (Rosenberg *et al.*, 2007); a common mechanism, such as cumulative unresolved endoplasmic reticulum stress, may underlie generation of liver injury due to the drug as well as the co-existent liver disease (Aithal, 2007, 2011).

#### GENETIC SUSCEPTIBILITY

Pathogenesis of DILI remains unexplained even after taking into account dosage regimen and other risk factors; therefore, host genetic susceptibility may be an important factor leading to the development of DILI. Ethnicity has been associated with distinct ALT response on exposure to therapeutic drugs (Watkins *et al.*, 2006). In a similar fashion, observations such as Asian males have double the rate of isoniazid hepatitis than white males and nearly 14 times that of black males indicate that genetic susceptibility may contribute substantially to the development of hepatotoxicity (Ramappa and Aithal, 2013).

Single nucleotide polymorphisms (SNPs) in the genes coding for the phase I and II drug-metabolizing enzymes, as well as transporters (involved in phase III), are associated with variations in the formation and the accumulation of reactive metabolites or their clearance; these have been shown to determine one's susceptibility to hepatotoxicity. In a series of case-control studies, allelic variants of UDP-glucuronosyltransferase-2B7, cytochrome P450 (CYP)-2C8, and ATP-binding cassette, sub-family C-member 2 (ABCC2), that could promote formation and accumulation of reactive diclofenac metabolites have been shown to be associated with susceptibility to diclofenac hepatotoxicity (Aithal and Day, 2007; Aithal, 2011). In the case of anti-tuberculosis drugs, SNPs in *N*-acetyltransferase 2, CYP2E1, and ABCC1 have been associated with increased risk of DILI (Huang *et al.*, 2002, 2003; Ramappa and Aithal, 2013). In the case of flucloxacillin, a promoter region polymorphism in gene coding for xeno-sensing pregnane X receptor, which regulates the transcription of phase I and II

drug-metabolizing enzymes such as CYPs and glutathione S-transferases (GSTs) and transporters, has been associated with DILI (Andrews *et al.*, 2010).

The magnitude of impact of reactive metabolites can be modified by cellular response to the oxidative stress that is generated. Hence, polymorphisms in the genes that influence antioxidant defense processes, such as GST1 and manganese superoxide dismutase, have been shown to determine one's predisposition to DILI from anti-tuberculosis drugs and carbamazepine (Huang *et al.*, 2007; Ueda *et al.*, 2007; Lucena *et al.*, 2008; Ramappa and Aithal, 2013).

Although protein binding of reactive metabolites may impair cellular function to cause toxicity, drug metabolite adducts may interact with the immune system. In order for the drug metabolite adduct to be recognized by the immune system, they should be presented by antigen-presenting cells in conjunction with major histocompatibility complex (MHC) molecules. Several candidate gene and genome-wide association studies have demonstrated that the human MHC plays a major role in increasing or decreasing susceptibility to DILI, hence highlighting the role of adaptive immunity in the pathogenesis. A seminal genome-wide association study demonstrated that possession of HLA-B\*5701 allele was associated with an 81-fold increased risk of DILI on exposure to flucloxacillin when compared with ancestry-matched controls (Daly *et al.*, 2009). A number of studies have confirmed association of co-amoxiclav DILI with the DRB1\*1501–DQB1\*0602 haplotype; recently, a novel protective association of DRB1\*07 family with co-amoxiclav DILI has been demonstrated (Hautekeete *et al.*, 1999; O'Donohue *et al.*, 2000; Donaldson *et al.*, 2010). HLA variants have also been associated with DILI secondary to a number of drugs, including ximelagatran, ticlopidine, lumiracoxib (Berson *et al.*, 1994; Aithal and Daly, 2010; Singer *et al.*, 2010) as well as anti-tuberculosis drugs (Ramappa and Aithal, 2013). HLA variants associated with toxicity are thought to increase the specificity of the peptide binding groove for the drug or drug-peptide complex, hence enhancing the presentation of these molecules as antigens to

T-cells and leading ultimately to immunological destruction of hepatocytes.

## MANAGEMENT OF IDIOSYNCRATIC HEPATOTOXICITY

Early detection and withdrawal of the causative drug is the single most important step in the management of adverse hepatic reaction. Cases of serious and often fatal hepatotoxicity due to isoniazid, halothane, valproate, nitrofurantoin, and perhexiline are often linked to continuation or resumption of the drug following symptoms that could have been attributable to drug-induced liver reaction (Farrell, 1994; Lo *et al.*, 1998; Moulding, 1999). Re-exposure to the offending drug is often unintended and rechallenge is associated with 2–13% mortality; the majority of these are preventable (Hunt, 2010).

Prompt withdrawal of the drug is also important because the long-term prognosis may be worse if the responsible agent is continued. In a retrospective study investigating persistence of liver injury after initial acute idiosyncratic DILI, it was found that continued drug intake after the initial liver injury predicted adverse outcome (Aithal and Day, 1999). Another cohort study also found that prolonged exposure to drug was associated with an eightfold excess risk of chronicity (Andrade *et al.*, 2006).

Management of acute hepatic failure secondary to idiosyncratic hepatic reaction is similar to that of viral hepatitis. Transplant-free survival is better in patients who are treated with *N*-acetyl cysteine in the early stages of acute liver failure (Lee *et al.*, 2009). The overall mortality of drug-induced hepatic failure (excluding paracetamol overdose) appears to be higher than that of viral hepatitis. Despite the availability of liver transplantation, 13% of those who develop jaundice due to severe hepatotoxicity die; and in patients with halothane-induced liver injury, a mortality rate of 40% has been reported (Bjornsson and Olsson, 2005). Acute liver failure secondary to idiosyncratic hepatotoxicity has poor prognosis, with 50–80% who either die or require transplantation in contrast to 15–40% of

those secondary to paracetamol overdose (Ostapowicz *et al.*, 2002; Kumar *et al.*, 2010).

Corticosteroid treatment has not been shown to be beneficial in the management of drug-induced hepatitis. However, it is difficult to distinguish drug-induced autoimmune hepatitis from the idiopathic form; hence, in practice, a number of patients are treated with immunomodulatory agents at the time of acute presentation. It is appropriate under such circumstances to consider withdrawal of all immunosuppressant drugs when clinically appropriate and closely monitor patients. Patients who do not relapse within a period of 18 months of complete withdrawal of immunosuppressive therapy can be considered to have suffered drug-induced adverse reaction (Aithal *et al.*, 2011; Bjornsson and Aithal, 2014). There is no clear evidence that ursodeoxycholic acid therapy changes outcome in chronic cholestasis, although the drug has been widely used for all forms of cholestasis.

## PREVENTION

Concern regarding morbidity and mortality due to drug-induced jaundice has led to several guidelines recommending serum liver enzyme monitoring during therapy. Although monitoring may be logical in the clinical trials, considering the lack of specific markers that distinguish transient self-resolving transaminitis from potentially serious DILI, the thresholds set for discontinuation of drugs remain pragmatic and variable depending on clinical circumstances rather than being evidence based. Severe liver injury may develop rapidly without pre-warning, and evidence that regular liver enzyme monitoring prevents clinically significant hepatotoxicity is limited. In addition, intensive monitoring protocols are seen as inconvenient, ineffective, and costly, leading to low compliance with such recommendations (Graham *et al.*, 2001; Senior, 2009).

Based on the observations that symptoms attributable to hepatic adverse reactions reflect potentially serious liver injury, the Seattle–King County Public Health Department used a protocol to monitor isoniazid therapy, which included advising

the patient at each visit to stop the medication and call the clinic if symptoms of hepatotoxicity occurred. With careful monitoring, the rate of hepatotoxicity in 11 141 patients was much lower (0.1–0.15%) than previously reported (1%), and there were no deaths (Nolan *et al.*, 1999). However, this approach has not been systematically evaluated.

In the past decade, medications such as ximelagatran and lumiracoxib, which were associated with an occurrence of serious liver injury leading to liver failure or death with a frequency of 1 in 10 000–15 000 individuals exposed, have been withdrawn from development or marketing. It is unrealistic to expect that serious DILI could become a “never event” in the near future, even with the most rigorous drug development pathway. However, this should not dissuade clinicians and researchers alike from identifying the risk factors that alter one’s susceptibility to develop an adverse hepatic reaction. Experience gained and data collated following marketing and wide clinical usage of a new medication have elucidated a number of drug, host, and environmental factors that alter the risk of clinically significant hepatotoxicity due to methotrexate, and hence a much better stratification of patients to a safer therapeutic regimen. This, combined with potential to monitor liver fibrosis noninvasively using serum or imaging-based biomarkers of liver fibrosis, has permitted a safer use of methotrexate, an effective medication accessible at very little expense. Recent discovery of HLA alleles as risk factors for DILI due to an increasing number and variety of drugs, such as flucloxacillin, co-amoxiclav, ximelagatran, lapatinib, and lumiracoxib, has undoubtedly highlighted the role of genetic susceptibility in the pathogenesis of acute DILI (Bjornsson and Aithal, 2014) and raised the possibility of clinical application (Aithal and Daly, 2010). Considering one such example, the performance characteristics of a particular HLA allele (HLA-DQA1\*0102) have a sensitivity of 74% and a negative predictive value of 99% as predictive markers to identify subjects at risk of developing hepatotoxicity from lumiracoxib (Singer *et al.*, 2010). In the case of flucloxacillin hepatotoxicity, HLA-B\*5701 genotyping may prove to be a useful diagnostic test, with

85% sensitivity and 94% specificity with a low probability of a false negative (Daly *et al.*, 2009). Despite this, as incidence of DILI is very low among the large number of exposed individuals, even with the strong association with HLA-B\*5701, only 1 in every 500–1000 individuals with this genotype will develop DILI when treated with flucloxacillin. Alternatively, a high negative predictive value may be of clinical utility when exclusion of DILI may allow continued use of an effective drug. In addition, DILI caused by a number of different drugs can be linked to two main haplotypes, widening the applicability of a test if it were to be available (Alfirevic *et al.*, 2012).

Improved understanding of drug, host genetic, and environmental factors that are associated with the risk of “idiosyncratic” DILI should be used to develop refined algorithms that allow better tailoring of medications based on accurate estimates of risk/benefit ratio. Hopefully, future research will unravel further genetic, proteinaceous, and metabolite biomarkers that will detect patients with increased susceptibility to DILI, and assist in early diagnosis and monitoring for DILI during therapy.

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# 36

## Ocular Side Effects of Prescription Medications

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### INTRODUCTION

According to the US National Center for Health Statistics, the most common therapeutic intervention performed by physicians is prescribing medications. In ophthalmology, adverse events caused by prescription medications are the third most common reason for lawsuits against the doctor (Edwards and Biriell, 1995; Easterbrook, 1999). Litigation from drug-related ocular side effects can be costly to defend, indemnify, and settle due to the serious and sometimes long-term effects of vision loss.

Many prescription and nonprescription drugs, homeopathic agents, herbal medicines, chemicals, and toxins are associated with ocular toxicity. Adverse effects on the eye are one of the most common reasons why drugs do not reach the marketplace. Although the liver and kidneys are the most common sites for drug toxicity, large areas of these organs may be damaged before laboratory

findings appear abnormal. However, if an adverse drug reaction affects the macula of the eye, even a small fraction of patients (1%) may show significant abnormality on testing.

Drug-induced adverse ocular effects are caused by topical medications, including their preservatives, and by systemic medications. Drugs (especially antimetabolites) may concentrate in the tears, causing marked irritation and even scarring of the mucous membrane overlying the eye. Dilation of the pupil by atropine and similar agents can cause acute glaucoma; oral and topical corticosteroids can cause open-angle glaucoma by depositing mucopolysaccharides in the ocular outflow channels. Lens opacification caused by steroids or allopurinol and disruption of the pigmented tissue of the macula by chloroquine or hydroxychloroquine are not uncommon.

The key to detecting an adverse ocular effect is a high degree of clinical suspicion and the recognition that the signs and symptoms of a disease do

Table 36.1 How to tell if a drug could be causing an adverse effect.

Temporal association – time of onset, pattern, etc.
Dose response
Positive dechallenge (effect disappears when drug therapy is stopped)
Positive rechallenge (effect reappears when drug therapy is resumed)
Scientific explanation as to the mechanism of action
Similar effects reported from others in same 'class' of drugs
No alternative explanation

not fit the expected clinical picture. The busy clinician can easily overlook a drug-related ocular adverse event, especially if patients are taking multiple topical or systemic medications. It is estimated that the incidence of adverse events from topical ocular medications alone is 13% (Wilson, 1983). How best to determine whether a drug-related adverse event has occurred is shown in Table 36.1. The World Health Organization (WHO) has defined these events, as summarized in Table 36.2 (WHO, 1972; Edwards and Biriell, 1995).

With more than 30 000 prescription drugs in the USA alone and many more worldwide, plus a multitude of over-the-counter and herbal products available, it is impossible to cover the subject entirely in this short chapter. Probably the two most comprehensive textbooks are Grant and Schuman's (1993) *Toxicology of the Eye* and Fraunfelder and Fraunfelder's (2001) *Drug-Induced Ocular Side Effects*.

The National Registry of Drug-Induced Ocular Side Effects is also a source of help to the busy clinician ([www.eyedrugregistry.com](http://www.eyedrugregistry.com)). The objectives of the registry are

- 1 to establish a national center where possible drug-induced ocular side effects can be accumulated;
- 2 to add to this database the spontaneous reports of possible drug-induced ocular side effects collected by the Food and Drug Administration (FDA – Rockville, MD, USA) and the WHO (Uppsala, Sweden);
- 3 to compile data from the world literature on possible drug-induced side effects in humans;

Table 36.2 WHO definitions – causality assessment of suspected adverse reactions.

<i>Certain:</i> A clinical event, including a laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
<i>Probable/likely:</i> A clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
<i>Possible:</i> A clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
<i>Unlikely:</i> A clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and for which other drugs, chemicals or underlying disease provide plausible explanations.
<i>Conditional/unclassified:</i> A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.
<i>Unassessable/unclassifiable:</i> A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

- 4 to publish this data every 4–5 years in book form; and
- 5 to make this data available to physicians who suspect possible drug-induced ocular side effects.

Clinicians may contact the database for help with a suspected drug reaction, to access data in the registry, or to report a case. When sending data, it would be ideal to include name of drug, dosage, duration of therapy, suspected reaction, what happened if the drug was stopped or rechal-

lenged, concomitant drugs, and the name and address of person reporting the case (optional but encouraged).

Reports can be mailed to National Registry of Drug-Induced Ocular Side Effects, Casey Eye Institute, 3375 SW Terwilliger Blvd. Portland, OR 97239-4197, USA; faxed to (503) 494-4286; or emailed to [www.eyedrugregistry.com](http://www.eyedrugregistry.com).

## DRUGS WITH OCULAR SIDE EFFECTS OF RECENT CLINICAL IMPORTANCE

### HYDROXYCHLOROQUINE (PLAQUENIL®) PRIMARY USE

Hydroxychloroquine is used primarily for the treatment of rheumatoid arthritis and lupus erythematosus, dermatologic conditions, and various other inflammatory disorders.

#### Clinical Concerns

##### *Definition of Hydroxychloroquine Maculopathy*

Maculopathy must be bilateral and reproducible by Amsler grid and visual field testing. Transient or unilateral defects are not sufficient to implicate the drug, nor are they an indication to stop therapy.

##### *Goal of Ocular Evaluation*

The goal is to find early changes; that is, relative scotomas. Later findings include retinal changes, color vision loss, absolute scotoma, or decreased vision, as even if the drug is stopped, two-thirds of these patients may continue to lose some vision and/or peripheral fields. Disease in patients with early paracentral relative scotomas seldom advances when the drug is discontinued.

#### Guidelines for Following Patients

The following guidelines are modified after Easterbrook (1999):

- *Baseline examination.* Patients should undergo a comprehensive ophthalmic examination, with the eyes dilated, within 1–2 years of starting

therapy. They should complete a statement of informed consent regarding possible permanent visual problems in rare instances. This baseline examination should include visual acuity testing, testing with Amsler grids (with instructions for monthly home use), and color vision testing (preferably including the blue–yellow axis, using equipment such as the pseudo-isochromatic plates for color by the American Optical Corporation). If any macular abnormality is seen, it would be ideal to obtain fundus photographs. If progressive ocular abnormality is suspected, a baseline Humphrey 10–2 or other automated perimetry test should be considered.

- *Follow-up examinations.* If the patient is not obese, frail, elderly, or extremely thin, does not have significant liver or kidney disease or macular disease of any type, and is below age 40, another complete examination is not necessary for 2–4 years. Patients should return sooner if
  - they experience any persistent visual symptoms or
  - their dosage exceeds 6.5 mg/kg.
- If between 40 and 64 years:
  - Same as above. Should be seen every 2–4 years.
- If age 64 and above:
  - Same as above. Should be seen every 2–4 years.
- Annual examinations should be done if
  - therapy continues for longer than 5 years;
  - patient is obese or lean and small – especially elderly;
  - there is progressive macular disease of any type;
  - there is significant kidney or liver disease present;
  - dosage exceeds 6.5 mg/kg.
- Follow-up examinations:
  - repeat baseline examination;
  - fundus photography if any macular abnormality noted;
  - consider fluorescein angiography only if suspect pigmentary changes of any cause;
  - automated central visual fields;
  - if available, but not essential, in selected cases, multifocal electroretinogram (ERG).

## Chloroquine

Perform same tests as above. See at least annually if dosage is less than 3.0 mg/kg of ideal body weight. See every 6 months if dosage is greater than 3.0 mg/kg body weight, if short/obese, or if kidney and/or liver impairment is present.

## ISOTRETINOIN (ACCUTANE®)

### Primary Use

Cystic acne, psoriasis, and various other skin disorders.

### Clinical Concerns

This drug, which competes with binding sites for retinoic acid and retinol in the retina, can cause decreased dark adaptation. However, only recently have data suggested the probability of *permanent night blindness* in rare cases (Fraunfelder *et al.*, 2001). Therefore, the *Physicians' Desk Reference* (PDR) for 2001 lists a warning about this in the package insert. This drug can cause blepharitis, meibomitis, and atrophy of the meibomian gland (in animals, complete destruction) (Mathers *et al.*, 1991) and can increase the risk of staphylococcus disease. Any or all of these conditions may decrease tear film break-up time and increase tear osmolality. Therefore, isotretinoin can probably cause a permanent, "evaporative" form of sicca.

Isotretinoin is secreted in the tears, causing irritative conjunctivitis, superficial punctate keratitis, drug deposits in the superficial cornea, and decreased tolerance for contact lens wear. Some sicca patients are made worse, or latent sicca becomes manifest. This photosensitizer can cause or significantly aggravate existing lid diseases, especially blepharitis. Other known side effects include acute myopia, papilledema secondary to pseudotumor cerebri, and optic neuritis. Recently, isotretinoin has been identified as the probable cause of reversible color vision defects.

### Guidelines for Following Patients

It is not practical to examine the eyes of every patient beginning therapy with these agents.

However, if the patient is younger than 40 and has not had an eye examination in the past few years, or older than 40 and has not had one in 1–2 years, baseline examination is appropriate. This is especially important if the patient has had any other ocular problems before starting therapy, both to prevent aggravation of the above conditions and to avoid having the drug unfairly blamed for latent ocular disease.

Explain risk–benefit ratio in patients with

- retinitis pigmentosa;
- dystrophic or degenerative retinal disease;
- severe or chronic blepharoconjunctivitis;
- significant tear film abnormalities;
- pre-existing night blindness.

In select patients with anterior segment or retinal pathology, consider prescribing UV-blocking lenses as this drug is a photosensitizer. Consider discontinuing the use or delaying the fitting of contact lenses during therapy. Patients taking isotretinoin long term should have annual eye examinations. Suggest more frequent visits if patients experience ocular irritation or vision changes or if any significant ocular signs or symptoms occur. If progressive or persistent night blindness occurs, consider stopping the drug. As many cases of night blindness are transitory, this condition is not in itself a reason to discontinue therapy. However, if night blindness persists for many weeks, consider closer monitoring and possibly further testing; that is, electroretinography, visual field testing, and dark adaptometry testing.

Therapy should be stopped if any of the following occur:

- pseudotumor cerebri;
- optic neuritis;
- persistent night blindness.

Permanent night blindness, permanent sicca, and transitory loss of color vision only occur in patients on long-term chronic therapy and are indeed rare events.

## SILDENAFIL (VIAGRA®)

### Primary Use

For the management of erectile dysfunction.

## Clinical Concerns

Ocular side effects are uncommon, dosage dependent, and thus far have all been fully reversible.

## Reported Side Effects

### *Non-Arteritic Ischemic Optic Neuropathy (NAION)*

- Possible side effect, but no plausible explanation for the mechanism has yet been described (Egan and Fraunfelder, 2005; Fraunfelder, 2005; Fraunfelder and Pomeranz, 2005).

### *Changes in Color Perception*

- Objects have colored tinges that are usually blue or blue/green; may be pink or yellow.
- Diminished color vision.
- Dark colors appear darker.

### *Blurred Vision*

- Central haze.
- Transitory decreased vision.

### *Changes in Light Perception*

- Increased perception of brightness.
- Flashing lights, especially when blinking.

## Conjunctival Changes

- Hyperemia.
- Subconjunctival hemorrhages – not proven to be drug related.
- Ocular pain.
- Photophobia.

The above ocular side effects are dose dependent. Incidence is as follows:

- 50 mg, 3%
- 100 mg, 10%
- 200 mg, 40–50%.

Ocular side effects occur in direct proportion to sildenafil levels in the blood. The side effects based

on dosage start at 15–30 min and usually peak 1 h after ingestion of the drug:

- 50 mg, gone in 1 h
- 100 mg, gone in 2 h
- 200 mg, gone in 4–6 h

## Guidelines for Following Patients

The following guidelines are modified after Laties and Fraunfelder (2000). This class of drugs is *contraindicated* or should be used with extreme caution in patients who have

- retinitis pigmentosa;
- congenital stationary night blindness;
- deficiency or mutation of photoreceptor cGMP PDE;
- history of NAION in either eye;
- informed consent advised; no data to prove it is harmful, but it theoretically could be.

## CORTICOSTEROIDS: INHALED (BECLOMETHASONE – BECLOVENT<sup>®</sup>, BECONASE<sup>®</sup>, VANCENASE<sup>®</sup>, VANCERIL<sup>®</sup>) (BUDESONIDE – RHINOCORT<sup>®</sup>)

### Primary Use

For treating asthmatic, allergic, and chronic lung diseases.

## Clinical Concerns

A report in the *Journal of the American Medical Association* (Garbe *et al.*, 1998) states that inhaled corticosteroids taken at high doses for longer than 3 years increased patients' risk of undergoing cataract extraction threefold compared with a control group.

### Comments

- Glaucoma induced by inhaled steroid use is well documented.
- Analysis of 416 cases in which patients used inhaled steroids but had not used systemic steroids for at least 5 years shows increased incidence of cataract surgery.

- This is the first report to investigate risk according to daily dose of inhaled steroids and duration of use ( $>1$  mg of beclomethasone or budesonide per day).
- Systemic steroid use causes a statistically significant increase, after just 1 year of therapy, in the incidence of cataract surgery in the elderly in this same study.
- As study points out, while there are many variables in this research, this indirect evidence suggests that we may have markedly underestimated the potential of inhaled steroids as a cataractogenic co-factor in the elderly.

### TAMOXIFEN (NOLVADEX®)

#### Primary Use

For metastatic breast cancer, pancreatic cancer, and malignant melanoma. Beginning to be used as prophylactic long-term therapy in patients with a strong family history of breast cancer. Clinicians should expect to see more patients for follow-up ocular examinations who are receiving long-term tamoxifen therapy.

#### Clinical Concerns

There are minimal data on long-term ( $>4$ –5 years) exposure to this drug with documented significant ocular side effects. Thus, all data are preliminary.

#### Known Side Effects

- Posterior subcapsular cataracts.
- Decreased color perception.
- Decreased vision.
- Retina or macula: refractile bodies, edema, degeneration, pigmentary changes, and hemorrhages.
- Visual fields: constriction, scotomata
- Papilledema.
- Optic neuritis.
- Corneal deposits.
- ERG changes.

#### Guidelines for Following Patients

The following guidelines are modified after Gorin *et al.* (1998):

- Baseline ophthalmic examination within the first year of starting tamoxifen therapy. This should include slit lamp biomicroscopy of the anterior and posterior segments in combination with an indirect ophthalmoscope or contact lens. Baseline color vision testing is important.
- In keeping with the American Academy of Ophthalmology's current recommendations, there should be a complete eye examination at least every 2 years for healthy adults. More frequent examinations are required if ocular symptoms occur.
- In the absence of macular edema or visual impairment, the discovery of a limited number of intraretinal crystals does not seem to warrant the discontinuation of therapy.
- Consultation with the oncologist is essential if significant ocular findings occur.
- The presence of age-related maculopathy is not a contraindication to the use of tamoxifen. However, informed consent may be advisable in our litigious society.
- The presence of posterior subcapsular cataracts is not an indication to stop tamoxifen therapy, as this condition usually progresses even if the drug is discontinued.
- Significant loss of color vision may be a valid reason to consider discontinuing the drug. Gorin *et al.* recommend considering stopping the drug for 3 months (in patients on prophylactic therapy) and retesting at the end of that time. If color vision has returned to normal, restart the drug and retest in 3 months. If at any time there is a lack of visual recovery or color vision loss progresses after therapy is stopped, the ophthalmologist may need to consult the oncologist and re-evaluate the risk/benefit ratio of tamoxifen therapy.

#### Comments

The incidence of ocular toxicity reported in the literature ranges from 1.5% to 12%; however, the incidence of ocular complications that required stopping therapy is less than 1%. Indications for stopping the drug require consultation with the oncologist, as there are many variables. Decreasing

the dosage may be an option if frequent ophthalmic observations are performed.

Indications for stopping tamoxifen therapy include

- macular edema;
- decreased vision (with or without the presence of refractile bodies or pigmentary change);
- optic neuritis;
- decreased color vision;
- presence of retinal crystals, though in itself this is not an indication to stop the drug;
- retinal changes, which can occur even at 20 mg dosage levels; and
- optic neuritis, which has been reported at a total dosage of only 2–3 g.

## AMIODARONE (CORDARONE®)

### Primary Use

Primarily used to treat various cardiac arrhythmias.

### Clinical Concerns

#### *Known Ocular Side Effects*

- Corneal deposits (100%) may interfere with vision, especially with night driving
- Color vision defects.
- This photosensitizing drug may cause discoloration of the eyelids and conjunctiva (typically yellow–brown or gray–blue).
- Cataracts – anterior subcapsular, seldom interfere with vision.

### Guidelines for Following Patients

The following guidelines are after Macaluso *et al.* (1999):

- Baseline ophthalmic examination.
- Follow-up examination every 6 months (controversial).
- Instruct patients to see ophthalmologist promptly in case of any visual disturbance.

Amiodarone-induced optic neuropathy is an important recent finding. As in many cases, it may be impossible to distinguish NAION from amiodarone optic neuropathy; consultation with a neuro-ophthalmologist may be necessary. Many patients taking amiodarone may already have compromised optic nerves due to vascular disease; amiodarone deposition in the axons further impedes neural function, causing vision loss.

The cause of amiodarone neuropathy is unknown but may be because of selective accumulation of intracytoplasmic lamellar deposits or by-product inclusions (primary lipidosis) in optic nerve axons. This may mechanically or biochemically decrease axoplasmic flow. Resultant optic nerve head edema may persist as long as transport is inhibited; that is, as long as several months following discontinuation of amiodarone, which has a half-life of up to 100 days. Edema caused by NAION resolves much more rapidly. To date, there are no reported cases of amiodarone neuropathy causing no light perception. Finally, the degree of amiodarone neuropathy may not be equal in each eye for a few months, but it usually will become equal if therapy is continued. Stopping the drug, in consultation with the cardiologist, at the first signs of optic nerve involvement must be considered unless the ophthalmologist is very confident of the diagnosis of NAION.

## TOPIRAMATE (TOPAMAX®)

### Primary Use

Topiramate is a novel agent used to treat patients with various types of epilepsy and migraine headaches. It is used off label as a “magic” weight-reduction medication and to treat bipolar disorder and clinical depression.

### Clinical Concerns

Recent case reports by Banta *et al.* (2001) have included almost 100 reports of a classic acute-angle closure glaucoma syndrome (Fraunfelder *et al.*, 2004).

In the registry series:

- patients range from 3 to 53 years of age;
- time to onset of reaction ranges from 3 to 14 days after the start of oral therapy.

## WHO Classification

### *Certain*

- Acute glaucoma (mainly bilateral).
- Anterior chamber shallowing.
- Ocular hyperemia.
- Increased ocular pressure.
- Mydriasis.
- Suprachoroidal effusions.
- Visual field defects – acute glaucoma.
- Ocular pain.
- Acute myopia (up to 6–8 diopters).

### *Probable/Likely*

- Blepharospasm.
- Oculogyric crisis.
- Retinal bleeds.
- Uveitis.

### *Possible*

- Teratogenic effects, including ocular malformations.
- Scleritis.
- Decreased vision.

Before the syndrome was recognized, most patients were treated with laser or peripheral iridectomy, which we now know is not beneficial.

## Guidelines for Following Patients

- Patients should stop the medication.
- Hyperosmotic therapy.
- Cycloplegic.
- Topical antiglaucoma medication.

**BISPHOSHONATES: PAMIDRONATE DISODIUM (AREDIA<sup>®</sup>), ALENDRONIC ACID (FOSAMAX<sup>®</sup>), IBANDRONATE, ZOLENDRONATE (ZOMETA<sup>®</sup>), RISEDRONATE SODIUM (ACTONEL<sup>®</sup>), CLODRONATE (BONEFOS<sup>®</sup>), ETIDRONATE DISODIUM (DIDROCAL<sup>®</sup>), AND OLPADRONATE**

### Primary Use

Pamidronate disodium (3-amino-1-hydroxy propylidene, disodium salt pentahydrate) inhibits bone

resorption in the management of hypercalcemia of malignancy, osteolytic bone metastases of both breast cancer and multiple myeloma, and Paget's disease of the bone.

## Clinical Concerns

This class of drug has been reported to cause anterior uveitis and nonspecific conjunctivitis. There are case reports of episcleritis, nerve palsy, ptosis, retrobulbar neuritis, and yellow vision. We previously reported a case of anterior scleritis and a case of posterior scleritis associated with pamidronate use, without rechallenge data. The most studied drug in this class, pamidronate, has caused 17 cases of unilateral scleritis and one case of bilateral scleritis. Onset is usually within 6–48 h of intravenous drug administration. Six patients had positive rechallenge testing, with scleritis recurring after repeat drug exposure. Other ocular side effects with positive rechallenge data include blurred vision, non-specific conjunctivitis, ocular pain, bilateral anterior uveitis, and episcleritis.

## WHO Classification

### *Certain*

- Blurred vision.
- Ocular irritation.
- Nonspecific conjunctivitis.
- Pain.
- Epiphoria.
- Photophobia.
- Anterior uveitis (rare – posterior).
- Anterior scleritis (rare – posterior).
- Episcleritis.

### *Probable*

- Periorbital, lid and/or orbital edema.

### *Possible*

- Retrobulbar neuritis.
- Yellow vision.
- Diplopia.
- Cranial nerve palsy.
- Ptosis.
- Visual hallucinations.

## Guidelines for Following Patients

This is the only class of drug proven to cause scleritis. Bisphosphonates can cause vision-threatening diseases. The seriousness of these conditions may dictate discontinuation of the drug in some uveitis cases and, in this series, all cases of scleritis. Further guidelines are as follows:

- If there is ocular pain or persistent decrease in vision, the patient should see an ophthalmologist.
- Bilateral anterior uveitis or, rarely, posterior or bilateral uveitis may occur and can vary markedly in severity. Many cases require intensive topical ocular or systemic medication. In some instances, the drug must be discontinued for the uveitis to resolve.
- Episcleritis may require topical ocular medication; however, pamidronate may be continued.
- In this series, for the scleritis to resolve, even on full medical therapy, the intravenous pamidronate had to be discontinued.

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# Renal Adverse Drug Reactions

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## INTRODUCTION

The kidney is particularly vulnerable to adverse drug reactions. Because it excretes many of their metabolites, it is exposed to high concentrations of these drugs (Riedmaier *et al.*, 2012). Moreover, there is evidence that several drugs with nephrotoxic potential are accumulating in renal cells as the result of renal handling by organic anion transporters (Hagos and Wolff, 2010). A constant abundant oxygen supply to renal tissue is required to support active ion and solute transport, making it particularly vulnerable to any change in blood flow and oxygen deprivation. The thick ascending limb of Henle's loop is the principal site of NaCl reabsorption and additionally is suffering from a marginal blood supply via the vasa recta. Any drug that interferes with renal blood flow at this site may induce acute tubular necrosis, which can lead to acute kidney injury (AKI).

## DEFINITIONS AND DIAGNOSIS

Since renal function is so diverse, it is impossible to give a unique definition of a renal adverse reaction. The physiological role of the kidney and the clinical manifestation of malfunction are summarized in Table 37.1.

Drug-induced decrease in renal function is a major side effect in clinical practice. AKI is defined as an acute-onset of severe deterioration of renal function necessitating renal replacement therapy in many cases. The severity of AKI can be determined by the RIFLE criteria (Englberger *et al.*, 2011). In the context of clinical studies, nephrotoxicity is more readily defined as a predefined level of decrease of renal function. In chronic kidney disease (CKD), deterioration of renal function proceeds more progressively. A clinical manifestation of drug-induced renal failure that is particularly frequent is the so-called acute-on-chronic renal

**Table 37.1** Physiological role of the kidney and clinical manifestation of malfunction.

Physiological function	Pathophysiology
Excretion of endogenous substances and xenobiotics	Renal failure
Maintenance of electrolyte balance	Electrolyte disturbances
Maintenance of fluid balance	Dehydration, edema
Regulation of blood pressure	Hypertension, orthostatic hypotension
Regulation of acid-base status	Alkalosis, acidosis
Stimulation of erythropoiesis by erythropoietin	Anemia

failure. In this setting, acute drug-induced injury is superimposed on chronically damaged renal tissue.

The absence of an effect on filtration function does not preclude a renal adverse effect. For example, owing to renal salt wasting, polyuria and orthostatic hypotension may be the first manifestation of an adverse reaction of the tubulotoxin cisplatin (Hutchison *et al.*, 1988).

## EPIDEMIOLOGY

The interpretation of incidence data of renal adverse reactions is hampered by the absence of a uniform definition. However, drug-induced nephrotoxicity is a major cause of hospital-acquired AKI, contributing to 4–19% of the cases (Hou *et al.*, 1983; Shusterman *et al.*, 1987; Nash *et al.*, 2002; Payen and Berton, 2005), also in developing countries (Jha *et al.*, 1992). Antibiotics (aminoglycosides, amphotericin B, piperacillin), nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, and angiotensin-converting enzyme (ACE) inhibitors are high on the list (Nash *et al.*, 2002). Especially in the setting of the intensive care unit (ICU), drug-induced renal failure is very frequent (Pera-zella, 2012). The reason is that many precipitating factors, such as hypovolemia, true hypovolemia or reduced effective circulating volume, sepsis, older

age, and the concomitant administration of other nephrotoxins, are present in ICU patients.

In the general community, drug-induced AKI is rare (Liano and Pascual, 1996), although its incidence may be growing due to the increased use of ACE inhibitors in combination with diuretics in the elderly population (Smets *et al.*, 2008). In children, drugs are a rare cause of AKI (Moghal *et al.*, 1998). NSAID-related nephrotoxicity may occur in newborns treated for patent ductus arteriosus (Musu *et al.*, 2011).

Renal adverse effects also contribute to the burden of chronic renal disease. In the 1980s, in some countries like Belgium, Switzerland, and Australia, up to 20% of dialysis patients were suffering from analgesic nephropathy. In these patients, renal papillary necrosis induced by chronic abuse of analgesics led to chronic renal failure. Prospective studies firmly linked the disease to the chronic use of analgesic mixtures. The relationship has been established for mixtures containing phenacetin (Dubach *et al.*, 1983) as well as for mixtures not containing phenacetin (Elseviers and De Broe, 1995). In the same patients, urinary tract tumors were also more prevalent. Nowadays, the disease is disappearing following legislative measures limiting the free access to the incriminated drugs.

The calcineurin inhibitors cyclosporine and tacrolimus are immunosuppressant agents used after organ transplantation and in the treatment of psoriasis and autoimmune diseases. The main adverse effect of these drugs not related to their immunosuppressive action is nephrotoxicity. Calcineurin nephrotoxicity is an important contributor to the development of chronic graft failure after kidney transplantation and may lead to end-stage renal disease in heart and liver allograft recipients. Even short time courses of cyclosporine may induce structural damage in psoriasis patients (Vercauteren *et al.*, 1998). As substrates of CYP3A4, calcineurin inhibitors are frequently involved in drug interactions.

## MECHANISMS OF RENAL ADVERSE DRUG REACTIONS

Drugs may adversely affect renal function by inducing structural injury to components of the nephron

Table 37.2 Classification of various drugs on pathophysiological categories of acute renal failure.

*Functional impairment*

NSAIDs, ACE inhibitors, cyclosporine, cephalothin, angiotensin receptor blockers, diuretics, interleukins, cocaine, mitomycin C, tacrolimus, estrogen, quinine

*Glomerular injury*

NSAIDs, D-penicillamine, captopril, gold salts

*Acute tubular necrosis*

Antibiotics: aminoglycosides, cephaloridine, cephalothin, amphotericin B, rifampicin, vancomycin, foscarnet, pentamidine

NSAIDs, glafenin, contrast media, acetaminophen, cyclosporine, cisplatin, IV immune globulin, dextran, maltose, sucrose, mannitol, heavy metals

*Acute interstitial nephritis*

Antibiotics: ciprofloxacin, methicillin, penicillin G, ampicillin, cephalothin, oxacillin, rifampicin.

NSAIDs, glafenin, ASA, fenoprofen, naproxen, phenylbutazone, piroxicam, tolemetin, zomepirac, contrast media, sulfonamides, thiazides, phenytoin, furosemide, allopurinol, cimetidine, omeprazole, phenindione

*Tubular obstruction*

Sulfonamides, methotrexate, methoxyflurane, glafenin, triamterene, ticrynafen, acyclovir, ethylene glycol, protease inhibitors, suprofen (?)

*Hypersensitivity angitis*

Penicillin G, ampicillin, sulfonamides

*Thrombotic microangiopathy*

Mitomycin C, cyclosporine, oral contraceptives

Adapted from Porter *et al.* (2003). With permission of Springer.

and/or by interfering with the filtration and transport processes or regulatory pathways (Table 37.2).

Drugs interfering with glomerular blood flow may induce functional renal impairment. Cyclosporine and epinephrine cause preglomerular arteriolar vasoconstriction, resulting in a decrease in intraglomerular pressure and filtration pressure. In clinical conditions in which systemic vasoconstriction is prominent, like dehydration or heart failure, glomerular blood flow is critically dependent from a counteracting vasodilation of the preglomerular arteriole mediated by compensatory PGE2 and PGI2 production (Whelton, 1999). In the same patients, maintenance of adequate glomerular filtration pressure is also dependent on postglomerular vasoconstriction mediated by angi-

otensin II. Disruption of these counter-regulatory mechanisms by the administration of NSAIDs or of drugs interfering with angiotensin II (ACE inhibitors and angiotensin II receptor blockers) can produce clinically important and even severe deterioration in renal function. When NSAIDs and ACE inhibitors are co-prescribed there is an accrued risk for functional renal impairment. This drug combination should be avoided, especially in elderly patients and in those taking diuretics.

The publication of the Randomized Aldactone Evaluation Study (RALES; Pitt *et al.*, 1999) promoted the combined use of the anti-aldosterone agent spironolactone and ACE inhibitors in heart failure patients. In the setting of this randomized clinical trial, the incidence of severe hyperkalemia was minimal, patients with renal failure or pre-existing hyperkalemia being excluded from the trial. In subsequent years, however, case reports of life-threatening hyperkalemia in patients treated with spironolactone appeared in the literature (Schepkens *et al.*, 2001). It became evident that hyperkalemia is episodic in these patients and linked to AKI. The main causes for AKI in this setting were dehydration and worsening heart failure. In a population-based time-series analysis conducted in Canada, an increase was found in hyperkalemia-associated morbidity and mortality in elderly patients after abrupt increases in the prescription rate for spironolactone following the publication of RALES (Juurlink *et al.*, 2004).

Drug-induced immune nephropathies include glomerulopathies and tubulointerstitial nephritis. NSAIDs are known to induce both types of renal injury. A review of NSAID-induced nephropathy reported an incidence of 39.2% of minimal change glomerulopathy, 19.6% of tubulointerstitial nephritis, 13.4% of focal glomerular sclerosis, and 8.2% of other types of nephropathy (Ravnskov, 1999). Gold salts previously used in rheumatoid arthritis induce a membranous glomerulopathy. The disease is neither related to dose nor to the duration of treatment, but susceptibility seemed to be genetically controlled, HLA DR3-positive patients being more prone to develop this adverse reaction. Drug-induced interstitial nephritis represents a minority of AKI cases. Clinically, the disease is characterized by bilateral lumbar pain, fever, and skin rash.

Many patients exhibit hypereosinophilia, hypereosinophyluria, and increased immunoglobulin E serum levels. In renal biopsy, the characteristic lesions are interstitial mononuclear cell infiltrates and tubular cell injury. Most often renal function recovers after withdrawal of the drug with or without concomitant steroid therapy. The drugs that are most frequently responsible for tubulointerstitial nephritis are antibiotics, mainly  $\beta$ -lactams, and NSAIDs.

The particular susceptibility of the tubular cell to nephrotoxic injury has several reasons. Tubular solute transport and other renal metabolic processes utilize considerable oxygen amounts and are susceptible to the action of metabolic inhibitors. It is worthwhile noting that the S3-segment of the proximal tubule has the highest rate of oxygen consumption per gram of tissue of the whole body. Moreover, the renal tubular epithelium is the only place where protein-bound drugs dissociate, traverse the renal epithelium, and either accumulate in the proximal tubular cell or reach the tubular lumen. An abundance of tubular enzymes involved in tubular transport may be blocked, in view of the high urinary to plasma concentration ratios, exceeding 1000 in some cases. Typical tubulotoxic drugs that are extensively studied are the aminoglycoside antibiotics (Verpoorten *et al.*, 2003; Lopez-Novoa *et al.*, 2011). Aminoglycosides are polar drugs that are freely filtered through the glomerular membrane. Following binding to megalin in the proximal tubular brush border, aminoglycosides traffic via the endocytic system to lysosomes, where they accumulate in large amounts. In lysosomes, aminoglycosides induce an intense phospholipidosis by inhibiting phospholipases A and C and sphingomyelinase. This phospholipidosis occurs rapidly, involving all major phospholipids, and is responsible for the formation of the so-called "myeloid bodies" (Figure 37.1). At present, it is unknown whether phospholipidosis is linked to tubular cell necrosis. Besides lysosomes, aminoglycoside-induced alterations of mitochondria have also been described. More recently, proteomic analysis following gentamicin administration indicated energy production impairment and a mitochondrial dysfunction occurring in parallel with the onset of nephrotoxicity (Charlwood *et al.*

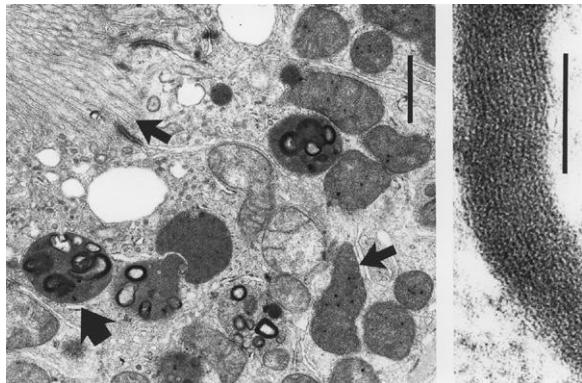


Figure 37.1 Ultrastructural appearance of proximal tubular cells in aminoglycoside-treated patients (4 days at therapeutic dose). Lysosomes (large arrow) contain dense lamellar and concentric structures. Brush border, mitochondria (small arrow), and peroxisomes are unaltered. Upon higher magnification, the structures in lysosomes show a periodic pattern. The bars represent 1  $\mu\text{m}$  (left) and 0.1  $\mu\text{m}$  (right). Source: De Broe *et al.* (1984). Reproduced with permission of Nature Publishing Group.

2002). The severity of aminoglycoside nephrotoxicity can be dissociated from the height of the peak of the aminoglycoside blood level. It became evident that for a given total daily dose the toxicity was greatest when the daily dose was being divided into multiple small administrations. The reason for this apparent paradox is that the renal cortical drug uptake is saturable, so that maintaining a low blood level maximizes tubular cellular drug uptake (Verpoorten *et al.*, 1989).

In the distal part of the nephron, urine is concentrated and the likelihood of crystalline precipitation increases substantially. AKI may result from tubular obstruction due to intratubular precipitation of the drug or its metabolite. This type of renal adverse event is one of the reasons why the protease inhibitor indinavir is now obsolete (Cooper and Tonelli, 2011). A few cases of crystalluria and associated nephropathy have also been reported for atazanavir. Tenofovir also has nephrotoxic potential, but is considered to be a tubulotoxin (Cooper *et al.*, 2010).

The immunosuppressive drug cyclosporine is of particular interest since it can display all types of nephrotoxicity (reviewed in Bosmans *et al.* (2006)).

Cyclosporine profoundly alters renal and glomerular hemodynamics. Administration of cyclosporine induces a decline in glomerular filtration rate (GFR) and renal blood flow by vasoconstriction at the level of the afferent arterioles. Catecholamines, endothelin, and eicosanoids like thromboxane are potential mediators of this effect. Effects of cyclosporine on tubular function consist of increased proximal reabsorption of sodium, resulting in decreased distal sodium delivery, interfering with the potassium secretory capacity of the distal tubule. This pathophysiologic effect may explain the observed hyperkalemic metabolic acidosis in cyclosporine-treated kidney allograft recipients. Besides these functional side effects, cyclosporine induces morphologic alterations in the kidney. First, cyclosporine induces dose-dependent acute tubular changes consisting of isometric vacuolization of tubular cells, accumulation of eosinophilic bodies representing giant mitochondria, and microcalcifications in proximal tubules. These pathologic alterations are reversible after dose reduction or withdrawal of cyclosporine. In contrast to the acute injury, chronic administration of cyclosporine may lead to irreversible histopathologic lesions. They include renal arteriolar damage (the so-called cyclosporine-associated arteriolopathy), tubular atrophy, and focal or striped interstitial fibrosis, as well as glomerular sclerosis (Figure 37.2). Clinically,

chronic cyclosporine nephrotoxicity is associated with hypertension, progressive renal failure, and a variable degree of proteinuria. Thrombotic microangiopathy is an uncommon but serious adverse effect of cyclosporine. The striking morphologic changes, resembling hemolytic-uremic syndrome, are extensive thrombotic processes in the renal microcirculation, with several glomerular capillaries occluded by thrombi extending from the afferent arterioles (Verpooten *et al.*, 1987). Laboratory findings include thrombocytopenia, hemolytic anemia, and deteriorating renal function. Although cyclosporine causes hypertension, it has a salt wasting effect. Salt depletion aggravates cyclosporine nephrotoxicity in animal models as well as in humans. Another almost constant feature of cyclosporine toxicity is renal magnesium wasting. Recently, our group showed, in a rodent model of cyclosporine nephrotoxicity, that these electrolyte disturbances are caused by a specific downregulation in the distal nephron of the thiazide-sensitive sodium-chloride-channel (NCC) and the magnesium transporter TRPM6 (Ledeganck *et al.*, 2011).

## DIAGNOSIS OF ADVERSE RENAL DRUG REACTIONS

None of the functional or morphologic alterations to the kidney described are pathognomonic to adverse drug reaction. So, general principles of renal diagnostic procedures apply to the evaluation of renal adverse renal drug reactions.

Although glomerular and tubular processes cooperate in renal excretory function, renal function is routinely expressed as GFR or creatinine clearance. Measurement of creatinine clearance requires a 24-h urine collection, which is cumbersome and prone to error. Therefore, it is now generally accepted to calculate creatinine clearance using nomograms like the Cockroft–Gault formula (Cockroft and Gault, 1976; Gault *et al.*, 1992) or the MDRD formula (Levey *et al.*, 1999, 2000); see Box 37.1. These equations all have their limitations and new equations are constantly tested for general use (Inker *et al.*, 2012) or in particular populations (Praditpornsilpa *et al.*, 2012). Care must be always taken to compare the result of the

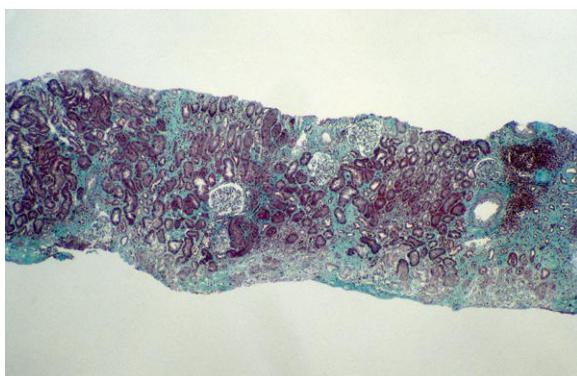


Figure 37.2 Renal biopsy of a hepatic allograft recipient, showing lesions characteristic for chronic cyclosporine nephrotoxicity. Areas of interstitial fibrosis and tubular atrophy alternate with areas of almost normal renal tissue. Source: Bosmans (2001).

**Box 37.1 Calculation of Creatinine Clearance/GFR**

The Cockroft–Gault formula (Gault *et al.*, 1992):

$$\frac{140 - \text{age (years)} \times \text{weight (kg)}}{72 \times \text{Screat (mg/dL)}} \text{ (ml/min)}$$

Male (18–92 years)

Female (18–92 years)  $\times 0.85$

The MDRD formula (Levey *et al.* 1999, 2000):

$$186 \times \text{Screat}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \\ \times 1.210 \text{ (if African-American)} \\ (\text{ml/min}/1.73 \text{ m}^2)$$

creatinine clearance calculation with an age- and gender-matched population (Elseviers *et al.*, 1987).

The determination of renal function by means of the creatinine clearance, however, remains a poorly sensitive method of monitoring the kidney function. Therefore, in experimental settings, a more accurate way of assessing changes in GFR is to measure the clearance of a compound that is freely filtered by the glomerulus but is neither secreted nor absorbed by the tubules. Radiolabeled sodium iodothalamate and ethylenediaminetetraacetic acid are substances commercially available for this purpose.

The most common urinary biomarker used in renal diagnosis is proteinuria. Under normal conditions, the glomerular filtration barrier restricts the transfer of high-molecular-weight proteins from the plasma to the lumen of the tubule. High-molecular-weight proteins appearing in the urine point to a pathological condition of the glomerulus, changing the permselectivity of the filter. Under normal conditions, a minute amount of low-molecular-weight proteins is filtered which then undergoes endocytic reabsorption by proximal tubular cells. When the reabsorptive capacity of the proximal tubule is compromised, low-molecular-weight proteins appear in the urine in measurable amounts. Determination of

the quantity and the quality of urinary proteins allows for the distinction between “glomerular” and “tubular” proteinuria.

Enzymuria has been extensively used by toxicologists to detect early renal damage. Urinary enzymes bear the potential of determining the site of damage because different enzymes are localized in specific segments of the nephron. For example, alanine aminopeptidase, alkaline phosphatase, and  $\gamma$ -glutamyltransferase are enzymes bound to the brush border of proximal tubular cells. Their appearance in the urine should be indicative for turnover of brush border. The general acceptance of urinary enzyme excretion as a measure of tubular dysfunction in human safety studies has been limited for several reasons. First, it has been impossible to link the presence of the different enzymes appearing in the urine to specific tubular disease states. Second, a relationship between the magnitude of the enzymuria and the severity of tubular injury has not been established. Furthermore, enzymuria may occur in normal situations due to increased brush border turnover, altered membrane permeability, or increased synthesis.

In general, a renal biopsy is not needed to establish the diagnosis of a renal adverse event. When a glomerulopathy is suspected, only a biopsy allows one to distinguish between the different histopathologic types. Ideally, the diagnosis of acute interstitial nephritis is also confirmed by histopathologic examination.

Presently, during drug development, preclinical toxicity tests involve the use of animal models. However, advances in cell and tissue culture will permit the development of *in vitro* toxicity assays. The aim of the development of *in vitro* tests is not only to replace *in vivo* animal testing, but also to study the mechanisms of cell modulation by toxic compounds (Loghman-Adham *et al.*, 2012). Several permanent and immortalized cell lines of human and nonhuman origin are available, offering several advantages over primary cultures, such as an unlimited life span and the lack of time-consuming isolation procedures. The most widely used renal epithelial cell lines of animal origin are the LLC-PK1 (Hampshire pig) and OK (American opossum) cell lines, exhibiting characteristics suggestive of proximal tubular origin, and the MDCK

(cocker spaniel) cell line, exhibiting characteristics suggestive of distal origin.

## PREVENTION OF RENAL ADVERSE DRUG REACTIONS

Clinically important drug nephrotoxicity results from the complex interplay between the intrinsic toxic capacity of the drug, the level of drug exposure (i.e., dosage and duration), and patient-related risk factors.

Drugs with a high nephrotoxic potential should be preserved for the treatment of life-threatening diseases. The use of aminoglycoside antibiotics, for example, should be limited to the treatment of sepsis or neutropenic fever. Cyclosporine is part of the standard immunosuppressive therapy after organ transplantation, but its use in the treatment of psoriasis is more questionable in view of the high incidence of chronic irreversible renal damage (Vercauteren *et al.*, 1998).

Many toxic insults to the kidney, with the obvious exception of idiosyncratic drug reactions, are related to the degree of exposure. In particular, in drugs that accumulate in renal tissue, prolonged or repetitive therapy is associated with an accrued risk for toxicity. For example, aminoglycoside nephrotoxicity occurred more frequently when therapy was prolonged for three or more days (Pateson *et al.*, 1998). Drug interactions interfering with drug disposition may lead to nephrotoxicity. Inhibition of drug-metabolizing enzymes or efflux transporters decreases the rate of metabolism of the object drug. This, in turn, can result in increased serum concentrations and potential drug toxicity if the drug has a narrow therapeutic index. For instance, a major dose-related adverse effect of statins is myopathy. If not recognized, rhabdomyolysis and AKI may result. The risk for AKI is significantly increased when statins are combined with drugs inhibiting the CYP3A4 system, such as cyclosporine, macrolide antibiotics, or itraconazole (Vlahakos *et al.*, 2002).

Age, along with pre-existing renal disease and volume depletion (i.e., true hypovolemia or reduced effective circulating volume) are well-recognized risk factors for hospital-acquired AKI (Shuster-

man *et al.*, 1987). The latter risk factor for nephrotoxicity is modifiable by intervention prior to exposure to a nephrotoxic insult. In the case of radiocontrast-induced nephropathy, hydration with sodium chloride or sodium bicarbonate (Merten *et al.*, 2004) before contrast exposure has been shown to protect against nephropathy.

## CONCLUSION

The kidney represents a major target for adverse drug reactions owing to its role in drug excretion and in the control of body fluid and electrolyte homeostasis. Early recognition by physicians of adverse renal drug reactions is critical, since prompt withdrawal of the nephrotoxin can be life saving. Many patients with overt nephrotoxicity have identifiable risk factors that could be modified or that should preclude the use of potentially nephrotoxic drugs.

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# The Cardiovascular Spectrum of Adverse Drug Reactions

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## INTRODUCTION

Undesired sequelae of pharmacologic agents encompass a wide range of adverse cardiovascular effects. These include proarrhythmic, atherogenic, myopathic, and valvular consequences (Table 38.1). Some agents directly affect cardiac tissue, whereas others act indirectly or modulate heart disease risk factors.

The underlying mechanisms are better understood for the agents with very specific targets, such as vascular endothelial growth factor inhibition, which leads to hypertension and endothelial dysfunction. Other mechanistic bases are less clear; for example, the ventricular hypertrophy and sudden death observed with anabolic steroids, which appear to directly affect cardiomyocytes as well as raising low-density lipoprotein cholesterol and possibly blood pressure.

In this chapter, we will focus on two examples of undesired clinical cardiovascular drug effects. The

mode of identification, subsequent regulatory steps, and movement into clinical practice are summarized for the adverse cardiovascular effects associated with rosiglitazone and estrogen's venous thrombogenic effect.

## ESTROGEN AND VENOUS THROMBOSIS

Estrogen has been used to treat menopausal symptoms since 1933, when emmenin was introduced. Premarin, a more easily manufactured estrogen, was approved in 1942 (CDER, 1997; FDA, 2003). By the 1960s, 12% of women in the USA were using postmenopausal estrogen therapy, a proportion that increased steadily. The National Prescription Audit and National Disease and Therapeutic Index databases tracked annual hormone therapy prescriptions rising from 58 million in 1995 to 90 million in 1999; prescriptions then remained stable through June 2002 (Hersh *et al.*, 2004). Analysis of

Table 38.1 Examples of drug cardiotoxicity.

Cardiac effect	Drug
Cardiomyopathy	Doxorubicin (Singal and Iliskovic, 1998) Sunitinib, tyrosine kinase inhibitor (Chu <i>et al.</i> , 2007) Bevacizumab, vascular endothelial growth factor inhibitor (Stone <i>et al.</i> , 2011)
Myocarditis	Trastuzumab, ErbB2 inhibitor (Jones <i>et al.</i> , 2007)
Proarrhythmic	Clozapine (Ronaldson <i>et al.</i> , 2010)
Atherothrombotic	Terfenadine (Monahan <i>et al.</i> , 1990) Cisapride (Rampe <i>et al.</i> , 1997) Cyclooxygenase inhibitors (Bresalier <i>et al.</i> , 2005; Konstantinopoulos and Lehmann, 2005; McGettigan and Henry, 2006)
Valvulopathic	Anabolic steroids (Vanberg and Atar, 2010) Postmenopausal hormone therapy (Manson <i>et al.</i> , 2003; Hsia <i>et al.</i> , 2006) Sibutramine (James <i>et al.</i> , 2010) Fenfluramine, dexfenfluramine (MMWR, 1997)

data from a large cohort study in the USA showed that 45% of postmenopausal women used estrogen for at least a month and more than 20% used it for 5 years or more, either alone or in combination with progestin (Brett and Madans, 1997).

These rates have been shown to differ based on a woman's hysterectomy status; in a study by Keating *et al.* (1999), current postmenopausal hormone use was 58.7% among women with prior hysterectomy compared with 19.6% among women with intact uteri. Most women started to take therapy shortly after menopause; median duration of use was 3 years (mean 6.6 years). Postmenopausal hormone use demonstrated a secular trend; only 19% of women born before 1904 ever used postmenopausal hormones, compared with 63% of women born between 1945 and 1954 (Brett and Madans, 1997).

In 1992, the American College of Physicians recommended hormone therapy for postmenopausal women who either had hysterectomy or were at risk of coronary heart disease (American College of Physicians, 1992). It quickly became standard medical practice to prescribe exogenous estrogens, either alone or in combination with progestin, for most menopausal women, with the expectation that most, if not all of these women, would benefit from treatment. Initially, most women received unopposed estrogen regardless of their hysterectomy status. After the National Heart, Lung and Blood Institute-funded Postmenopausal Estrogen/Progestin Interventions (PEPI) trial reported an increased risk of endometrial hyperplasia when women with intact uteri were treated with unopposed estrogen in 1995, most women with intact uteri were switched to combination estrogen-progestin therapy (The Writing Group for the PEPI Trial, 1995). Indeed, when the Women's Health Initiative was being planned in the early 1990s, there was debate about the ethics of withholding postmenopausal hormone therapy from the women who would be randomized to placebo.

A cloud was introduced to that climate of enthusiasm for estrogen in the 1960s when an apparent increased risk of venous thromboembolism (VTE) – that is, deep venous thrombosis and pulmonary embolism – was associated with oral contraceptive use (Royal College of General Practitioners 1967; Vessey and Doll, 1968, 1969; Jick *et al.*, 1995). The relationship between VTE and exogenous estrogen was explored in several small case-control and cohort studies in the 1970s (Boston Collaborative Drug Surveillance Program, 1974; Nachtigall *et al.*, 1979; Petitti *et al.*, 1979). In these analyses, VTE was more common in women taking oral contraceptives, but the relationship with postmenopausal hormone therapy was less clear. These epidemiologic studies were followed by large randomized, controlled trials.

PEPI was a 3-year randomized, placebo-controlled trial in 875 postmenopausal women comparing the effects of several postmenopausal hormone regimens on cardiovascular disease risk factors. The cohort was healthy and relatively young; consequently, only 10 VTE cases were identified among women on active hormone therapy

Table 38.2 Annualized rates (%/year) of venous thromboembolism in randomized trials of postmenopausal hormone therapy.

	Placebo	Unopposed estrogen	Estrogen plus progestin
PEPI	0	0.76	0.38
HERS	0.23		0.62
Year 1	0.29		0.96
Year 2	0.15		0.61
Year 3	0.23		0.55
Year $\geq 4$	0.20		0.40
WHI	0.17		0.35
Estrogen plus Progestin trial			
WHI	0.22	0.30	
Estrogen Alone trial			

PEPI, Postmenopausal Estrogen/Progestin Interventions trial; HERS, Heart & Estrogen/Progestin Replacement Study. WHI, Women's Health Initiative.

and none on placebo during the 3-year follow-up (The Writing Group for the PEPI Trial, 1995). The rate of VTE in women taking conjugated estrogens (0.625 mg daily) alone was twice that of women taking any of three estrogen plus progestin regimens (Table 38.2), but the overall number of cases was small.

The Heart & Estrogen/Progestin Replacement Study (HERS) randomized 2763 women with documented coronary heart disease to placebo or conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily (Hulley *et al.*, 1998; Grady *et al.*, 2000). Combination hormone therapy increased VTE risk (relative hazard 2.7, 95% confidence interval (CI) 1.4–5.0); the relative hazard for deep venous thrombosis was 2.8 (95% CI 1.3–6.0) and for pulmonary embolism was 2.8 (95% CI 0.9–8.7) with estrogen plus progestin.

The Women's Health Initiative (WHI) includes two randomized, placebo-controlled hormone trials, one with unopposed conjugated estrogens (0.625 mg daily) in 10 739 women with prior hysterectomy, and the other with conjugated estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg

daily in 16 608 women with intact uterus. In the trial of unopposed estrogen, the hazard ratio for deep vein thrombosis was 1.47 (95% CI 1.06–2.06) and for VTE was 1.32 (95% CI 0.99–1.75). The increased risk associated with conjugated estrogens did not depend significantly ( $p = 0.70$ ) on factor V Leiden or plasminogen activator inhibitor-1 ( $p = 0.57$ ) genotype (Curb *et al.*, 2006). In the trial of combination estrogen plus progestin, the hazard ratio for deep vein thrombosis was 1.95 (95% CI 1.43–2.67) and for VTE was 2.06 (95% CI 1.57–2.70). For women with the factor V Leiden variant, the odds of VTE among women taking estrogen plus progestin were slightly higher in white women than in the overall group (odds ratio, OR 8.53, 95% CI 3.78–19.23) (Cushman *et al.*, 2004). In these predominantly healthy women, the annualized rates of VTE were lower than in HERS (Table 38.2), but the studies demonstrated a similar pattern of risk by year of treatment. In the WHI Estrogen Alone trial, the hazard ratio for VTE during the first 2 years of treatment was 2.22, and 1.17 thereafter. In the Estrogen Plus Progestin trial, the yearly hazard ratios for VTE were 4.01 in year 1, 1.97 in year 2, 1.74 in year 3, 1.70 in year 4, 2.90 in year 5, and 1.04 in year 6 or later. Following discontinuation of postmenopausal hormone therapy, the increased VTE risk was no longer observed (Heiss *et al.*, 2008; LaCroix *et al.*, 2011).

In a meta-analysis of oral postmenopausal hormone therapy which included PEPI, HERS and the WHI, the odds ratio for venous thromboembolism was 2.1 (95% CI 1.4–3.1) (Canonico *et al.*, 2008). Although no randomized trials have evaluated the risk of VTE with transdermal estrogen, observational studies suggest the risk may be less severe.

The labels for estrogen formulations have been repeatedly updated to reflect new findings, including the risk of VTE. A warning was added in 1998 stating:

In some epidemiological studies, women on oestrogen replacement therapy, given alone or in combination with a progestin, have been reported to have an increased risk of thrombophlebitis, and/or thromboembolic disease, although the evidence is conflicting.

Following release of the WHI results, a boxed warning pertaining to cardiovascular risks including VTE was added to the label for estrogens:

The WHI estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625mg]-alone, relative to placebo.

The boxed warning for estrogen with progestin also includes a statement about venous thrombosis risk: "The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism, and myocardial infarction."

These data have also been interpreted by professional societies. The North American Menopause Society's position is that

Growing evidence suggests that women with a prior history of VTE or women who possess factor V Leiden are at increased risk for VTE with HT [hormone therapy] use. There are limited observational data suggesting lower risks of VTE with transdermal than with oral ET [estrogen therapy], but there are no comparative RCT [randomized controlled trial] data on this subject. Lower doses of oral ET may also confer less VTE risk than higher doses, but no comparative RCT data are available to confirm this assumption. (North American Menopause Society, 2010)

The Royal College of Obstetricians and Gynaecologists' guideline on VTE and postmenopausal hormone therapy states, "From the available evidence, the most convincing evidence relates to a greater risk in the 1st year of use than in subsequent years and a lack of continuing risk in those who have stopped hormone replacement therapy" (Greer *et al.*, 2011).

The sequence of data generation and uptake by the medical community in addressing the relationship between postmenopausal hormone therapy and VTE reflects a well-functioning collaboration focused on improving patient outcomes. The fairly rapid succession of randomized trials demonstrated consistent results, findings were widely publicized,

promptly evaluated by health authorities and professional societies, and implemented by practitioners and patients (Hersh *et al.*, 2004).

## ROSIGLITAZONE

Rosiglitazone is an antidiabetic agent in the thiazolidinedione class indicated for improvement of glycemic control in patients with type 2 diabetes mellitus as an adjunct to diet and exercise. It is a highly selective peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) agonist and acts to increase insulin sensitivity by regulating transcription of insulin-responsive genes (GlaxoSmithKline, 2011a). The drug was approved under the brand name Avandia in the USA in May 1999 and in the EU in July 2000, and subsequently gained widespread use worldwide as a primary treatment for type 2 diabetes mellitus (Lofstedt, 2010).

Initial concerns about the cardiovascular safety of rosiglitazone, and indeed the entire thiazolidinedione class of drugs, focused on reports of fluid retention and congestive heart failure and ultimately resulted in a warning being added to the rosiglitazone label (Nissen, 2010). Data from a large randomized trial, the DREAM study (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication), supported this concern by revealing statistically significantly higher rates of heart failure with rosiglitazone compared with placebo (Gerstein *et al.*, 2006). Further data from the ADOPT study (A Diabetes Outcome and Progression Trial), a long-term safety and efficacy study conducted by rosiglitazone's manufacturer, GlaxoSmithKline (GSK), showed a higher risk of cardiovascular events with rosiglitazone compared with glyburide (Kahn *et al.*, 2006). An independent assessment of the data on myocardial infarction from the ADOPT study revealed more events in the rosiglitazone group compared with both metformin and glyburide, with a crude OR of 1.33 (95% CI 0.80–2.21) (Nissen, 2010).

In August of 2006, a meta-analysis of rosiglitazone trials was submitted by GSK to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) that indicated an increased risk of ischemic events with rosiglitazone

(Kazi, 2007). In May 2007, a meta-analysis of 42 clinical trials was published that raised significant concerns about serious adverse cardiovascular effects with rosiglitazone therapy (Nissen and Wolski, 2007). The authors found that when rosiglitazone was compared with controls (consisting of patients receiving drug therapy other than rosiglitazone), the risk of myocardial infarction was increased by 43% (OR 1.43, 95% CI 1.03–1.98,  $P = 0.03$ ). In addition, although not quite statistically significant, the OR for cardiovascular death was 1.64 (95% CI 0.98–2.74,  $P = 0.06$ ). In July 2007, the FDA held an advisory committee, which included a discussion of the FDA's own meta-analysis of cardiovascular events from rosiglitazone trials, the outcome of which was the addition of information regarding the potential risk of myocardial infarction to the existing boxed warning in the rosiglitazone US package insert (Nissen, 2010; Woodcock *et al.*, 2010). In January 2008, based upon a benefit–risk review conducted by the EMA, the rosiglitazone summary of product characteristics (SPC) was updated to include a contraindication in acute coronary syndrome as well as a warning regarding the increased risk of myocardial ischemic events (Blind *et al.*, 2011).

In 2010, further data on rosiglitazone and cardiovascular risk emerged, including an update of the original meta-analysis by Nissen and Wolsky, based upon 56 randomized trials including 19 509 patients receiving rosiglitazone (Nissen and Wolski, 2010). This meta-analysis continued to show an increased risk of myocardial infarction with rosiglitazone, but failed to demonstrate an increase in either cardiovascular or all-cause mortality. In addition, a retrospective, observational study comparing cardiovascular outcomes in 227 571 elderly patients receiving either rosiglitazone or pioglitazone (the other commercially available thiazolidinedione) revealed an increased risk of stroke, heart failure, and all-cause mortality, as well as an increased risk for the composite of acute myocardial infarction, stroke, heart failure and all-cause mortality in patients receiving rosiglitazone compared with pioglitazone in this population (Graham *et al.*, 2010).

In July of 2010, a second FDA advisory committee was convened to consider the available data, and

the majority of members concluded that there was a concern for ischemic cardiovascular events with rosiglitazone compared with other antidiabetic agents (Woodcock *et al.*, 2010). Of the 32 voting committee members, the majority voted for more restrictive measures, with 12 voting to withdraw rosiglitazone from the market and another 10 voting to increase warnings and restrict access to the drug. In assessing the committee's recommendations and the benefit–risk of rosiglitazone use, the FDA recognized the benefit in glycemic control offered by rosiglitazone in light of the known short- and long-term benefits of glycemic control in diabetes. However, the agency assessed the cardiovascular risks with rosiglitazone to be concerning, although not definitive. As such, they determined that there may be patients who do not have adequate glycemic control on other antidiabetic agents and either cannot tolerate or are unable to take pioglitazone for medical reasons. In these patients, the benefit of glycemic control with rosiglitazone may outweigh the increase in cardiovascular risk (Woodcock *et al.*, 2010). In September of 2010, the FDA announced it would be requiring a risk evaluation and mitigation strategy (REMS) for rosiglitazone, with the intent of restricting access to the drug (Woodcock *et al.*, 2010). The REMS for rosiglitazone went into effect on November 18, 2011, and required that rosiglitazone-containing products be prescribed only by specially certified healthcare providers (GlaxoSmithKline, 2011b). Access to the drug will be restricted to patients who are either already receiving rosiglitazone or are not able to adequately achieve glycemic control on other medications and are unable to take pioglitazone based upon consultation with their healthcare provider. The drug will be dispensed for outpatient use only through mail order via certified pharmacies. In addition, medication guides will be required to be submitted with each prescription dispensed, and the pharmacies will be subject to auditing in order to ensure that they are compliant with the REMS program and the associated procedures (GlaxoSmithKline, 2011b; Traynor, 2011).

Concurrent with the FDA's most recent review, the EMA undertook a review of all available evidence regarding rosiglitazone and cardiovascular risk. In July of 2010, the EMA's Scientific Advisory

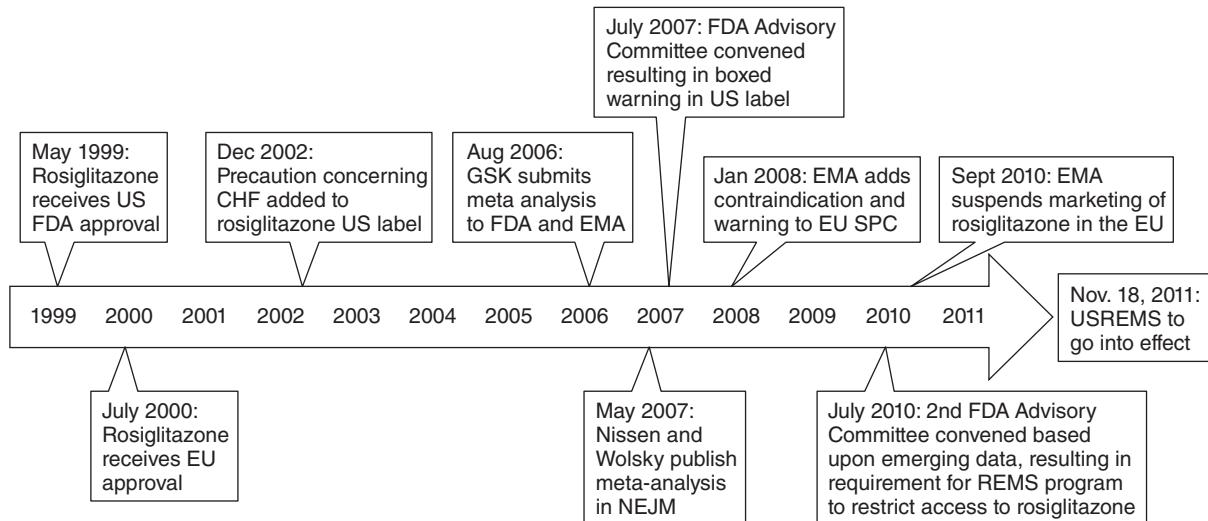


Figure 38.1 Timeline of events for rosiglitazone.

Groups concluded that additional evidence had further altered the benefit–risk balance against rosiglitazone. The EMA considered additional risk minimization measures and label restrictions, but concluded that they were not feasible alternatives given the difficulty in identifying a subgroup of patients that might benefit from rosiglitazone therapy over pioglitazone (Blind *et al.* 2011). As a result, the EMA withdrew rosiglitazone from the European market in September of 2010. Figure 38.1 summarizes the timeline of events for rosiglitazone.

In an effort to prevent such safety issues from recurring, the FDA has issued a guidance for industry that provides recommendations for assessing cardiovascular risk in development programs for new antidiabetic therapies (FDA, 2008). Important recommendations within the guidance include: (1) designing and conducting trials appropriately so that meta-analyses may be performed at the time of program completion, and proposing in the protocol the statistical methods to be used to evaluate the meta-analysis; (2) establishing an independent endpoints committee to adjudicate cardiovascular events in a prospective, blinded fashion; (3) prior to new drug application/biologic license application submission, comparing the occurrence of events with the investigational compound versus compa-

rator for the phase 2–3 combined meta-analysis to show that the upper bound of the 95% CI for the risk ratio is less than 1.8, and considering a large safety trial to show this result if the meta-analysis does not meet this standard. In addition, if a drug's benefit–risk profile is otherwise supportive of approval and the meta-analysis indicates the upper bound of the 95% CI to be 1.3–1.8, the FDA will generally require that a postmarketing safety trial be conducted that definitively shows the upper bound of the 95% CI for the estimated risk ratio to be less than 1.3.

The experience with rosiglitazone illustrates the importance of identifying and thoroughly evaluating potential safety issues during the development phase of a drug's lifecycle and performing ongoing periodic reevaluations of the emerging benefit–risk profile of a drug as it reaches larger populations in the postmarketing setting. This process needs to involve a partnership between industry and regulatory agencies working together to best serve the safety of the public at large.

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# Neurological Adverse Events

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## INTRODUCTION

The human nervous system is arguably the most complex organization of matter known to man. Acting in concert, its receptors, neurons, and their supporting glia enable us to perceive the world, analyze it, and affect it. As such, enumerating the vast number of known and possible neurological adverse events (NAEs) greatly exceeds the space limitations of this chapter (cf., Jain, 2012). Volumes have been written about small subsections of the topic (e.g., White and Sweet, 1969). This review will categorize drug-related NAEs by presentation and drug class, populated with an idiosyncratic and incomplete selection of examples. Psychiatric manifestations, visual phenomena, direct effects on skeletal muscle, and congenital effects are excluded, as are the myriad secondary NAEs that can result from perturbations of the coagulation system and/or platelets. The interested reader can pursue greater detail in textbooks of neurology (e.g.,

Ropper and Samuels, 2009) and pharmacology (e.g., Brunton *et al.*, 2011).

As with other adverse events, individual susceptibility interacts with the pharmacology of the agents. Both genetic polymorphisms and phenotype (age, environmental and other drug and disease interactions, comorbidities, etc.) can affect absorption, distribution, metabolism, and excretion of the drug, as well as alter the mechanism of action. Such complications will not be discussed, but certainly are confounding variables in the adverse events summarized in prescribing information and excerpted here.

Vaccinations are not broken out separately, but NAEs associated with them are included in the relevant sections and have been recently reviewed (Miravalle *et al.*, 2010); fortunately, they tend to resolve over time (e.g., Guillain–Barré syndrome). As is particularly the case with such population-based medical interventions, background rates of disease must be kept in mind (Black *et al.*, 2009).

Similarly, immunomodulatory drugs also can have pleomorphic NAEs (e.g., anti-tumor necrosis factor (TNF)- $\alpha$  agents; Tristano, 2010) which tend to improve but which can lead to permanent disability and death (particularly progressive multifocal leukoencephalopathy, PML). They, too, are listed by their symptomatology. Of course, management of any suspected drug-related NAE begins with discontinuation of the presumed offending agent, if possible. Mechanism-of-action-related toxicities typically resolve.

No specific references for individual drugs are given when the NAEs have been described in prescribing information (e.g., PDR® on CD-ROM (PDR Network, 2011)) or cited reviews. Those drugs for which the incidence of a given NAE is described as  $\geq 3\%$  in these materials are indicated by an asterisk (N.B.: many older and some new drugs do not appear in the PDR®).

## ADVERSE EVENTS INVOLVING SENSATION

The body contains many sensory receptor structures (e.g., Golgi tendon organs, intraganglionic laminar endings, intramuscular arrays, Krause end bulbs, Meissner corpuscles, Merkel discs, muscle spindles, Pacini corpuscles, Ruffini plumes) as well as freely branching nerve endings (Robinson and Gebhart, 2008. McGlone and Reilly, 2010). Though initially it was believed that each of these served a specific function (e.g., touch, pain, warm, cold, vibration), specificity is not absolute, and the sensations elicited by stimulation are more a function of the peripheral nerve fibers that are activated (Ropper and Samuels, 2009). The segmental dorsal root ganglia contain the cell bodies of all sensory neurons, whose centripetal processes enter the spinal cord via the dorsal (posterior) roots. The region of skin whose innervation pertains to a given spinal segment is called a dermatome (e.g., Keegan and Garrett, 1948), and similarly for muscle and bone a sclerotome (e.g., Inman and Saunders, 1944).

Neuropathies of the cranial and peripheral nerves can be caused by many different drugs (e.g., Weimer and Sachdev, 2009; Argyriou *et al.*, 2012)

and result from damage to the axons, their myelin sheaths (which serve as insulation and greatly increase the speed at which the nervous impulse travels), or both. Demyelination in particular has been associated with anti-TNF- $\alpha$  (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) and anti-IL-6 (tocilizumab) immunomodulatory therapies. Neuropathies can result in symptoms that are primarily sensory (agents described in this section), primarily motor, or mixed motor and sensory (e.g., Blain and Lane, 1998). The combination is the most common and also will be included in this section.

## TOUCH/PAIN

Large, heavily myelinated A- $\alpha$  and A- $\beta$  fibers primarily convey touch and pressure sensation from the skin. Their central projections pass into the dorsal horns of the spinal cord and synapse in the ipsilateral medulla with neurons whose axons cross to synapse within the contralateral thalamus, whence third-order axons then pass to the primary somatosensory cortex (McGlone and Reilly, 2010). Disturbances can occur anywhere along this pathway, causing alterations in touch sensation – increased (hyperesthesia), decreased (hypesthesia), absent (anesthesia), or aberrant (paresthesia, dysesthesia).

Peripheral pain messages are carried in the small, thinly myelinated A- $\delta$  and C peripheral nerve fibers. These continue into the lateral part of the dorsal root entry zone and synapse in the ipsilateral dorsal horn. Axons from the secondary neurons cross the spinal cord, ascending contralaterally primarily via the lateral spinothalamic tract to synapse on neurons in the thalamus. Visceral pain mechanisms are more complex and localize less well (Cervero, 1994; Sengupta, 2009).

Examples of specific drugs associated with sensory NAEs are provided below, and the same format is used subsequently.

- Antineoplastic drugs
  - *antimetabolites* – cytarabine, gemcitabine\*
  - *DNA agents* – chlorambucil, cisplatin, doxorubicin\*, nelarabine\*, oxaliplatin\*, procarbazine, temozolomide\*, topotecan\*

- *inducers of differentiation* – acitretin\*, alitretinoin\*, arsenic trioxide\*, bexarotene\*
  - *microtubule inhibitors* – cabazitaxel, colchicine, docetaxel, ixabepilone, taxol, vinblastine, vincristine
  - *targeted therapies* – adalimumab\*, bevacizumab\*, bortezomib\*, brentuximab vedotin\*, dasatinib (abdominal pain), erlotinib\*, exemestane\*, fulvestrant\*, imatinib\*, leuprorelin\*, nilotinib\*, ofatumumab\*, sorafenib\*, trastuzumab\*
  - immunosuppressant/immunomodulatory/anti-inflammatory drugs
    - gold salts
    - *nonsteroidal anti-inflammatory drugs (NSAIDs)* – indomethacin
    - *targeted* – adalimumab\*, basiliximab\*, certolizumab pegol, cyclosporine\*, everolimus\*, etanercept, fingolimod\*, infliximab, natalizumab\*, rituximab\*
    - thalidomide
  - anti-infective drugs
    - *antimicrobials* – chloramphenicol, ciprofloxacin, dapsone, ethambutol, isoniazid, linezolid, metronidazole (incl. burning hands/feet), nalidixic acid, nitrofurantoin, nitrofurazone, polymyxin E, streptomycin
    - *antiparasitics* – chloroquine, clioquinol
    - *antivirals* – emtricitabine\*, lamivudine\*, interferon alfa-2b\*, maraviroc\*, ritonavir\*, tenofovir
  - cardiovascular drugs
    - *antiarrhythmics* – amiodarone, disopyramide
    - *antihypertensives* – carvedilol\*, hydralazine, propranolol
    - *anti-pulmonary artery hypertension (PAH)* – prostacyclin\*
    - *cardiac glycosides* – digitalis (face, limb pain)
    - *lipid-lowering agents* – clofibrate, statins
  - nervous system drugs
    - *antiaddiction* – calcium carbimide, disulfiram
    - *anticonvulsants* – phenytoin, tiagabine\*, zonisamide\*
    - *antidepressants* – amitriptyline, desvenlafaxine\*, duloxetine\*, paroxetine\*, phenelzine, trazodone\*, vigabatrin\*
    - *antimigraine* – ergotamine, frovatriptan\*, methysergide, naratriptan\*, rizatriptan\*, sumatriptan\*, zolmitriptan\*
    - *anti-Parkinson's* – rasagiline\*, ropinirole\*
    - *antipsychotics* – olanzapine\*, quetiapine\*, risperidone\*
    - *anxiolytics/hypnotics* – fospropofol\*, zaleplon\*
    - *opiates* – morphine\*
  - endocrinological drugs
    - *anti-diabetes mellitus (DM)* – chlorpropamide
    - *bone metabolism* – zoledronate\* (bone pain)
    - *hypothalamic/pituitary* – somatropin\*
    - *sex hormones* – Enjuvia®\*
    - *thyroid* – propylthiouracil
  - gastrointestinal drugs
    - *antianorexics/anticachectics* – megestrol\*
    - *antiemetics* – aprepitant\*, thalidomide (including burning, cramping in extremities)
  - hematological drugs
    - *anti-idiopathic thrombocytopenic purpura (ITP)* – eltrombopag\*
    - *bone marrow stimulants* – romiplostim\*
    - *chelators* – deferasirox (abdominal pain)
    - *coagulation factors* – Alphanate®\*
    - *erythropoiesis-stimulating agents (ESAs)* – epoetin alfa\*.
- Headache comprises a specific subset of pain, and can be generated from multiple intracranial and extracranial structures (e.g., arteries and veins, dura mater, periosteum, skin, muscle, cranial nerves). One variant, idiopathic intracranial hypertension (IIH, also called benign intracranial hypertension and pseudotumor cerebri), can lead to permanent visual loss if not managed effectively (Thurtell *et al.*, 2010), and has been associated with a variety of medications (Anon., 1998; Friedman, 2005). In the subsequent list, “+IIH” indicates headache and IIH have been associated with the drug, while “IIH” indicates an association of IIH without additional description of headache.
- Antineoplastic drugs
    - *antimetabolites* – cladribine\*, decitabine\*, fludarabine\*, fluorouracil\*, gemcitabine\*

- *DNA agents* – bendamustine\*, doxorubicin\*, mitoxantrone\*, nelarabine\*, oxaliplatin\*, temozolomide\*, topotecan\*, valrubicin\*
- *inducers of differentiation* – acitretin\* (+IIH), arsenic trioxide\*, bexarotene\*, isotretinoin (IIH), retinol (IIH), vorinostat\*
- *microtubule inhibitors* – cabazitaxel\*, eribulin\*
- *targeted* – adalimumab\*, bevacizumab\*, bortezomib\*, brentuximab vedotin\*, cetuximab\*, dasatinib\*, denileukin diftitox\*, exemestane\*, fulvestrant\*, imatinib\*, lapatinib\*, letrozole\*, leuprorelin\*, nilotinib\*, ofatumumab\*, pazopanib\*, sunitinib\*, tositumomab\*, trastuzumab\*
- immuno-suppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – desloratadine\*, fexofenadine\*, olopatadine\*
  - hyaluronate\*
  - *immunoglobulins* – Flebogamma®, Gammagard®, Gamunex®\*
  - *NSAIDs* – aspirin/dipyridamole\*, celecoxib\*, ibuprofen\*, mesalamine\*, naproxen/esomeprazole\*, nepafenac\*, sulindac\*
  - *steroids* – dexamethasone\*, fluocinonide\*, loteprednol\*
  - *targeted* – abatacept\*, adalimumab\*, basiliximab\*, canakinumab\*, cyclosporine\* (+IIH), everolimus\*, fingolimod\*, imiquimod\*, infliximab\*, interferon beta-1a\*, interferon beta-1b\*, interferon gamma-1b\*, muromonab-CD3\*, mycophenolate\*, natalizumab\*, omalizumab\*, pimecrolimus\*, rituximab\*, temsirolimus\*, tocilizumab\*, ustekinumab\*
- anti-infective drugs
  - *antifungals* – caspofungin\*, miconazole\*, posaconazole\*
  - *antiparasitics* – albendazole\*, artemether/lumefantrine\*, atovaquone\*, atovaquone/proguanil\*
  - *antimicrobials* – amoxicillin\*, ciprofloxacin\* (+IIH), clarithromycin\*, dapson\*, doxycycline (IIH), ertapenem\*, levofloxacin\*, linezolid\*, minocycline\* (+IIH), mupirocin\*, nalidixic acid(IIH), piperacillin/tazobactam\*, rifaximin\*, telithromycin\*, tetracycline (+IIH), tobramycin\*, tigecycline\*
- *antivirals* – abacavir, abacavir/lamivudine/zidovudine\*, adefovir\*, atazanavir\*, delavirdine\*, efavirenz\*, efavirenz/emtricitabine/tenofovir\*, emtricitabine\*, emtricitabine/tenofovir\*, entecavir\*, fosamprenavir\*, indinavir\*, interferon alfa-2b\*, interferon alfa-n3\*, lamivudine\*, lamivudine/zidovudine\*, lopinavir/ritonavir\*, peginterferon alfa-2b\*, ribavirin\*, ritonavir\*, tenofovir\*, valacyclovir\*, zanamivir\*, zidovudine\*
- *vaccines* – Boostrix®, Cervarix®, Engerix-B®, Fluarix®, FluLaval®, FluMist®, Gardasil®, Havrix®, Twinrix®, Vaqta®\*
- cardiovascular drugs
  - *antiangina* – nitroglycerin\*, ranolazine\*
  - *antiarrhythmics* – amiodarone (IIH), propafenone\*
  - *antihypertensives* – amlodipine/valsartan/hydrochlorothiazide\*, carvedilol\*, clonidine\*, diltiazem\*, eprosartan/hydrochlorothiazide\*, indapamide\*, irbesartan/hydrochlorothiazide\*, isradipine\*, lisinopril\*, lisinopril/hydrochlorothiazide\*, nebivolol\*, ramipril\*, trandolapril/verapamil\*
  - *anti-PAH* – ambrisentan\*, prostacyclin\*
  - *antiplatelet* – prasugrel\*
  - *cardiac glycosides* – digoxin\*
  - *lipid-lowering agents* – ezetimibe/simvastatin\*, fenofibrate\*, lovastatin\*, niacin/lovastatin\*, rosvastatin\*, simvastatin\*, simvastatin/niacin\*
- nervous system drugs
  - *antiaddiction* – varenicline\*
  - *anti-attention deficit hyperactivity disorder (ADHD)* – dexmethylphenidate\*, guanfacine\*, methylphenidate\*
  - *anti-amytrophic lateral sclerosis (ALS)* – riluzole\*
  - *anti-Alzheimer's* – donepezil\*, memantine\*, rivastigmine\*
  - *antichorea* – tetrabenazine\*
  - *anticonvulsants* – lacosamide\*, lamotrigine\*, pregabalin\*, rufinamide\*, vigabatrin\*, zonisamide\*
  - *antidepressants* – bupropion\*, desvenlafaxine\*, duloxetine\*, escitalopram\*, fluoxetine\*, paroxetine\*, trazodone\*
  - *antidystonia/antispasm* – abobotulinumtoxinA\*, onabotulinumtoxinA\*

- *antimigraine* – frovatriptan\*
- *antinarcolepsy* – armodafinil\*, modafinil\*, oxybate\*
- *anti-Parkinson's* – rasagiline\*, ropinirole\*, selegiline\*
- *antipsychotics* – aripiprazole\*, asenapine\*, olanzapine\*, paliperidone\*, quetiapine\*, risperidone\*, ziprasidone\*
- *anxiolytics/hypnotics* – zaleplon\*, zolpidem\*
- *opioids* – buprenorphine\*, fentanyl\*, morphine\*, oxycodone\*, oxymorphone\*, tramadol\*
- endocrinological drugs
  - *anti-DM* – exenatide\*, insulin\*, liraglutide\*, pioglitazone\*, pioglitazone/glimepiride\*, pioglitazone/metformin\*, pramlintide\*, rosiglitazone\*, rosiglitazone/glimepiride\*, rosiglitazone/metformin\*, saxagliptin\*, sitagliptin/metformin\*
  - *bone metabolism* – denosumab\*, raloxifene\*, risedronate\*, teriparatide\*, zoledronate\*
  - *hypothalamic/pituitary* – octreotide\*, paricalcitol\*, recombinant somatropin\* (+IIH)
  - *sex hormones* – drospirenone/estradiol\*, Enjuvia®, estradiol\*, etonogestrel\*, Follistim® AQ®, Gonal-F®, levonorgestrel\*, levonorgestrel/ethynodiol estradiol\*, Premarin®, Premphase®, Prempro®, progesterone\*, testosterone\*
  - *uric acid reduction* – rasburicase\*
  - *weight reduction* – sibutramine\*
- gastrointestinal drugs
  - *antianorexics/anticachectics* – megestrol\*
  - *anticonstipation* – lubiprostone\*
  - *antiemetics* – aprepitant\*, dolasetron\*, ondansetron\*, palonosetron\*
  - *H2 blockers* – cimetidine (+IIH), esomeprazole\*, famotidine\*, nizatidine\*, ranitidine
  - *motility stimulants* – metoclopramide\*
  - *pancreatic replacements* – Creon®, Zenpep®\*
  - *proton pump inhibitors* – rabeprazole\*
  - *saliva reduction* – glycopyrrolate\*
  - *saliva stimulants* – pilocarpine\*
- genitourological drugs
  - *anti-benign prostatic hyperplasia (BPH)* – alfuzosin\*
  - *anti-erectile dysfunction (ED)* – sildenafil\*, tadalafil\*, vardenafil\*
  - *anti-overactive bladder* – darifenacin\*, tolterodine\*
- hematological drugs
  - *antianemia* – cyanocobalamin\*
  - *anti-heparin-induced thrombocytopenia* – argatroban\*
  - *anti-ITP* – romiplostim\*
  - *coagulation factors* – Advate\*, BeneFIX®, XynthaTM\*
  - *ESAs* – darbepoetin alfa\*, epoetin alfa\*
  - *granulocyte stimulators* – filgrastim\*
- respiratory drugs
  - *anti-allergic rhinitis* – beclomethasone\*, fluticasone\*
  - *asthma* – albuterol\*, budenoside\*, fluticasone/salmeterol\*, mometasone\*, mometasone/formoterol\*, montelukast\*, salmeterol\*, triamcinolone\*
  - *anti-congenital alpha<sub>1</sub>-proteinase inhibitor deficiency* – Aralast NP\*
  - *anti-chronic obstructive pulmonary disease (COPD)* – tiotropium\*
- ocular drugs
  - *anti-glaucoma* – bimatoprost\*, brimonidine\*, brinzolamide\*.

## PRURITUS

Pruritus (itch) is an unpleasant, specific sensation limited to the skin that leads to a desire to scratch the offending site. It can be caused by problems all along the sensory pathways. Drugs causing pruritus recently have been reviewed by Reich *et al.* (2009).

- Antineoplastic drugs
  - *antimetabolites* – cladribine\*, decitabine\*, gemcitabine\*, pemetrexed\*
  - *DNA agents* – bendamustine\*, doxorubicin\*, oxaliplatin\*, temozolomide\*
  - *inducers of differentiation* – acitretin\*, alitretinoin\*, arsenic trioxide\*, bexarotene\*, vorinostat\*
  - *microtubule inhibitors* – docetaxel\*
  - *targeted* – bortezomib\*, brentuximab vedotin\*, cetuximab\*, dasatinib\*, denileukin diftitox\*, erlotinib\*, exemestane\*, gefitinib\*,

- ibritumomab\*, imatinib\*, lapatinib\*, nilotinib\*, panitumumab\*, sorafenib\*, sunitinib\*, temsirolimus\*, tosimumab\*
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *immunoglobulins* – Gamunex®\*
  - *NSAIDs* – mesalamine\*, sulindac\*
  - *steroids* – betamethasone\*, mometasone\*
  - *targeted* – basiliximab\*, etanercept\*, everolimus\*, fingolimod\*, glatiramer\*, infliximab\*, mycophenolic acid\*, natalizumab\*, rituximab\*
- anti-infective drugs
  - *antifungals* – caspofungin\*, posaconazole\*
  - *antimicrobials* – azelaic acid\*, minocycline\*, piperacillin/tazobactam\*, rifaximin\*
  - *antiparasitics* – artemether/lumefantrine\*, atovaquone\*, atovaquone/proguanil\*, ivermectin\*
  - *antivirals* – delavirdine\*, efavirenz\*, emtricitabine/tenofovir\*, indinavir\*, interferon alfa-2b\*, maraviroc\*, peginterferon alfa-2b\*, ribavirin\*
- cardiovascular drugs
  - *antiarrhythmics* – dronedarone\*
  - *antihypertensives* – indapamide\*
  - *anti-PAH* – prostacyclin\*
  - *lipid-lowering agents* – niacin\*, simvastatin/niacin\*
- nervous system drugs
  - *anesthetics* – fospropofol\*
  - *anti-ADHD* – dexmethylphenidate\*
  - *anti-ALS* – riluzole\*
  - *anticonvulsants* – lamotrigine\*, rufinamide\*, valproate\*
  - *antidystonic/antispasm* – onabotulinumtoxinA\*
  - *antidepressants* – bupropion\*, duloxetine\*, fluoxetine\*
  - *antipsychotics* – risperidone\*
  - *opioids* – buprenorphine\*, fentanyl\*, morphine\*, oxycodone\*, oxymorphone\*, tapentadol\*, tramadol\*
- endocrinological drugs
  - *hypothalamic/pituitary* – octreotide\*
  - *sex hormones* – estradiol\*, etonogestrel\*, levonorgestrel\*, Premarin®, Premphase®, Prempro®\*
- gastrointestinal drugs
  - *antianorexics/anticachetics* – megestrol\*
  - *antiemetics* – aprepitant\*, dolasetron\*, ondansetron\*
  - *liver protectants* – acetylcysteine\*
- hematological drugs
  - *antianemia* – sodium ferric gluconate complex\*
  - *coagulation factors* – Alphanate®\*
  - *ESAs* – darbepoetin alfa\*, epoetin alfa\*
- respiratory drugs
  - *antiasthma* – fluticasone\*.

## SMELL (CRANIAL NERVE I)

The nasal olfactory mucosa comprises olfactory (receptor) cells, sustentacular (supporting) cells, and basal cells (stem cells that replenish the other populations; receptor cells turn over approximately every month). The olfactory cell axons pass through the cribiform plate into the olfactory bulb to synapse on granule and mitral cells. Their axons form the olfactory tract and travel directly to the primary olfactory cortex, as well as to the amygdaloid nucleus and septal area. Olfaction plugs directly into the emotional brain, and its importance is reflected in the approximately 1000 human genes (~3% of the genome) that are dedicated to olfactory receptors (Young and Trask, 2002). Many opportunities exist for adverse events (e.g., Doty and Bromley, 2004). Olfaction may be increased (hyperosmia), decreased (hyposmia), absent (anosmia), or aberrant (parosmia/dysosmia). Resolution of symptoms upon drug discontinuation may be slow and incomplete.

- Antineoplastic drugs
  - *microtubule inhibitors* – docetaxel\*
- immunosuppressants/immunomodulators/anti-inflammatory drugs
  - *NSAIDs* – celecoxib
  - *steroids* – beclomethasone, fluticasone
- anti-infective drugs
  - *antimicrobials* – aminoglycosides, ciprofloxacin, clarithromycin, levofloxacin, moxifloxacin, tetracyclines
  - *antivirals* – delavirdine, interferon alfa-2b\*, ritonavir

- cardiovascular drugs
  - *antiarrhythmics* – amiodarone, tocainide
  - *antihypertensives* – aliskiren/amlodipine, amlodipine/valsartan, doxazosin, enalapril, verapamil
  - *combined* – amlodipine/atorvastatin
  - *lipid-lowering agents* – atorvastatin
- nervous system drugs
  - *antiaddiction* – varenicline
  - *anticonvulsants* – lamotrigine, pregabalin, tiagabine, zonisamide
  - *antidepressants* – mirtazapine, paroxetine
  - *antimigraine* – zolmitriptan
  - *anti-Parkinson's* – rasagiline
  - *anxiolytics/hypnotics* – zaleplon, zolpidem
- gastrointestinal drugs
  - *proton pump inhibitors* – esomeprazole
- homeopathic drugs
  - intranasal zinc gluconate (Davidson and Smith, 2010) (anosmia may be permanent).

## HEARING (CRANIAL NERVE VIII)

Sounds vibrate the basilar membrane of the organ of Corti in the inner ear as a function of their frequency, bending the stereocilia of the neuroepithelial cells resting on the membrane and generating afferent signals in the cochlear neurons, which then pass through the auditory nerve to relay stations in the pontomedullary region. Some of that output travels to the primary auditory cortex and then to secondary and tertiary cortices for processing and interpretation. The sense of hearing can be dulled or heightened; another common adverse effect is tinnitus aurium or “ringing of the ears.” These NAEs have been reviewed recently and comprehensively by Cianfrone *et al.* (2011). Hearing loss associated with aminoglycoside antibiotics and antineoplastic agents in particular may be permanent.

- Antineoplastic drugs
  - *antimetabolites* – gemcitabine\*
  - *DNA agents* – cisplatin, oxaliplatin
  - *inducers of differentiation* – acitretin\*, arsenic trioxide\*
  - *microtubule inhibitors* – docetaxel\*

- *targeted* – dasatinib\*, imatinib, leuprorelin\*, sorafenib
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – chlorpheniramine
  - *NSAIDs* – aspirin, celecoxib, etoricoxib, ibuprofen/dexibuprofen, meloxicam, naproxen, sulindac\*
- anti-infective drugs
  - *antimicrobial* – aminoglycosides, capreomycin\*, fluoroquinolones, linezolid, macrolides, sulfonamides, tetracyclines
  - *antiparasitics* – antimarials
  - *antivirals* – interferon alfa-2b\*, ribavirin
- cardiovascular drugs
  - *antiarrhythmics* – flecainide
  - *antihypertensives* – benazepril, enalapril, furosemide, valsartan/hydrochlorothiazide
  - *lipid-lowering agents* – atorvastatin
- nervous system drugs
  - *anticonvulsants* – valproate\*
  - *antidepressants* – bupropion\*, citalopram, clomipramine, desipramine, dosulepin, trazodone\*, trimipramine, venlafaxine
  - *antimigraine* – almotriptan, eletriptan, frovatriptan
  - *antinarcolepsy* – sodium oxybate\*
  - *anxiolytics/hypnotics* – zaleplon
- gastrointestinal drugs
  - *antiemetics* – aprepitant\*, palonosetron
- hematological drugs
  - *chelators* – desferrioxamine
- ocular drugs
  - *antiangiogenic* – pegaptanib.

## TASTE (CRANIAL NERVES V, VII, IX, X)

Primary taste sensations comprise sweet, sour, salty, bitter, and umami. Receptor cells are preferentially sensitive to one of these and reside in the taste buds, most of which are on the tongue. Like olfactory receptor cells, they are continuously replaced, with a cycle of about 10 days. Gustatory fibers terminate in a variety of brainstem nuclei and have polysynaptic pathways to the thalamus and cortex.

Taste can be abnormally acute (hypergeusia), diminished (hypogeusia), absent (ageusia), or

aberrant (dysgeusia). Drugs causing alterations in taste have been reviewed by Ackerman and Kasbekar (1997) and Doty *et al.* (2008).

- Antineoplastic drugs
  - *antimetabolites* – 5-fluorouracil, methotrexate, nelarabine\*, pemetrexed\*
  - *DNA agents* – bendamustine\*, cisplatin, doxorubicin\*, oxaliplatin\*, temozolomide\*, valrubicin
  - *inducers of differentiation* – acitretin\*, isotretinoin
  - *microtubule inhibitors* – cabazitaxel\*, docetaxel\*, eribulin\*
  - *targeted* – bevacizumab\*, bortezomib, dasatinib\*, denileukin diftitox\*, imatinib\*, leuprorelin\*, nilotinib, pazopanib\*, sunitinib\*, temsirolimus\*, trastuzumab\*, vorinostat\*
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – olopatadine\*
  - *NSAIDs* – celecoxib, diclofenac, mesalamine, sulindac
  - *steroids* – fluticasone, triamcinolone
  - *targeted* – cyclosporine, everolimus\*, glatiramer
- anti-infective drugs
  - *antifungals* – griseofulvin, miconazole\*, posaconazole, terbinafine
  - *antimicrobials* – amoxicillin\*, ampicillin, ciprofloxacin, clarithromycin\*, ertapenem, ethambutol, imipenem/cilastatin, levofloxacin, linezolid, metronidazole, moxifloxacin, norfloxacin, penicillin G, rifaximin, telithromycin, tetracycline, ticarcillin/clavulanate, tigecycline, tobramycin\*, sulfamethoxazole
  - *antiparasitics* – atovaquone\*, pentamidine, tinidazole
  - *antivirals* – acyclovir, amantadine, delavirdine, indinavir\*, interferon alfa-2b\*, interferon alfa-n3, oseltamivir, peginterferon alfa-2b, ribavirin\*, ritonavir\*, zidovudine
  - *vaccines* – Havrix®, Twinrix®
- cardiovascular drugs
  - *antiarrhythmics* – amiodarone, bretylium, flecainide, mexiletine, propafenone\*
- antihypertensives – amlodipine, captopril, clonidine, diltiazem, enalapril, labetalol, lisinopril, losartan, metoprolol, nifedipine, nisoldipine, propranolol, ramipril
- *antiplatelet agents* – clopidogrel
- *lipid-lowering agents* – atorvastatin, gemfibrozil, lovastatin, pravastatin, simvastatin
- nervous system drugs
  - *antiaddiction* – varenicline\*
  - *anti-ALS* – riluzole
  - *anticonvulsants* – lamotrigine, pregabalin, tiagabine, valproate, zonisamide
  - *antidepressants* – bupropion\*, desvenlafaxine, duloxetine\*, lithium, mirtazapine, paroxetine, trazodone\*
  - *antimigraine* – frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan\*
  - *anti-Parkinson's* – entacapone, rasagiline, rivastigmine, ropinirole, selegiline
  - *antipsychotics* – asenapine\*, quetiapine
  - *anxiolytics/hypnotics* – zaleplon
  - *opioids* – buprenorphine, fentanyl, hydromorphone, morphine\*
- endocrinological drugs
  - *bone metabolism* – alendronate, zoledronate
  - *thyroid* – methimazole, propylthiouracil, thiamazole
- gastrointestinal drugs
  - *antiemetics* – aprepitant, dolasetron
  - *H2 blockers* – famotidine
  - *proton pump inhibitors* – dexlansoprazole, esomeprazole\*
- hematological drugs
  - *coagulation factors* – Advate, BeneFIX®, Hemofil M (also human albumins Buminate, Flexbumin)
- respiratory drugs
  - *asthma* – albuterol\*, budesonide\*, salbutamol
- homeopathic drugs
  - zinc gluconate lozenges.

## ADVERSE EVENTS INVOLVING STRENGTH

The main volitional motor pathway begins with pyramidal neurons in the primary motor cortex

(upper motor neurons, UMN). Their axons extend through the ipsilateral internal capsule and cerebral peduncle; most cross to the contralateral side in the pontomedullary region and travel in the lateral corticospinal tract until they reach the appropriate spinal level, terminating on anterior horn cells (lower motor neurons, LMN) that send their axons out the anterior spinal roots and then via peripheral nerves to form neuromuscular junctions (NMJs) on skeletal muscle fibers. A motor unit comprises the LMN and all the muscle fibers it innervates (which can number from fewer than 10 to more than 1000). Problems anywhere along this pathway (UMNs, LMNs, peripheral nerve, or their connections) can result in weakness or paralysis.

Two motor syndromes often thought of in the context of vaccine-associated NAEs are Bell's palsy (BP) (acute facial palsy; Rath *et al.*, 2007) and Guillain–Barré syndrome (GBS; Sejvar *et al.*, 2011). GBS is an acute demyelinating inflammatory polyneuropathy that presents with ascending (distal to proximal leg, distal to proximal arm, occasionally progressing to total body) flaccid paralysis. It may begin with slight numbness in the toes and fingers, and most patients complain of muscular aching as well. Very fortunately, both tend to resolve with time and/or treatment. In GBS the recovery may be remarkable. The author had a patient who over the course of approximately 2 weeks became paraplegic, then quadriplegic, then locked in (only able to communicate by blinking his eyes, his sole volitional movement) and requiring a respirator to breathe; a year later his only residual problem was a mild foot drop on one side.

- Antineoplastic drugs

- *antimetabolites* – cladribine\*, decitabine\*, fludarabine\*, nelarabine\*
- *DNA agents* – bendamustine\*, doxorubicin\*, mitoxantrone\*, oxaliplatin\*, temozolomide\*, temsirolimus\*, topotecan\*, valrubicin\*
- *inducers of differentiation* – arsenic trioxide\*, bexarotene\*, vorinostat (GBS)
- *microtubule inhibitors* – cabazitaxel\*, docetaxel\*, eribulin\*, vincristine
- *targeted* – adalimumab, alemtuzumab (GBS), bevacizumab\*, bortezomib\*, brentuximab

vedotin\*, cetuximab\*, dasatinib\*, denileukin diftitox\*, exemestane\*, fulvestrant\*, gefitinib\*, imatinib\*, lapatinib\*, letrozole\*, leuprorelin\*, nilotinib\*, pazopanib\*, sunitinib\*, tositumomab\*, trastuzumab\*

- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – olopatadine\*
  - gold salts (GBS)
  - *immunoglobulins* – Gamunex®\*
  - *NSAIDs* – indomethacin, mesalamine\* (+GBS), penicillamine
  - *targeted* – adalimumab (GBS), basiliximab\*, certolizumab pegol (GBS), etanercept (GBS), everolimus\*, fingolimod\*, glatiramer\*, infliximab (GBS), interferon beta-1b\*, rituximab\*
- anti-infective drugs
  - *antifungals* – amphotericin, caspofungin\*, posaconazole\*
  - *antimicrobials* – aminoglycosides, dapsone, indomethacin, polymyxins, nitrofurantoin, norfloxacin (GBS), sulfonamides, tigecycline\*
  - *antiparasitics* – artemether/lumefantrine\*, atovaquone\*, atovaquone/proguanil\*
  - *antivirals* – adefovir\*, delavirdine\*, emtricitabine\*, indinavir\*, interferon alfa-2b\* (also pegylated\*), ribavirin\*, ritonavir\*, tenofovir\*, zidovudine\*
  - *vaccines* (all GBS) – Boostrix®, Comvax®, Enerix-B®, Fluarix®, FluLaval®, FluMist® (also asthenia\*), Gardasil®, Havrix®, Infanrix®, Kinrix®, M-M-R® II, Pediarix®, Pedvax-HIB®, Pneumovax® 23, ProQuad®, Recombivax HB®, Twinrix®, Vaqta® (also asthenia\*), Varivax®
- cardiovascular drugs
  - *antiarrhythmics* – dronedarone\*, propafenone\*
  - *antihypertensives* – captoril (GBS), carvedilol\*, clonidine\*, indapamide\*, losartan\*, propranolol, trandolapril\*
  - *anti-PAH* – prostacyclin\*
  - *lipid-lowering agents* – lovastatin
- nervous system drugs
  - *antiaddiction* – varenicline\*
  - *anti-ALS* – riluzole\*

- *anti-Alzheimer's* – rivastigmine\*
- *anticonvulsants* – lamotrigine\*, phenytoin, pregabalin\* (GBS), tiagabine\*, valproate\*, vigabatrin\*
- *antidepressants* – amitriptyline (+GBS), bupropion\*, duloxetine\*, fluoxetine\*, imipramine (+GBS), mirtazapine\*, paroxetine\* (+GBS)
- *antidystonia/antispasm* – onabotulinumtoxinA\*
- *antimigraine* – rizatriptan\*, sumatriptan
- *anti-Parkinson's* – ropinirole\*
- *antipsychotics* – paliperidone\*, quetiapine\*, ziprasidone\*
- *anxiolytics/hypnotics* – zaleplon\*
- *opioids* – buprenorphine\*, fentanyl\*, morphine\*, oxycodone\*, tramadol\*
- endocrinological drugs
  - *anti-DM* – exenatide\*, sitagliptin/metformin\*
  - *bone metabolism* – denosumab\*, risedronate\*, teriparatide\*, zoledronate\*
  - *hypothalamic/pituitary* – octreotide\*, tolvaptan\*
  - *parathyroid* – cinacalcet\*, paricalcitol\*
  - *sex hormones* – etonogestrel\*, Premarin®, Premphase®, Prempro®\*
  - *uric acid reduction* – febuxostat (GBS)
  - *weight reduction* – sibutramine\* (withdrawn)
- gastrointestinal drugs
  - *antianorexics/anticachectics* – megestrol\*
  - *antiemetics* – aprepitant\*
  - *H2 blockers* – cimetidine, nizatidine\*
  - *saliva stimulants* – pilocarpine\*
- genitourological drugs
  - *anti-BPH* – finasteride\*
- hematological drugs
  - *antianemia* – cyanocobalamin\*
  - *bone marrow stimulants* – filgrastim\*
  - *coagulation factors* – Alphanate®, Xyntha™\*
  - *ESAs* – darbepoetin alfa\*, epoetin alfa\*
- respiratory drugs
  - *antiasthma* – budesonide\*
- ocular drugs
  - *antiglaucoma* – bimatoprost\*, brimonidine\*
- supplements
  - carnitine.

## ADVERSE EVENTS INVOLVING COORDINATED MOVEMENT

### BALANCE AND GAIT

Gait is a complex phenomenon that integrates multiple motor and sensory systems, adding nested networks involving the cerebellum and basal ganglia to the “simple” primary motor and sensory systems previously described. Many things can go wrong (Wick and Zanni, 2010), not the least of which can be iatrogenic mischief. Drug-related gait difficulties are common in the elderly, and if an offending medication can be identified and discontinued, ambulation and quality of life can be improved.

- Antineoplastic drugs
  - *antimetabolites* – gemcitabine, nelarabine\*
  - *DNA agents* – carboplatin, cisplatin, oxaliplatin, temozolomide\*
  - *inducers of differentiation* – acitretin
  - *microtubule inhibitors* – vinblastine, vincristine
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *NSAIDs* – aspirin, indomethacin, ketoprofen, naproxen, piroxicam, sulindac
  - *targeted* – interferon gamma-1b
- anti-infective drugs
  - *antimicrobials* – amikacin, azithromycin, capreomycin, ciprofloxacin, dibekacin, erythromycin, gentamicin, levofloxacin, moxifloxacin, neomycin, streptomycin, tobramycin, vancomycin
  - *antiparasitics* – artemether/lumefantrine, chloroquine, quinine
  - *antivirals* – cidofovir, didanosine, efavirenz, efavirenz/emtricitabine/tenofovir, interferon alfa-2b\*, lamivudine, lopinavir/ritonavir, ritonavir, stavudine, zalcitabine, zidovudine
  - *vaccines* – FluLaval®
- cardiovascular drugs
  - *antiarrhythmics* – propafenone
  - *antihypertensives* – bumetanide, diltiazem, ethacrynic acid, furosemide, nicardipine, nifedipine, nimodipine, nitrendipine, trandolapril/verapamil, verapamil

- nervous system drugs
  - *antiaddiction* – varenicline
  - *anti-ALS* – riluzole
  - *anti-Alzheimer's* – donepezil, memantine, rivastigmine
  - *antichorea* – tetrabenazine\*
  - *anticonvulsants* – lacosamide\*, lamotrigine\*, levetiracetam, phenytoin, pregabalin\*, rufinamide\*, tiagabine\*, valproate\*, vigabatrin\*, zonisamide
  - *antidepressants* – duloxetine, escitalopram, olanzapine/fluoxetine, paroxetine, trazodone\*
  - *antimigraine* – frovatriptan, rizatriptan
  - *antinarcolepsy* – oxybate
  - *anti-Parkinson's* – carbidopa/levodopa/entacapone, rasagiline, ropinirole, selegiline
  - *antipsychotics* – asenapine, haloperidol, loxapine, olanzapine\*, paliperidone, quetiapine, risperidone\*, thiothixene, ziprasidone
  - *anxiolytics/hypnotics* – midazolam, zaleplon, zolpidem
  - *opioids* – buprenorphine, fentanyl, morphine\*, oxycodone, tramadol
- endocrinological drugs
  - *sex hormones* – progesterone
  - *uric acid reduction* – febuxostat
  - *weight reduction* – sibutramine
- hematological drugs
  - *antianemia* – cyanocobalamin\*.

## SWALLOWING

Swallowing moves food material and saliva from the mouth to the stomach (at a baseline frequency of about once per minute). The medulla coordinates the oro- and nasopharyngeal muscles, the laryngeal complex, and the esophagus in a complex dance that allows a bolus of material not only to pass to and through the lower esophageal sphincter, but equally critically to stay out of the trachea. Difficulty swallowing (dysphagia) has been associated with multiple medications.

- Antineoplastic drugs
  - *microtubule inhibitors* – docetaxel\*
  - *inducers of differentiation* – arsenic trioxide

- *targeted* – bortezomib, dasatinib, imatinib, leuprorelin\*, trastuzumab\*
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *targeted* – cyclosporine, everolimus\*, glatiramer, infliximab\*, muromonab-CD3
- anti-infective drugs
  - *antimicrobials* – ciprofloxacin, ertapenem, minocycline, moxifloxacin, norfloxacin, piperacillin/tazobactam, rifaximin
  - *antiparasitics* – artemether/lumefantrine
  - *antivirals* – delavirdine, interferon alfa-2b\*, ritonavir, zidovudine
  - *vaccines* – FluLaval®
- cardiovascular drugs
  - *antiarrhythmics* – propafenone
  - *antibradycardics* – atropine
  - *antihypertensives* – aliskiren/amlodipine, amlodipine/valsartan, captopril, ramipril
  - *combination* – amlodipine/atorvastatin
- nervous system drugs
  - *antiaddiction* – varenicline
  - *anti-ALS* – riluzole
  - *anti-Alzheimer's* – donepezil, memantine, rivastigmine
  - *antichorea* – tetrabenazine
  - *anticonvulsants* – lamotrigine, pregabalin, tiagabine, valproate, zonisamide
  - *antidepressants* – bupropion, escitalopram, fluoxetine, paroxetine
  - *antidystonia/antispasm* – abobotulinumtoxin A\*, onabotulinumtoxin A\*
  - *antimigraine* – frovatriptan, rizatriptan, sumatriptan, zolmitriptan
  - *antinarcolepsy* – armodafinil, modafinil, oxybate
  - *anti-Parkinson's* – carbidopa/levodopa/entacapone, rasagiline, ropinirole, selegiline
  - *antipsychotics* – aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine\*, risperidone, thioridazine, thiothixene, ziprasidone
  - *anxiolytics/hypnotics* – zaleplon, zolpidem
  - *opioids* – buprenorphine, fentanyl, morphine\*, oxycodone, tramadol
- endocrinological drugs
  - *anti-DM* – liraglutide

- *hypothalamic/pituitary* – tolvaptan
- *sex hormones* – progesterone
- gastrointestinal drugs
  - *antiemetics* – aprepitant
  - *proton pump inhibitors* – dexlansoprazole, esomeprazole
  - *saliva stimulants* – pilocarpine
- genitourological drugs
  - *anti-ED* – sildenafil, tadalafil, vardenafil.

## ADVERSE EVENTS INVOLVING INVOLUNTARY MOVEMENT AND MUSCLE TONE

### MYOCLONUS, SPASMS, AND TICS

Myoclonus refers to sudden, short-lasting, involuntary muscle contractions that can be single or in bursts. This is a somewhat more specific term than “spasm,” and drug-related causes have been reviewed (e.g., Brefel-Courbon *et al.*, 2006). Tics are apparently random and involuntary, sudden, repetitive/stereotyped movements or vocalizations. Drug-related hyperkinetic movement disorders have been reviewed recently by Zesiewicz and Sullivan (2011).

- antineoplastic drugs
  - *DNA agents* – chlorambucil, oxaliplatin
  - *targeted* – trastuzumab\*
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *NSAIDs* – ketoprofen
  - *targeted* – brentuximab vedotin\*, glatiramer, muromonab-CD3, ofatumumab\*, rituximab\*
- anti-infective drugs
  - *antimicrobials* – acyclovir, carbenicillin, ceftazidime, ciprofloxacin, dapsone, ertapenem, imipenem/cilastatin, isoniazid, norfloxacin, penicillin, tetracycline
  - *vaccines* – Cervarix®, Gardasil®
- cardiovascular drugs
  - *antiarrhythmics* – amiodarone, propafenone
  - *antihypertensives* – diltiazem, furosemide, lisinopril, nifedipine

- nervous system drugs
  - *anesthetics* – enflurane, isoflurane
  - *anti-ADHD* – dexmethylphenidate, lisdexamfetamine, methylphenidate\*
  - *anti-ALS* – riluzole
  - *anti-Alzheimer's* – memantine, rivastigmine
  - *anticonvulsants* – carbamazepine, clonazepam, gabapentin, lamotrigine, phenobarbital, phenytoin, pregabalin, tiagabine, valproate, vigabatrin, zonisamide
  - *antidepressants* – bupropion, duloxetine, escitalopram, fluoxetine, imipramine, lithium, mirtazapine, paroxetine\*, sertraline, tranylcypromine
  - *antimigraine* – naratriptan, sumatriptan
  - *antinarcolepsy* – oxybate
  - *anti-Parkinson's* – amantadine, entacapone, levodopa, rasagiline, selegiline
  - *antipsychotics* – aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, ziprasidone
  - *anxiolytics/hypnotics* – buspirone, lorazepam, midazolam, propofol, zaleplon, zolpidem
  - *opioids* – buprenorphine, fentanyl, hydromorphone, meperidine, morphine, tramadol
- endocrinological drugs
  - *bone metabolism* – teriparatide
  - *sex hormones* – prednisolone
- gastrointestinal drugs
  - *motility stimulants* – domperidone, metoclopramide
  - *proton pump inhibitors* – omeprazole.

### AKATHISIA/RESTLESS LEGS SYNDROME

Akathisia is involuntary, continuous motor restlessness. Restless legs syndrome may be a variant. Akathisia is commonly seen in the setting of selective serotonin reuptake inhibitors (Koliscak and Makela, 2009).

- antineoplastic drugs
  - *targeted* – imatinib
- anti-infective drugs
  - *antimicrobials* – clindamycin
- cardiovascular drugs
  - *antihypertensives* – reserpine
- nervous system drugs
  - *antiaddiction* – varenicline

- *anti-ADHD* – atomoxetine
- *anti-Alzheimer's* – rivastigmine
- *antichorea* – tetrabenazine\*
- *anticonvulsants* – carbamazepine, lamotrigine, topiramate, zonisamide
- *antidepressants* – amoxapine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, imipramine, lithium, mirtazapine, nortriptyline, paroxetine, sertraline, tranylcypromine, trazodone, venlafaxine
- *antimigraine* – sumatriptan, zolmitriptan
- *antinarcolepsy* – oxybate
- *anti-Parkinson's* – levodopa, ropinirole
- *antipsychotics* – aripiprazole\*, asenapine\*, haloperidol, iloperidone, lurasidone\*, olanzapine\*, paliperidone\*, perphenazine, quetiapine\*, risperidone\*, thioridazine, thiophexene, ziprasidone\*
- *anxiolytics/hypnotics* – buspirone
- *opioids* – tramadol
- endocrinological drugs
  - *thyroid* – levothyroxine
- gastrointestinal drugs
  - *antiemetics* – droperidol, prochlorperazine
  - *H2 blockers* – cimetidine
  - *motility stimulants* – metoclopramide
  - *proton pump inhibitors* – dexlansoprazole.
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *targeted* – cetuximab, dasatinib, histrelin, imatinib, leuprolide, nilotinib, tamoxifen
- anti-infective drugs
  - *antifungals* – caspofungin\*, posaconazole
  - *antimicrobials* – ciprofloxacin, clarithromycin, cycloserine, ertapenem, imipenem/cilastatin, levofloxacin, moxifloxacin, norfloxacin, penicillin, piperacillin/tazobactam, quinupristin/dalfopristin, rifaximin\*
  - *antiparasitics* – artemether/lumefantrine, ivermectin
  - *antivirals* – acyclovir, delavirdine, efavirenz, efavirenz/emtricitabine/tenofovir, interferon alfa-2b\*, interferon alfa-n3, lopinavir/ritonavir, maraviroc, ritonavir, valacyclovir, vidarabine, zidovudine
  - *vaccines* – FluLaval®, ProQuad®
- cardiovascular drugs
  - *angina* – ranolazine
  - *antiarrhythmics* – amiodarone, mexiletine, procainamide, propafenone
  - *antihypertensives* – aliskiren/amlodipine, amlodipine/valsartan, diltiazem, eprosartan, hydrochlorothiazide/triamterene, irbesartan/hydrochlorothiazide, lisinopril, losartan, nifedipine, pindolol, ramipril, reserpine, trandolapril/verapamil
  - *PAH* – prostacyclin\*
  - *combination* – amlodipine/atorvastatin
  - *lipid-lowering agents* – lovastatin, niacin
- nervous system drugs
  - *anesthetics* – lidocaine
  - *antiaddiction* – varenicline
  - *ADHD* – atomoxetine\*, clonidine\*, dextroamphetamine, lisdexamfetamine, methylphenidate

## TREMOR

Tremor is an involuntary, oscillatory, usually rhythmic muscle movement involving one or more parts of the body. It can be present at rest (as in Parkinson's disease) or brought on by movement (action tremor; Arbaizar *et al.*, 2008). Pathophysiological mechanisms involve the thalamus, the cerebellum, midbrain and brainstem nuclei, and their interconnections (often described in the aggregate as the “extrapyramidal system,” which is also the substrate for the movement disorders described subsequently).

- Antineoplastic drugs
  - *antimetabolites* – cytarabine
  - *DNA agents* – chlorambucil, ifosfamide, nelarabine\*
  - *inducers of differentiation* – arsenic trioxide\*

- *anti-ALS* – riluzole
  - *anti-Alzheimer's* – donepezil, memantine, rivastigmine\*
  - *antichorea* – tetrabenazine
  - *anticonvulsants* – lacosamide\*, lamotrigine\*, phenytoin, pregabalin\*, rufinamide\*, tiagabine\*, valproate\*, vigabatrin\*, zonisamide
  - *antidepressants* – amitriptyline, bupropion\*, citalopram, desvenlafaxine\*, duloxetine\*, escitalopram, fluoxetine\*, lithium, mirtazapine, olanzapine/fluoxetine\*, paroxetine\*, tranylcypromine, trazodone\*
  - *antidystonia/antispasm* – cyclobenzaprine
  - *antimigraine* – flunarizine, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
  - *antinarcolepsy* – armodafinil, modafinil, oxybate
  - *anti-Parkinson's* – carbidopa/levodopa/entacapone, levodopa, rasagiline, ropinirole\*, selegiline
  - *antipsychotics* – aripiprazole\*, asenapine, haloperidol, iloperidone\*, lurasidone, paliperidone\*, quetiapine\*, risperidone\*, thioridazine, ziprasidone
  - *anxiolytics/hypnotics* – zaleplon, zolpidem
  - *opioids* – buprenorphine, fentanyl, hydromorphone, morphine\*, oxycodone, tapentadol, tramadol\*
  - endocrinological drugs
    - *anti-DM* – pramlintide
    - *bone metabolism* – calcitonin, zoledronate
    - *hypothalamic/pituitary* – octreotide
    - *sex hormones* – medroxyprogesterone
    - *thyroid* – levothyroxine
    - *uric acid reduction* – febuxostat
    - *weight reduction* – phentermine, sibutramine
  - gastrointestinal drugs
    - *anticonstipation* – lubiprostone
    - *antiemetics* – aprepitant, dolasetron, droperidol
    - *H2 blockers* – cimetidine
    - *motility stimulants* – metoclopramide
    - *proton pump inhibitors* – dexlansoprazole, esomeprazole
    - *saliva stimulants* – pilocarpine
  - genitourological drugs
    - *anti-ED* – sildenafil
  - hematological drugs
    - *coagulation factors* – BeneFIX®, Recombinate
  - respiratory drugs
    - *antiasthma* – albuterol\*, arformoterol, budesonide, fluticasone/salmeterol, formoterol, mometasone/formoterol, montelukast, theophylline, salbutamol, salmeterol.
- ## CHOREA/CHOREOATHETOSIS
- Chorea refers to involuntary, arrhythmic, continuous, rapid movements, often complex, usually of the face or limbs. Subjects often incorporate these into exaggerated “voluntary” movements.
- Antineoplastic drugs
    - *antimetabolites* – 5-fluorouracil
  - immunosuppressant/immunomodulatory/anti-inflammatory drugs
    - *antihistamines* – cyproheptadine, diphenhydramine
    - *NSAIDs* – mefenamic acid
  - cardiovascular drugs
    - *antihypertensives* – nifedipine, verapamil
    - *cardiac glycosides* – digoxin
  - nervous system drugs
    - *anti-ADHD* – amphetamine, methylphenidate
    - *anticonvulsants* – carbamazepine, ethosuximide, gabapentin, lamotrigine, phenytoin, phenobarbital, primidone, tiagabine, valproate, zonisamide
    - *antidepressants* – amoxapine, doxepin, escitalopram, fluoxetine, lithium, paroxetine
    - *anti-Parkinson's* – carbidopa/levodopa/entacapone, levodopa, ropinirole, selegiline, trihexyphenidyl
    - *antipsychotics* – olanzapine, paliperidone, quetiapine, thioridazine, ziprasidone
    - *anxiolytics/hypnotics* – diazepam
    - *opioids* – methadone
  - endocrinological drugs
    - *sex hormones* – Enjuvia®, estradiol, Menest®
  - gastrointestinal drugs
    - *antiemetics* – cyclizine
    - *H2 blockers* – cimetidine, ranitidine
    - *motility stimulants* – metoclopramide.

## TARDIVE DYSKINESIA

When chorea develops as a consequence of chronic medication administration it is known as tardive (delayed) dyskinesia (Paulson, 2005). Tardive dyskinesia is most commonly seen in the setting of first-generation antipsychotic use in psychiatry and following long-term dopamine use in Parkinson's disease. It may take months or years to resolve after drug discontinuation.

- Nervous system drugs
  - *anti-Alzheimer's* – memantine
  - *antichorea* – tetrabenazine
  - *anticonvulsants* – carbamazepine, valproate
  - *antimigraine* – zolmitriptan
  - *anti-Parkinson's* – levodopa, selegiline
  - *antidepressants* – escitalopram, fluoxetine, lithium, olanzapine/fluoxetine, paroxetine, trazodone
  - *antipsychotics* – aripiprazole, asenapine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine\*, risperidone\*, thioridazine, thiothixene, ziprasidone
  - *anxiolytics/hypnotics* – buspirone, lorazepam
  - *opioids* – fentanyl
- gastrointestinal drugs
  - *motility stimulants* – metoclopramide.

## DYSTONIA/ATHETOSIS

In this NAE there is slow, writhing movement of primarily the axial musculature, resulting in unnatural postures; orofacial musculature also can be involved.

- Immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – diphenhydramine
- anti-infective drugs
  - *antiparasitics* – chloroquine
- cardiovascular drugs
  - *antihypertensives* – nifedipine
- nervous system drugs
  - *anesthetics* – ketamine
  - *antiaddiction* – disulfiram
  - *anti-Alzheimer's* – rivastigmine

- *anticonvulsants* – carbamazepine, felbamate, lamotrigine, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide
- *antidepressants* – amitriptyline, amoxapine, bupropion, doxepin, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, tranylcypromine, trazodone
- *antimigraine* – sumatriptan, zolmitriptan
- *anti-Parkinson's* – benzatropine, levodopa, rasagiline\*, ropinirole, selegiline
- *antipsychotics* – aripiprazole, asenapine, iloperidone, lurasidone\*, olanzapine\*, paliperidone\*, quetiapine\*, risperidone\*, thioridazine, thiothixene, ziprasidone
- *anxiolytics/hypnotics* – diazepam, midazolam, zaleplon
- *opioids* – dextromethorphan, fentanyl
- gastrointestinal drugs
  - *antiemetics* – droperidol, ondansetron
  - *H2 blockers* – ranitidine
  - *motility stimulants* – metoclopramide.

## DRUG-INDUCED PARKINSONISM

“Drug-induced Parkinsonism” refers to a syndrome that resembles idiopathic Parkinson's disease (whose core features are bradykinesia, resting tremor, postural instability, and rigidity). It usually is reversible, and is a common and often unrecognized cause of disability in the elderly (Thanvi and Treadwell, 2009).

- Antineoplastic drugs
  - *antimetabolites* – cytarabine
  - *microtubule inhibitors* – paclitaxel
  - *targeted* – tamoxifen
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *NSAIDs* – naproxen
  - *targeted* – cyclosporine, interferon gamma-1b
  - thalidomide
- anti-infective drugs
  - *antifungals* – amphotericin B
  - *antimicrobials* – cephaloridine
- cardiovascular drugs
  - *antiarrhythmics* – amiodarone
  - *antihypertensives* – amlodipine, diltiazem, methyldopa, reserpine, verapamil
  - *lipid-lowering agents* – lovastatin

- nervous system drugs
  - *antiaddiction* – disulfiram
  - *anti-ADHD* – methylphenidate
  - *anti-Alzheimer's* – donepezil, memantine, rivastigmine, tacrine
  - *antichorea* – tetrabenazine\*
  - *anticonvulsants* – lamotrigine, phenytoin, valproate
  - *antidepressants* – amoxapine, bupropion, escitalopram, fluoxetine, lithium, paroxetine, phenelzine, sertraline, trazodone
  - *antimigraine* – flunarizine
  - *antipsychotics* – aripiprazole, asenapine, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone, lurasidone\*, olanzapine\*, paliperidone\*, pimozide, promazine, quetiapine\*, risperidone\*, trifluoperazine
  - *anxiolytics/hypnotics* – diazepam
  - *opioids* – meperidine
- endocrinological drugs
  - *sex hormones* – medroxyprogesterone
  - *thyroid* – levothyroxine
- gastrointestinal drugs
  - *antiemetics* – droperidol, prochlorperazine, trimethobenzamide
  - *motility stimulants* – metoclopramide.
- anti-infective drugs
  - *antimicrobials* – furazolidone, linezolid
- cardiovascular drugs
  - *antihypertensives* – pargyline
- nervous system drugs
  - *anti-ADHD* – amphetamine
  - *antidepressants* – citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, imipramine, lithium, mirtazapine, olanzapine/fluoxetine, paroxetine, phenelzine, sertraline, toloxatone, tranylcypromine, trazodone, venlafaxine
  - *antifibromyalgia* – milnacipran
  - *antimigraine* – almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
  - *anti-Parkinson's* – selegiline
  - *antipsychotics* – ziprasidone
  - *opioids* – dextromethorphan, fentanyl, meperidine, methadone, pentazocine, tapentadol, tramadol
- endocrinological drugs
  - weight reduction – sibutramine
- supplements
  - L-tryptophan, 5-hydroxytryptophan.

## SEROTONIN SYNDROME

Serotonin syndrome (recently reviewed by Sun-Edelstein *et al.*, 2008) results when medications increase serotonin (5-hydroxytryptamine) concentrations at postsynaptic 5-HT<sub>2A</sub> receptors. The classic presentation includes neuromuscular hyperactivity (akathisia, tremor, clonus, myoclonus, hyperreflexia, rigidity, nystagmus), autonomic hyperactivity (diaphoresis, fever, tachycardia, tachypnea), and altered mental status (agitation, excitement, confusion), though not all signs and symptoms may be present. Frequently, it results from combinations of medications with serotonergic actions. Severe cases are medical emergencies.

- Antineoplastic drugs
  - *DNA agents* – procarbazine
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – brompheniramine, chlorpheniramine

## NEUROLEPTIC MALIGNANT SYNDROME

This syndrome derives its name from its association with neuroleptic (antipsychotic) drugs and comprises fever, autonomic instability, extrapyramidal symptoms (hence its inclusion in this section), and altered mental state (for a recent review, see Trollor *et al.* (2009)). It is observed with other drugs that block dopamine, as well as with the withdrawal of dopaminergic drugs. As is the case for serotonin syndrome, if untreated it can result in significant disability or death.

- Nervous system drugs
  - *anti-ADHD* – dexmethylphenidate, methylphenidate
  - *anti-Alzheimer's* – donepezil, memantine
  - *antichorea* – tetrabenazine
  - *anticonvulsants* – carbamazepine
  - *antidepressants* – desvenlafaxine, duloxetine, escitalopram, fluoxetine, paroxetine, trazodone

- *anti-Parkinson's* – carbidopa/levodopa/entacapone, rasagiline
- *antipsychotics* – amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, thioridazine, thiothixene, ziprasidone
- gastrointestinal drugs
  - *motility stimulants* – metoclopramide
  - *weight reduction* – sibutramine.

## ADVERSE EVENTS INVOLVING CONSCIOUSNESS

### SEIZURES

For the purposes of this discussion, a seizure is a paroxysmal and synchronized discharge of cerebral neurons that has a clinical effect. Generalized seizures are symmetric, without local onset, and cause a loss of consciousness; they include tonic-clonic (grand mal) and absence (petit mal) seizures. Partial (also described as focal) seizures begin locally, and can either be simple (without alteration of consciousness) or complex (with impaired consciousness). Unfortunately, there is no phenotypic distinction between drug-induced and all other seizures. Drugs in bold are associated with clear loss of consciousness (generalized/grand mal seizures) in their prescribing information or the data cited in reviews (e.g., Jain, 2012). Fortunately, most seizures are self-limited and brief. Those of new onset need to be evaluated by a neurologist. Repetitive or continuous seizures are a medical emergency and can cause permanent disability or death if not treated effectively.

- Antineoplastic drugs
  - *antimetabolites* – methotrexate, **nelarabine\***
  - *DNA agents* – altretamine, **busulfan**, **chlorambucil**, cisplatin, mitoxantrone\*
  - *inducers of differentiation* – isotretinoin
  - *microtubule inhibitors* – docetaxel, vincristine
  - *targeted* – sunitinib
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – desloratadine, **terfenadine**
  - *immunoglobulins* – Flebogamma®, Gammagard, Gamunex®

- *NSAIDs* – **aspirin**, **diclofenac**
- *targeted* – certolizumab pegol, **cyclosporine**, etanercept, infliximab, interferon beta-1a\*, interferon gamma-1b, **muromonab-CD3**, ustekinumab
- anti-infective drugs
  - *antifungals* – **amphotericin B**, miconazole
  - *antimicrobials* – **ampicillin**, **carbenicillin**, cefdinir, cefixime, ceftazidime, cefuroxime, **ciprofloxacin**, cycloserine, ertapenem, **imipenem**, isoniazid, levofloxacin, **norfloxacin**, **penicillin**, ticarcillin/clavulanate
  - *antiparasitics* – atovaquone/proguanil, **chloroquine**, **dapsone**, ivermectin, metronidazole, tinidazole
  - *antiviral* – abacavir, acyclovir, lamivudine/zidovudine, peginterferon alfa-2b, **ritonavir**, valacyclovir, zanamivir, zidovudine
  - *vaccines* – Comvax®, Enerix-B®, FluLaval®, Gardasil®, Infanrix®, Kinrix®, Pediarix®, Recombivax HB®, RotaTeq®, Vaqta®
- cardiovascular drugs
  - *antiarrhythmics* – **mexiletine**, propafenone
  - *antihypertensives* – **aliskiren**, **aliskiren/amlodipine**, **aliskiren/valsartan**, hydrochlorothiazide, **propranolol**
- nervous system drugs
  - *anesthetics* – **bupivacaine**, **ketamine**, **lidocaine**
  - *anti-ADHD* – atomoxetine, dextroamphetamine, lisdexamfetamine, methylphenidate
  - *anti-Alzheimer's* – **memantine**, rivastigmine
  - *antidepressants* – **amitriptyline**, **bupropion**, **citalopram**, **chlorpromazine**, **clomipramine**, desvenlafaxine, **escitalopram**, **fluoxetine**, **imipramine**, **mianserin**, **mirtazapine**, **paroxetine**, risperidone, **trazodone**
  - *antimigraine* – frovatriptan, rizatriptan, **sumatriptan**
  - *antinarcolepsy* – oxybate
  - *anti-Parkinson's* – **levodopa**
  - *antipsychotics* – **ariPIPRAZOLE**, asenapine, **clozapine**, **haloperidol**, thiothixene
  - *benzodiazepine antagonists* – flumazenil
  - *opioids* – buprenorphine, **meperidine**, **morphine**, oxycodone, tapentadol, tramadol
- endocrinological drugs
  - *hypothalamic/pituitary* – octreotide, tolvaptan
  - *parathyroid* – **cinacalcet**
  - *thyroid* – levothyroxine

- gastrointestinal drugs
  - *antiemetics* – **ondansetron, promethazine**
  - *H<sub>2</sub> blockers* – famotidine
  - *motility stimulants* – metoclopramide
- genitourological drugs
  - *anti-ED* – sildenafil, tadalafil, vardenafil
- hematological drugs
  - *coagulation factors* – Alphanate®
  - *ESAs* – darbepoetin alfa, epoetin alfa\*
- respiratory drugs
  - *antiasthma* – aminophylline, budesonide, fluticasone/salmeterol, mometasone/formoterol, montelukast, terbutaline, **theophylline**.

## DEPRESSION OF CONSCIOUSNESS

Depression of consciousness (e.g., confusion, delirium, stupor, coma) is among the most common NAEs. Etiologies can include direct pharmacologic action (with resolution upon removal) or the development of demyelination and/or inflammation. When the latter alterations are focused in the white matter (myelinated tracts) they are described as “leukoencephalopathies.” Recently, these have been identified in association with TNF inhibitors (adalimumab, etanercept, infliximab; Ryu *et al.*, 2012); most of these subjects’ symptoms have improved or resolved with discontinuation of the offending agent with or without additional treatment. PML is a currently untreatable and frequently fatal subcategory caused by JC virus infection that is seen with immunomodulatory agents, including monoclonal antibodies (alemtuzumab, brentuximab vedotin, natalizumab, ofatumumab, rituximab), as well as with antineoplastic drugs (Piccinni *et al.*, 2010). A significantly more benign variant is reversible posterior leukoencephalopathy syndrome (RPLS, also PRES – e.g., Connolly *et al.*, 2007; Sánchez-Carteyron *et al.*, 2010). Drugs that in the PDR® are associated with the NAE “encephalitis,” “encephalomyelitis,” or “encephalopathy” (vaccines in particular) are included in this section.

- Antineoplastic drugs
  - *antimetabolites* – cytarabine (PML), decitabine\*, fludarabine (+PML), fluorouracil (PML), methotrexate (PML), nelarabine\* (+PML)

- *DNA agents* – altretamine, chlorambucil, cyclophosphamide (PML), doxorubicin (PML), mitoxantrone, temozolomide\*
- *inducers of differentiation* – arsenic trioxide\*, bexarotene
- *microtubule inhibitors* – docetaxel, vincristine (PML)
- *targeted* – adalimumab, alemtuzumab (PML), bevacizumab (RPLS), bortezomib (+RPLS), brentuximab vedotin (PML), cetuximab\*, dasatinib, exemestane\*, imatinib, leuprolide\*, mycophenolate, nilotinib, ofatumumab (PML), rituximab (PML, RPLS), sorafenib (RPLS), sunitinib (RPLS)
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - azathioprine (PML)
  - *immunoglobulins* – Flebogamma®, Gammagard, Gamunex®
  - *NSAIDs* – 4-aminosalicylic acid, ibuprofen, mesalamine
  - *steroids* – prednisone (PML), prednisolone (PML)
  - *targeted* – adalimumab\* (+PML), cyclosporine (PML), etanercept, fingolimod (RPLS), glatiramer, infliximab (+RPLS), interferon beta-1a\* (PML), interferon beta-1b, interferon gamma-1b, muromonab-CD3, mycophenolate (PML), natalizumab (PML), peginterferon alpha-2a (PML), rituximab (PML, RPLS), tacrolimus (PML), ustekinumab (+RPLS)
- anti-infective drugs
  - *antifungals* – amphotericin B, caspofungin\*
  - *antimicrobials* – amoxicillin, cefdinir, ceftazidime, ciprofloxacin, clarithromycin, cycloserine, ertapenem, imipenem/cilastatin, levofloxacin, methenamine mandelate, moxifloxacin, norfloxacin, penicillin G, piperacillin/tazobactam, quinupristin/dalfopristin, rifaximin\*, telithromycin
  - *antiparasitics* – ivermectin, levamisole (PML), tinidazole
  - *antivirals* – acyclovir, delavirdine, efavirenz, efavirenz/emtricitabine/tenofovir, interferon alfa-2b\*, interferon alfa-n3\*, lopinavir/ritonavir, maraviroc\*, peginterferon alfa-2b, ritonavir, valacyclovir, zanamivir, zidovudine

- vaccines – Boostrix®, Engerix-B®, Fluarix®, FluLaval®, Gardasil®, Havrix®, Infanrix®, M-M-R® II, Pediarix®, ProQuad®, Recombivax HB®, Twinrix®, Vaqta®, Varivax®
- cardiovascular drugs
  - antiangina – ranolazine
  - antiarrhythmics – propafenone
  - antihypertensives – aliskiren, amlodipine/valsartan/hydrochlorothiazide, captopril, clonidine, hydrochlorothiazide/triamterene, irbesartan/hydrochlorothiazide, lisinopril, losartan, metoprolol, trandolapril/verapamil, valsartan/hydrochlorothiazide
  - anti-PAH – prostacyclin\*
  - cardiac glycosides – digoxin
  - lipid-lowering agents – fenofibrate
- nervous system drugs
  - anesthetics – lidocaine, sevoflurane
  - antiaddiction – varenicline
  - anti-ADHD – methylphenidate
  - anti-ALS – riluzole\*
  - anti-Alzheimer's – donepezil, memantine\*, rivastigmine\*
  - anticonvulsants – carbamazepine, lacosamide, lamotrigine, phenytoin, pregabalin\*, rufamide, tiagabine\*, valproate, vigabatrin\*, zonisamide\*
  - antidepressants – bupropion\*, desvenlafaxine, duloxetine, escitalopram, fluoxetine, lithium, mirtazapine, paroxetine, tranylcypromine, trazodone\*
  - antimigraine – frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
  - anti-motion sickness – scopolamine
  - antinarcolepsy – modafinil, oxybate\*
  - anti-Parkinson's – carbidopa/levodopa/entacapone, entacapone, rasagiline, ropinirole\*, selegiline\*
  - antipsychotics – aripiprazole, iloperidone, olanzapine\*, paliperidone, quetiapine, risperidone, ziprasidone
  - anxiolytics/hypnotics – midazolam, zaleplon, zolpidem
  - opioids – buprenorphine, fentanyl\*, hydrocodone, hydromorphone, morphine\*, oxycodone\*, oxymorphone\*, tapentadol, tramadol
- endocrinological drugs
  - bone metabolism – etidronate, zoledronate\*
  - hypothalamic/pituitary – somatropin, tolvaptan
  - sex hormones – levonorgestrel/ethinyl estradiol, progesterone
  - thyroid – methimazole
  - weight reduction – sibutramine
- gastrointestinal drugs
  - antianorexics/anticachectics – megestrol\*
  - antiemetics – aprepitant, dolasetron, droperidol, trimethobenzamide
  - H<sub>2</sub> blockers – famotidine, nizatidine, ranitidine
  - motility stimulants – metoclopramide
  - proton pump inhibitors – esomeprazole, rabeprazole
  - saliva stimulants – pilocarpine
- genitourological drugs
  - anti-overactive bladder – darifenacin, tolterodine, trospium
- hematological drugs
  - anticoagulants – enoxaparin, fondaparinux
  - antiplatelet agents – aspirin/dipyridamole, clopidogrel
  - coagulation factors – Recombinate
- ocular drugs
  - antiglaucoma – brimonidine/timolol.

## MEMORY DISTURBANCES

The physiology of memory remains poorly understood. The hippocampi and amygdala are critical for laying down memory, but the system is broadly distributed among other subcortical and cortical structures (see Rissman and Wagner (2012) for a recent review).

- Antineoplastic drugs
  - DNA agents – temozolomide\*
  - targeted – imatinib, letrozole, leuprorelin\*
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - targeted – glatiramer
- anti-infective drugs
  - antimicrobials – cycloserine, rifaximin\*
  - antivirals – maraviroc\*, peginterferon alfa-2b

- cardiovascular drugs
  - antiarrhythmics – propafenone
  - antihypertensives – lisinopril, losartan, losartan/hydrochlorothiazide, metoprolol, nadolol, nadolol/bendroflumethiazide, propranolol
  - combination – amlodipine/atorvastatin
  - lipid lowering agents – atorvastatin, ezetimibe/simvastatin, lovastatin, rosuvastatin, simvastatin
- nervous system drugs
  - *anticonvulsants* – lacosamide, lamotrigine, levetiracetam, pregabalin\*, tiagabine\*, vigabatrin\*, zonisamide\*
  - *antidepressants* – bupropion\*, desvenlafaxine, duloxetine, escitalopram, fluoxetine, paroxetine, tranylcypromine, trazodone\*
  - *antimigraine* – rizatriptan, sumatriptan
  - *anti-motion sickness* – scopolamine
  - *anti-narcolepsy* – oxybate
  - *anti-Parkinson's* – carbidopa/levodopa/entacapone, ropinirole, selegiline
  - *antipsychotics* – aripiprazole
  - *anxiolytics/hypnotics* – midazolam, zaleplon, zolpidem\*
  - *opioids* – buprenorphine, morphine, tapentadol
- endocrinological drugs
  - *sex hormones* – testosterone
  - *uric acid reduction* – febuxostat
- gastrointestinal drugs
  - *proton pump inhibitors* – dexlansoprazole
  - *weight reduction* – sibutramine
- genitourological drugs
  - *anti-overactive bladder* – tolterodine.

## ADVERSE EVENTS INVOLVING SLEEP

Sleep-wake behavior is yet another complex derivative of multiple, interlinked brain systems (España and Scammell, 2011). Many medications have a neurological impact (comprehensively reviewed by Foral *et al.*, 2011) that can be mitigated by medication adjustment.

## INSOMNIA

- Antineoplastic drugs
  - *antimetabolites* – cladribine\*, decitabine\*, gemcitabine, nelarabine\*
  - *DNA agents* – bendamustine\*, oxaliplatin\*, procarbazine, temozolomide\*
  - *inducers of differentiation* – acitretin\*, arsenic trioxide\*, bexarotene\*
  - *microtubule inhibitors* – eribulin\*
  - *targeted* – bortezomib\*, brentuximab vedotin\*, cetuximab\*, dasatinib\*, exemestane\*, fulvestrant\*, histrelin, imatinib\*, lapatinib\*, letrozole\*, leuprolide\*, nilotinib\*, ofatumumab\*, sunitinib\*, temsirolimus\*, trastuzumab\*
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – brompheniramine, cetirizine/pseudoephedrine, desloratadine, fexofenadine
  - *NSAIDs* – celecoxib, diclofenac, mesalamine, sulindac
  - *steroids* – prednisolone, triamcinolone
  - *targeted* – basiliximab\*, cyclosporine\*, everolimus\*, imiquimod, interferon beta-1b\*, mycophenolate\*
- anti-infective drugs
  - *antifungals* – amphotericin B, caspofungin\*, posaconazole\*
  - *antimicrobials* – amoxicillin, amoxicillin/clavulanate, cefdinir, ciprofloxacin, clarithromycin, dapsone, ertapenem\*, levofloxacin\*, linezolid, moxifloxacin, norfloxacin, piperacillin/tazobactam\*, quinupristin/dalfopristin, rifaximin\*, telithromycin
  - *antiparasitics* – artemether/lumefantrine, atovaquone\*, atovaquone/proguanil\*, tinidazole
  - *antivirals* – abacavir/lamivudine, atazanavir\*, delavirdine\*, efavirenz\*, efavirenz/emtricitabine/tenofovir\*, emtricitabine\*, emtricitabine/tenofovir\*, entecavir, interferon alfa-2b\*, interferon alfa-n3, lamivudine\*, lamivudine/zidovudine\*, lopinavir/ritonavir\*, maraviroc\*, peginterferon alfa-2b\*, raltegravir\*, ribavirin\*, ritonavir\*, tenofovir\*, zidovudine\*

- *vaccines* – Engerix-B®, FluLaval®, Gardasil®, Havrix®, Pediarix®, Prevnar® 13\*, Recombivax HB®, Twinrix®, Vaqta®
- cardiovascular drugs
  - *antiarrhythmics* – amiodarone, propafenone
  - *antihypertensives* – aliskiren/amldipine, amlodipine/valsartan, candesartan/hydrochlorothiazide, captopril, carvedilol, clonidine\*, clonidine/chlorthalidone, diltiazem, eprosartan, felodipine, indapamide\*, isradipine, lisinopril, lisinopril/hydrochlorothiazide, losartan, losartan/hydrochlorothiazide, metoprolol, nebivolol, nisoldipine, propranolol, ramipril, trandolapril, trandolapril/verapamil, valsartan
  - *anti-pulmonary artery hypertension* – prostacyclin
  - *antithrombotics* – fondaparinux\*
  - *combinations* – amlodipine/atorvastatin
  - *lipid-lowering agents* – atorvastatin\*, ezetimibe/simvastatin, fenofibrate\*, fluvastatin, lovastatin, niacin, niacin/lovastatin, omega-3-acid ethyl esters, rosuvastatin, simvastatin\*
  - pentoxifylline
- nervous system drugs
  - *antiaddiction* – varenicline
  - *anti-ADHD* – amphetamine, atomoxetine\*, dexmethylphenidate\*, dextroamphetamine, guanfacine\*, lisdexamfetamine\*, methylphenidate\*
  - *anti-ALS* – riluzole\*
  - *anti-Alzheimer's* – donepezil\*, memantine, rivastigmine\*, tacrine
  - *antichorea* – tetrabenazine\*
  - *anticonvulsants* – ethosuximide, felbamate, lamotrigine\*, phenytoin, pregabalin, tiagabine\*, valproate\*, vigabatrin\*, zonisamide\*
  - *antidepressants* – amitriptyline, bupropion\*, buspirone, citalopram, desipramine, desvenlafaxine\*, duloxetine\*, escitalopram\*, fluoxetine\*, mirtazapine, paroxetine\*, phenelzine, tranylcypromine, trazodone, venlafaxine
  - *antidystonia/antispasm* – carisoprodol, cyclobenzaprine, tizanidine
  - *anti-insomnia* – ramelteon\*, zaleplon, zolpidem
- antimigraine – frovatriptan, rizatriptan, sumatriptan/naproxen, zolmitriptan
- *anti-motion sickness* – prochlorperazine
- *antinarcolepsy* – armodafinil\*, modafinil\*, oxybate
- *anti-Parkinson's* – amantadine, carbidopa/levodopa/entacapone, levodopa, ropinirole, selegiline
- *antipsychotics* – aripiprazole\*, asenapine\*, lurasidone\*, olanzapine\*, paliperidone\*, quetiapine\*, risperidone\*, thiothixene, ziprasidone\*
- *opioids* – buprenorphine\*, fentanyl\*, hydromorphone, morphine\*, oxycodone\*, oxymorphone\*, tapentadol, tramadol
- endocrinological drugs
  - *bone metabolism* – denosumab\*, raloxifene\*, risedronate\*, teriparatide\*, zoledronate\*
  - *hypothalamus/pituitary* – somatropin\*
  - *parathyroid* – paricalcitol\*
  - *sex hormones* – etonogestrel\*, levonorgestrel/ethinyl estradiol, norelgestromin/ethinyl estradiol, Premarin®, Premphase®, Prempro®, testosterone
  - *thyroid* – levothyroxine
  - *uric acid reduction* – febuxostat
  - *weight reduction* – phentermine
- gastrointestinal drugs
  - *antianorexics/anticachectics* – megestrol\*
  - *antiemetics* – aprepitant, palonosetron
  - *antiulcer* – sucralfate
  - *H2 blockers* – famotidine, nizatidine, ranitidine
  - *motility stimulants* – metoclopramide
  - *proton pump inhibitors* – dexlansoprazole, esomeprazole
  - *saliva stimulants* – pilocarpine
  - *weight reduction* – phentermine, sibutramine\*
- genitourological drugs
  - *anti-BPH* – dutasteride/tamsulosin
  - *anti-ED* – sildenafil, tadalafil, vardenafil
  - *anti-overactive bladder* – fesoterodine
- hematological drugs
  - *anti-ITP* – romiplostim\*
  - *chelators* – deferasirox
  - *coagulation factors* – Alphanate®

- *erythropoiesis-stimulating agents* – epoetin alfa\*
- respiratory drugs
  - *anti-allergic rhinitis* – pseudoephedrine
  - *antiasthma* – albuterol, budesonide\*, fluticasone/salmeterol, formoterol, ipratropium, metaproterenol, mometasone/formoterol, montelukast, salmeterol, theophylline
  - *anti-COPD* – arformoterol, tiotropium\*
- ocular drugs
  - *antiglaucoma* – brimonidine\*.

## DROWSINESS

- Antineoplastic drugs
  - *antimetabolites* – gemcitabine\*, methotrexate, nelarabine\*
  - *DNA agents* – bendamustine, doxorubicin\*, oxaliplatin\*, procarbazine, temozolomide\*
  - *inducers of differentiation* – acitretin\*, arsenic trioxide\*
  - *targeted* – dasatinib\*, imatinib, letrozole\*, leuprorelin, tositumomab\*
- immunosuppressant/immunomodulatory/anti-inflammatory drugs
  - *antihistamines* – cetirizine, desloratadine, desloratadine/pseudoephedrine\*, diphenhydramine, fexofenadine, levocetirizine\*, olopatadine
  - *immunoglobulins* – Flebogamma®, Gammagard, Gamunex®
  - *NSAIDs* – celecoxib, diclofenac, ibuprofen, ketorolac, mesalamine, naproxen, sulindac
  - *targeted* – cyclosporine, everolimus\*, interferon beta-1a\*, natalizumab
  - thalidomide
- anti-infective drugs
  - *antifungals* – caspofungin\*, posaconazole
  - *antimicrobials* – cefdinir, cefuroxime, ciprofloxacin, cycloserine, ertapenem, imipenem/cilastatin, levofloxacin, minocycline, moxifloxacin, norfloxacin, penicillin, piperacillin/tazobactam, telithromycin
  - *antiparasitics* – ivermectin, tinidazole
  - *antivirals* – acyclovir, delavirdine, efavirenz, efavirenz/emtricitabine/tenofovir\*, entecavir, indinavir\*, interferon alfa-2b\*, interferon alfa-n3\*, lopinavir/ritonavir, ritonavir, zidovudine

- *vaccines* – Comvax®, Engerix-B®, Fluarix®, FluLaval®, Havrix®, Infanrix®, Kinrix®, Pediarix®, PedvaxHIB®, Prevnar® 13®, ProQuad®, Recombivax HB®, Twinrix®
- cardiovascular drugs
  - *antiarrhythmics* – propafenone
  - *antihypertensives* – amlodipine/valsartan, candesartan, captopril, carvedilol\*, clonidine\*, clonidine/chlorthalidone\*, diltiazem, eprosartan, furosemide, hydrochlorothiazide/triamterene, indapamide\*, irbesartan, irbesartan/HCTZ, isradipine, labetalol, lisinopril, losartan, methyldopa, metoprolol, nadolol/bendroflumethiazide, nebivolol, nitroprusside, prazosin, ramipril, reserpine, spironolactone, trandolapril, trandolapril/verapamil, valsartan
  - *anti-pulmonary artery hypertension* – prostacyclin\*
  - *combination* – amlodipine/atorvastatin
  - *lipid-lowering agents* – fenofibrate
- nervous system drugs
  - *anesthetics* – lidocaine, sevoflurane
  - *antiaddiction* – varenicline
  - *anti-ADHD* – atomoxetine\*, clonidine\*, dexmethylphenidate, guanfacine\*, lisdexamfetamine, methylphenidate
  - *anti-ALS* – riluzole
  - *anti-Alzheimer's* – donepezil, memantine\*, rivastigmine
  - *antichorea* – tetrabenazine\*
  - *anticonvulsants* – carbamazepine, ethosuximide, lacosamide\*, lamotrigine\*, levetiracetam\*, oxcarbazepine, phenobarbital, phenytoin, pregabalin\*, primidone, rufinamide\*, tiagabine\*, valproate\*, vigabatrin\*, zonisamide\*
  - *antidepressants* – amitriptyline, bupropion\*, buspirone, citalopram, clomipramine, desipramine, desvenlafaxine\*, doxepin, duloxetine\*, escitalopram\*, fluoxetine\*, imipramine, lithium, maprotiline, mirtazapine, nortriptyline, paroxetine\*, phenelzine, tranylcypromine, trazodone\*
  - *antidystonia/antispasm* – baclofen, carisoprodol, cyclobenzaprine, dantrolene, metaxalone, onabotulinumtoxinA\*
  - *anti-insomnia* – ramelteon\*

- *antimigraine* – frovatriptan, naratriptan, rizatriptan\*, sumatriptan\*, zolmitriptan\*
  - *anti-motion sickness* – meclizine, prochlorperazine, scopolamine
  - *antinarcolepsy* – modafinil, oxybate\*
  - *anti-Parkinson's* – amantadine, apomorphine, benzatropine, carbidopa/levodopa/entacapone, entacapone, lisuride, pramipexole, rasagiline\*, ropinirole\*, selegiline, trihexyphenidyl
  - *antipsychotics* – aripiprazole\*, asenapine\*, chlorpromazine, clozapine, fluphenazine, haloperidol, iloperidone\*, loxapine, lurasidone\*, olanzapine\*, paliperidone\*, perphenazine, quetiapine\*, risperidone\*, thioridazine, thiothixene, ziprasidone\*
  - *anxiolytics/hypnotics* – zaleplon, zolpidem\*
  - *opioids* – buprenorphine\*, dextromethorphan, fentanyl\*, morphine\*, oxycodone\*, oxymorphone\*, tapentadol\*, tramadol\*
  - endocrinological drugs
    - *anti-DM* – exenatide, pioglitazone/metformin, rosiglitazone/metformin, sitagliptin/metformin
    - *anti-pheochromocytoma* – phenoxybenzamine
    - *bone metabolism* – zoledronate\*
    - *hypothalamus/pituitary* – bromocriptine, cabergoline
    - *parathyroid* – calcitonin, paricalcitol
    - *sex hormones* – etonogestrel\*, follitropin alfa, progesterone
    - *thyroid* – methimazole
    - *uric acid reduction* – febuxostat
    - *weight reduction* – sibutramine
  - gastrointestinal drugs
    - *antidiarrheal* – dicyclomine, diphenoxylate, loperamide
    - *antiemetics* – dolasetron, droperidol, granisetron, ondansetron\*, palonosetron, trimethobenzamide
    - *antiulcer* – sucralfate
    - *H<sub>2</sub> blockers* – famotidine, nizatidine, ranitidine
    - *motility stimulants* – metoclopramide\*
    - *proton pump inhibitors* – dexlansoprazole, esomeprazole
    - *saliva reduction* – glycopyrrolate
    - *saliva stimulants* – pilocarpine
  - genitourological drugs
    - *anti-BPH* – dutasteride/tamsulosin, finasteride
    - *anti-ED* – sildenafil, tadalafil, vardenafil
    - *anti-overactive bladder* – oxybutynin, tolterodine\*, trospium
  - hematological drugs
    - *antiplatelet agents* – aspirin/dipyridamole
    - *coagulation factors* – Alphanate®, BeneFIX®, Profilnine® SD
  - respiratory drugs
    - *alpha<sub>1</sub>-antitrypsin replacement* – alpha<sub>1</sub>-proteinase inhibitor
    - *antiasthma* – albuterol, arformoterol, montelukast
  - ocular drugs
    - *antiglaucoma* – brimonidine\*, brimonidine/timolol\*.
- ## NIGHTMARES
- Immunosuppressant/immunomodulatory/anti-inflammatory drugs
    - *antihistamines* – chlorpheniramine
    - *NSAIDs* – naproxen
    - *steroids* – dexamethasone, hydrocortisone
  - anti-infective drugs
    - *antimicrobials* – ciprofloxacin, clarithromycin, levofloxacin
    - *antivirals* – efavirenz, ganciclovir, zanamivir
  - cardiovascular drugs
    - *antiarrhythmics* – amiodarone, propafenone
    - *antihypertensives* – atenolol, clonidine\*, clonidine/chlorthalidone, enalapril, labetalol, losartan, methyldopa, metoprolol, nadolol, propranolol, quinapril, reserpine, sotalol, verapamil
    - *cardiac glycosides* – digoxin
    - *combinations* – amlodipine/atorvastatin
    - *lipid-lowering agents* – atorvastatin, rosuvastatin, simvastatin
  - nervous system drugs
    - *antiaddiction* – varenicline
    - *anti-ADHD* – guanfacine
    - *anti-Alzheimer's* – donepezil, rivastigmine
    - *antidepressants* – amitriptyline, bupropion, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, imipramine,

- mirtazapine, nortriptyline, paroxetine, phenelzine, venlafaxine
- *antinarcolepsy* – oxybate\*
- *anti-Parkinson's* – amantadine, carbidopa/levodopa/entacapone, levodopa, ropinirole, selegiline
- *antipsychotics* – clozapine, paliperidone, quetiapine, risperidone
- *anxiolytics/hypnotics* – temazepam, triazolam
- *opioids* – buprenorphine
- *endocrinological drugs*
- *weight reduction* – sibutramine.

## NARCOLEPSY

Narcolepsy (reviewed by Nishino and Mignot (2011)) presents with frequent attacks of excessive daytime sleepiness that result in short episodes of real sleep. Often, the clinical condition includes cataplexy (temporary paralysis during laughter or other states of heightened emotion) and hypnagogic (just preceding the onset of sleep) paralysis and hallucinations. Population prevalence is probably much less than 0.1%. The condition most commonly results from loss of hypocretin-producing cells in the hypothalamus, perhaps from an autoimmune process. Observations in the USA, UK, and France during the H1N1 pandemic of 2009–2010 suggested a temporal link between H1N1 infection or vaccination and subsequent narcolepsy (Dauvilliers *et al.*, 2010). Studies in China with much larger numbers of cases have demonstrated a high correlation between H1N1 infection in 2009–2010 and the onset of narcolepsy (Han *et al.*, 2011); 96% of those subjects did not report a prior H1N1 vaccination. After investigation in Finland and Sweden, the European Medicines Agency stated there was “a six to 13-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated children/adolescents” and recommended against the use of Pandemrix in persons under 20 years of age if seasonal trivalent influenza vaccine was available (EMA, 2011). Current treatment of narcolepsy is symptomatic and often unsatisfactory.

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## **Part IV: PHARMACOVIGILANCE AND DRUG/SYSTEM ORGAN CLASSES**

### **Special Populations**

**40**

# **Drug Safety in Pregnancy**

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### **INTRODUCTION**

Following the recognition in the 1960s that thalidomide, when used by pregnant women, induced a characteristic pattern of severe congenital anomalies in many of the offspring, pharmaceutical manufacturers, regulatory agencies, and a variety of public health entities have faced the challenge and responsibility of assessing the safety of medication with respect to the developing fetus (Lenz, 1961; McBride, 1961). This is a daunting task for a variety of reasons, not the least of which is the number and variety of medications to which a pregnant woman is likely to be exposed. Although pharmacovigilance for a spectrum of adverse reproductive outcomes, ranging from spontaneous abortion to long-term postnatal functional deficits or learning disabilities, is appropriate in assessing pharmaceutical safety during pregnancy, the focus of this chapter will be limited to major congenital anomalies. As congenital anomalies are the leading cause

of infant mortality and number of years of potential life lost in the USA, the prevention of even the small proportion that are likely to be attributable to maternal medication use is a worthy goal of any pharmacovigilance effort (Rosenberg *et al.*, 1996; Yang *et al.*, 1997).

### **FREQUENCY AND VARIETY OF MEDICATION USE AMONG PREGNANT WOMEN**

In the USA alone, 35 innovative new drugs were approved by the Food and Drug Administration (FDA, 2012). New drugs do not come to market with clinical trial safety data specifically designed to address questions related to human pregnancy. Once a new drug is available for clinical use, or a previously marketed drug is approved for a new indication, the frequency with which it is prescribed and the specific medical conditions that it is used

to treat influence the likelihood that women of reproductive age and pregnant women will use the drug.

However, numerous studies have demonstrated that pregnant women are commonly using several medications over the course of gestation. For example, in a review of drug utilization studies, Bonati *et al.* (1990) identified 13 publications originating from sites in the USA and Europe in which pregnant women used an average of 4.7 drugs per person, with the mean number ranging from 3 to 11. A 1996 survey of records of the French Health Insurance Service demonstrated that, in a sample of 1000 women living in southwest France, 99% of women received a prescription for at least one drug during pregnancy with a mean of 13.6 medications prescribed per woman (Lacroix *et al.*, 2000). Similarly, a 2004 study conducted across eight health maintenance organizations in the USA, in which prescription records for 152 531 pregnant women were reviewed, found that 64% of these women were prescribed at least one drug other than a vitamin or mineral sometime during pregnancy. Moreover, 39% of all women in the sample received at least one prescription during the first trimester. On average, women received 2.7 drug dispensings and 1.7 different chemical entities over the course of pregnancy (Andrade *et al.*, 2004).

In addition to the frequent occurrence of prescription medication use during pregnancy, recent evidence suggests that over-the-counter medications are used even more commonly. Using two large case-control data sets, Werler *et al.* (2005) demonstrated that acetaminophen, ibuprofen, and pseudoephedrine were used by at least 65%, 18%, and 15% of pregnant women, respectively. Furthermore, for some over-the-counter medications, use was reportedly higher during pregnancy than in the period before conception.

Given that a substantial proportion of pregnancies occur without prior planning – in the USA estimates are that as many as 56% of pregnancies are not planned – women may be inadvertently exposed to medications before pregnancy is recognized, and this vulnerable period may extend into the first 4–6 weeks or longer following conception (Forrest, 1994). Thus, unintentional fetal exposures can occur during part or all of the most critical

period in embryonic development for drug-induced malformations.

In addition to medication exposures that take place before pregnancy recognition, many maternal conditions, both acute and chronic, may require treatment after pregnancy is confirmed. A variety of relatively common diseases that occur in women of reproductive age may necessitate treatment throughout the course of pregnancy. For example, the prevalence of clinical depression among women in their reproductive years is estimated to be as high as 8.0–20.0% (Kessler *et al.*, 1993), asthma 3.7–8.4% (Kwon *et al.*, 2003), epilepsy 0.4–1.0% (Yerby, 2000; Holmes *et al.*, 2004), and rheumatoid arthritis and other autoimmune disorders 1.0–2.0% (Belilos and Carsons, 1998). For some of these maternal conditions, a decision not to treat (or to undertreat) could lead to events, such as uncontrolled seizure activity or psychiatric episodes, that could be detrimental to the woman, the pregnancy, and/or the fetus itself (Goldberg and Nissim, 1994; Bracken *et al.*, 2003; Cohen *et al.*, 2006). Thus, the development of adequate information on drug safety in pregnancy involves two equally important objectives: the identification of potentially harmful exposures that might be avoided or managed, and the establishment of acceptable margins of safety for drugs that offer potential benefit to women during their pregnancies.

## **PREMARKETING SOURCES OF DATA REGARDING REPRODUCTIVE AND DEVELOPMENTAL SAFETY OF PRENATAL DRUG EXPOSURES**

The traditional methods for evaluating drug safety in the premarketing phases of drug development (i.e., animal reproductive and developmental toxicity studies and randomized clinical trials) have limited application with respect to human pregnancy.

Reproductive and developmental toxicity studies conducted in selected animal species provide the first source of information about potential human risks for a variety of pregnancy outcomes. Results of these experiments are considered in the context of existing knowledge about the reproductive or

developmental effects of similar chemical entities and the presence or absence of any theoretical concerns due to the drug's mechanisms of action or pharmacologic properties. On the basis of this overall evaluation, a new drug can be marketed with reassurances that the animal data do not raise concerns about human pregnancy exposure or, conversely, with the recommendation that, until human data are available, pregnancy should be avoided (Moore *et al.*, 1995). However, there can be differences in the sensitivity and human comparability of the various animal species that are selected for toxicity testing; there may be differences in the dose, route of administration, and metabolism in the animal model relative to usual human clinical use; and maternal toxic effects in the test species may play a role. For these and other reasons, there are limitations to the predictive value of these preclinical studies for human pregnancy exposures and outcomes (Brent, 1986; Scialli *et al.*, 2004). Thus, human pregnancy data are ultimately necessary to establish human pregnancy drug safety.

Clinical trials are the second traditional method of evaluating drug safety. For obvious ethical reasons, pregnant women typically are not recruited for trials during any phase of drug development. If and when unintended pregnancies occur during the course of a trial or postmarketing study, pregnancy outcomes can provide useful preliminary information regarding the risks of exposure (O'Quinn *et al.*, 1999). However, these data usually involve a small number of subjects. There is a trend to include larger numbers of women of childbearing age in clinical trials, and this will undoubtedly result in a larger number of exposed pregnancies in such trials. Nevertheless, these numbers are likely to be too small to provide meaningful information.

## **POSTMARKETING SOURCES OF DATA REGARDING REPRODUCTIVE AND DEVELOPMENTAL SAFETY OF PRENATAL DRUG EXPOSURES**

Once a medication is marketed, there are many resources that can provide observational data regarding drug safety in pregnancy.

1. *Clinician case reports* published in the medical literature can delineate a phenotype in an affected infant born to a mother with a specific prenatal medication exposure. However, these reports must be initiated spontaneously and, therefore, may involve investigator as well as publication bias. Furthermore, without a known denominator of exposed pregnancies that do or do not result in infants with the specific malformation, it is difficult to determine if the reported defect(s) represent an increase over baseline. If the phenotype is sufficiently unique (e.g., the isotretinoin embryopathy – Lammer *et al.*, 1985), then a series of case reports can strongly suggest a hypothesis that can be confirmed using other methods.

2. *Centralized adverse event reporting systems* (AERSs) can provide a systematic method for the accumulation of case reports from a variety of resources. For example, under the US FDA's AERS, manufacturers and distributors of FDA-approved pharmaceuticals are mandated to report events such as congenital anomalies as they are reported to them or are published in the scientific literature, in association with prenatal exposures to their drugs. The FDA receives additional reports through the MedWatch program, an educational and promotional effort, which facilitates spontaneous reporting from healthcare providers (Kessler, 1993; Goldman and Kennedy, 1998). And finally, consumers may provide information to the manufacturer or directly to the FDA.

One advantage of such systems is that reports can be accumulated from a variety of resources in a timely fashion. Although these systems have typically not been fruitful in terms of identifying new human teratogens, once a possible teratogenic exposure has been identified through other methods, these systems have been useful resources for exploring the specific characteristics surrounding exposed and affected pregnancies. For example, the angiotensin II converting enzyme (ACE) inhibitor fetopathy, which includes a unique pattern of renal tubular dysplasia and hypocalvaria occurring in association with second or third trimester use of one of the drugs in the ACE inhibitor group, was first reported by a clinician (Pryde *et al.*, 1993). However, the frequency of similar or related abnormalities in relation to gestational timing of

exposure and dose of the drug was identifiable through review of a series of 110 ACE inhibitor adverse event reports submitted to the FDA through 1999 (Tabacova *et al.*, 2000). Similarly, case reports and cohort studies that identified the increased risk for a variety of neonatal complications with late pregnancy exposure to some antidepressants (Spencer, 1993; Chambers *et al.*, 1996) have been confirmed and classified into possible pathogenetic subtypes using adverse event reporting data (Moses-Kolko *et al.*, 2005; Sanz *et al.*, 2005).

The primary limitations of such systems are similar to those of case reports appearing in the medical literature. Reports must be initiated spontaneously, which may involve bias in the types and number of actual events that are reported as well as an erosion in the motivation to report these events the longer a product is on the market. Spontaneous reporting systems rely on the "prepared mind" to make a link between medication exposure and pregnancy outcome, a link more likely for outcomes normally rare and extremely severe and less likely for outcomes considered common or with subtle presentation. In addition, adverse event reports do not provide denominator information on the number of exposed, affected, or unaffected pregnancies that could be used to develop a birth prevalence rate for purposes of comparison with baseline rates for a specified outcome in the general population.

3. *Pregnancy drug exposure registries* have been one method of evaluating drug safety in pregnancy dating back to the Swedish lithium registry established in 1962 (Schou *et al.*, 1973). Similar manufacturer-sponsored registries have been successfully completed for fluoxetine (Goldstein *et al.*, 1997) and acyclovir (Andrews *et al.*, 1992; Preboth, 2000), whereas several others are presently ongoing. A current listing is available on the US FDA's website (<http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm>). All traditional pregnancy registries involve spontaneous reporting of exposed pregnancies. The collection of exposure and outcome data is usually accomplished through the healthcare provider who initiates contact with the registry; however, in some registry designs, exposure and outcome data are collected from the preg-

nant woman herself. Although pregnancy outcome reports can be collected retrospectively, most current drug registries also identify and follow exposed pregnancies prospectively; that is, ascertain women during gestation, and collect exposure and other information before the known outcome of that pregnancy. In these cases, the registry may be considered a targeted follow-up study. The registry approach has many advantages, including timely and centralized ascertainment of exposed pregnancies that can parallel prescribing practices for newly marketed medications. Particularly if the exposure is rare, this may be the most efficient method for collecting pregnancy outcome data as quickly as possible. Industry-sponsored registries can utilize the existing mechanism of pregnancy exposures and events that are reported to the sponsor's medical information departments both nationally and internationally to more efficiently identify potential registry participants (Shields *et al.*, 2004). The registry approach when used to accumulate prospective reports can provide good-quality information about the temporal association between exposure and outcome. In addition, prospective registry designs provide a defined denominator of exposed women that facilitates comparisons of congenital anomaly rates with those of a reference group.

These registries generally have the ability to detect a meaningful increase in the overall frequency of major congenital anomalies that are evident at birth relative to the overall birth prevalence of major congenital anomalies in the general population (Koren *et al.*, 1998; White and Andrews, 1999; Shields *et al.*, 2004). Especially for high-risk teratogens such as isotretinoin or thalidomide, such an approach is arguably the most efficient, cost-effective, and timely method for identifying such agents quickly. For high-risk teratogens associated with a characteristic and frequently occurring pattern of major congenital anomalies recognizable at birth, only a small number of exposed pregnancies is necessary to infer potential teratogenicity (Koren *et al.*, 1998).

However, in the broader sense of pharmacovigilance for human teratogenicity, there are several limitations of the traditional pregnancy registry approach. As these studies depend on spontaneous

reporting of exposed pregnancies, selection bias may be involved. It is also difficult to project sample sizes. Even with successful identification and recruitment of a high proportion of all exposed pregnancies occurring in the population, the absolute number of exposed pregnancies in the registry, and/or the specific timing of those exposures in gestation, is unlikely to provide sufficient power to rule out or identify any but the most dramatic increased risks of specific congenital anomalies. This is of particular concern in that most known human teratogens are associated with increased risks for specific patterns of birth defects and other adverse outcomes rather than an increase in all birth defects across the spectrum.

Thus, an important function of a typical pregnancy registry is to generate hypotheses on the basis of "signal" detection when higher than expected numbers of specific malformations are reported, with additional studies required to confirm or refute the signal (Chambers *et al.*, 2006).

Other limitations of traditional pregnancy registries include the difficulty in identifying an appropriate comparison group. Many registry designs do not include a registry-specific comparison group. Instead, outcomes in exposed pregnancies are frequently compared with externally derived reference rates for the general population. Depending on the characteristics of exposed pregnant women who are included in the registry, the use of external reference statistics, without the ability to adjust for possible confounding, may not represent the most appropriate comparison. Some registry designs do involve recruitment of an internal comparison group with collection of information on potential confounders so that comparisons can adjust for differences between groups (Scialli, 1999). Other registry designs that involve multiple drugs used for the same disease can address this problem in part by comparing pregnancies with the exposure of interest to pregnancies with exposure to other medications used for the same disease (Scialli, 1999; Holmes *et al.*, 2004). Another approach is that used by the Antiretroviral Pregnancy Registry. In this design, pregnancies with first-trimester exposure to the drugs of interest are compared with pregnancies in which exposure did not begin until the second or third trimester (Watts *et al.*, 2004).

Finally, as registries typically rely on a wide variety of individual healthcare providers and/or mothers themselves to report pregnancy outcome, there is a potential for the misclassification of outcomes such as major congenital anomalies with respect to accurate and complete diagnosis and/or suspected etiology (Honein *et al.*, 1999). Furthermore, subtle or less easily recognizable teratogenic effects, such as the fetal alcohol syndrome or the minor structural abnormalities that comprise the anticonvulsant embryopathy, are unlikely to be identified by the obstetrician or general pediatrician who is reporting outcomes to a registry. In addition, especially when the healthcare provider is the primary source of registry information, there is concern that a substantial proportion of pregnancy exposure reports will be lost to follow-up, thereby potentially biasing conclusions that can be drawn from registry data.

In recent years, with the increasing number of pregnancy registries established by industry sponsors as part of postmarketing commitments or initiated by other groups interested in generating pregnancy safety data, the US FDA has produced a guidance document (US FDA Office of Women's Health, 2002) that establishes principles for the design and conduct of pregnancy registries. The guidance document is intended to improve and standardize the overall quality and ultimate value of the data collected through pregnancy registry methods. In addition, a second Center for Drug Evaluation and Research (CDER) guidance document sets standards for reviewers who are evaluating human data on the effects of *in utero* drug exposure on the developing fetus (US FDA Office of Women's Health, 2005). Taken together, these guidelines provide a framework for the collection and interpretation of pregnancy exposure and outcome data that can contribute to consistency and improved quality in the collection and evaluation of safety data generated through pregnancy registries.

4. *Birth defects monitoring or surveillance systems* are designed to provide population- or hospital-based identification of congenital anomalies to measure trends and to respond to unusual clusters of events. At this level of information gathering, if an upward trend in the birth prevalence of a certain

defect or a time-related cluster of an unusual pattern of defects coincides with the widespread use of a new medication, then surveillance programs can function as an early warning system (Khoury *et al.*, 1993). Because an unusual pattern of congenital anomalies may occur with extreme rarity within any one surveillance system, these efforts are enhanced by collaborations such as the International Clearinghouse of Birth Defects Monitoring Systems, which has been in existence since 1974 (Erickson, 1991; Khoury *et al.*, 1994a).

5. *Birth defects case-control studies* can be classified into one of the two general approaches. The first group might be termed classical hypothesis-testing case-control designs, whereas the second involves ongoing case-control surveillance for drug-induced congenital malformations.

Using the first design, cases and controls are identified with the specific intent to measure the association between a risk factor and a specified birth defect or group of defects. This approach requires that *a priori* decisions be made regarding the research questions, selection of the appropriate control group, and adequate power and sample size. For example, based on concerns raised in the literature, this design was successfully used to document an association between congenital facial nerve paralysis, or Möbius's syndrome, and first-trimester use of misoprostol (Pastuszak *et al.*, 1998).

The second approach, case-control surveillance, is not based on a predefined set of hypotheses but is instead focused on gathering a broad range of exposure and potential confounder information for malformed cases and controls over an indeterminate period to create a large repository of data suitable for testing multiple future hypotheses. This approach has been incorporated into some birth defects monitoring programs in the USA and is the general design of the US National Birth Defects Prevention Study (Carmichael *et al.*, 2006). These methods are also used on an ongoing basis in programs such as the Sloane Epidemiology Center's hospital-based surveillance study based at Boston University (Mitchell *et al.*, 1981; Hernandez-Diaz *et al.*, 2000), the Latin American Collaborative Study of Congenital Malformations that involves over 70 hospitals in several South American countries (Castilla and Peters, 1992), and the population-

based Hungarian Congenital Malformation Registry (Czeizel *et al.*, 2000). These programs usually involve ascertainment of malformed cases as well as systematic sample selection of non-malformed infants who can be used as controls. Exposure and other risk-factor information is generally gathered by postnatal maternal interview either in person or by telephone and, in some cases, is supplemented by review of medical records or pregnancy log books. In addition, some designs have incorporated DNA sampling and banking from case and control children and their parents so that future hypotheses regarding genetic susceptibility or gene-environment interaction can be tested.

The primary advantage of any case-control approach in studies of rare events such as congenital anomalies is the enhanced power to detect or rule out a meaningful association for a given sample size. In contrast to pregnancy registries or other prospective designs, this method is often the only appropriate approach for detecting moderate or low-level teratogenic exposures associated with specific major malformations. Furthermore, to the extent that case-control surveillance studies collect comprehensive information on potential confounders, including vitamin use, tobacco, and alcohol, this approach can provide reassurances that moderate effect sizes are not attributable to these other factors. Other advantages of case-control surveillance include, to a varying degree, relatively complete ascertainment of the congenital anomalies of interest within a defined population, concurrent selection of controls from the same population, and the ability to validate the classification of diagnoses.

In addition, this approach provides flexibility in the ultimate use of the data; that is, based on specific research questions, subsets of cases and controls can be selected from the entire data set to test or confirm specific hypotheses. For example, this method was useful in confirming the protective effect of antenatal folic acid supplementation in reducing the incidence of neural tube defects (Werler *et al.*, 1993) and in refuting a previous finding of an association between maternal loratadine use and the genito-urinary tract anomaly hypospadias (CDC, 2004). Furthermore, case-control

surveillance data are amenable to hypothesis generation. For example, these data were used to first raise the question of an association between pseudoephedrine and gastroschisis (Werler *et al.*, 1992).

The limitations of case-control studies of any type generally relate to the use of retrospective data collection and the selection of controls. For example, maternal interviews may be conducted in some cases many months after completion of the pregnancy, which raises the possibility, although controversial, of limited recall of early pregnancy medication use (Tomeo *et al.*, 1999). In addition, the potential for serious differential recall bias among mothers of malformed infants relative to mothers of non-malformed controls has been cited by some (Khoury *et al.*, 1994b), whereas the potential bias associated with the use of malformed controls has been suggested by others (Prieto and Martinez-Frias, 2000). With respect to the use of appropriate controls, case-control surveillance studies have the advantage of flexibility in the selection of one or multiple control groups, malformed or not, from the larger data set as judged necessary for any specific analysis.

Because case-control surveillance programs are ongoing, they have the potential to recognize an association with a newly marketed medication; however, they may have limited sensitivity in this regard. These studies may miss an association if the medication of interest is related to a relatively unusual or uncommon congenital anomaly and/or that specific defect is not included in the range of selected anomalies for which maternal interviews are conducted. In addition, if new medications are infrequently used among pregnant women, then weak or moderate associations may be difficult to detect. However, for medications that are more commonly used – for example, by 1% or more of pregnant women – given the rarity of congenital anomalies in general, these approaches provide a relatively powerful method of hypothesis testing and hypothesis generating and can be effectively used alone and in conjunction with other methods.

6. *Large cohort studies* can involve open cohorts that are population based and ongoing or can be hospital or health insurer based and/or of limited duration. For example, the Swedish Registry of Congenital Malformations in combination with the

Swedish Medical Birth Registry encompasses nearly all births in Sweden and utilizes exposure interviews conducted by midwives during the first trimester of pregnancy as well as data recorded prospectively in medical records (Ericson *et al.*, 1999). The Collaborative Perinatal Project conducted in the 1960s was a study involving over 50 000 mother-child pairs identified at multiple sites throughout the USA (Chung and Myriantopoulos, 1975). Similar large longitudinal cohort studies, each to some extent addressing risk factors for congenital anomalies, have recently been initiated in other countries, such as Denmark and Norway (Olsen *et al.*, 2001; Nordeng *et al.*, 2012), and are in the process of being organized in the USA under the auspices of the National Children's Study (<http://www.nationalchildrensstudy.gov/>).

These studies have the advantage of large and representative sample sizes, prospective ascertainment of exposure information, and data regarding a variety of potential confounders and ability to collect outcome information over a long term of follow-up. In addition, women with and without the exposure of interest are concurrently enrolled as members of the cohort, facilitating the identification of one or more appropriate reference groups. Like ongoing case-control designs, studies of this type can address multiple hypotheses that need not be formulated *a priori* (Irl and Hasford, 2000).

However, even in large cohort studies, issues of sample size can be a limitation. For example, the Collaborative Perinatal Project had inadequate power to detect weak to moderate associations with any but the most common major congenital malformations and the most commonly used drugs due to the relatively small numbers of women exposed to most specific medications of interest. By contrast, the Swedish Registry with approximately 120 000 annual births, accumulated over more than a 25-year span, has enhanced power to identify these associations, assuming the frequency of exposure in pregnant women is sufficient to test such hypotheses. For example, using the Swedish data, Kallen *et al.* (1999) were able to identify over 2000 first-trimester inhaled corticosteroid (budesonide)-exposed pregnancies and rule out with acceptable confidence an increased risk in overall rate of major congenital anomalies. However, the numbers of

exposed and affected infants were too small even in this relatively large cohort to address the hypothesis of an increased risk for oral clefts, which is the specific type of major congenital malformation that has previously been associated with maternal systemic corticosteroid use and is, therefore, of theoretical concern.

7. *Small cohort studies* focused on specific medications have been conducted by Teratology Information Services (TIS) both in North America and in Europe. These studies draw on a base of callers who contact a TIS seeking counseling regarding the safety of a medication used in pregnancy. Follow-up of pregnancy outcome is obtained for selected exposures. These studies have strengths similar to the registries described above with respect to the potential for rapid identification of exposed women, particularly for a new drug, as well as prospective collection of exposure and other risk factor information. TIS studies usually employ a concurrently enrolled unexposed control group, often both a disease-matched and a non-diseased group, which may provide the most appropriate reference groups in this context.

Similar to traditional pregnancy registries, the primary limitation of TIS studies relates to sample size. Individual TIS sites either independently or in collaboration have published studies typically involving between 100 and 200 exposed subjects (Pastuszak *et al.*, 1993; McElhatton *et al.*, 1999). Also, similar to pregnancy registry designs, TIS studies rely on spontaneous callers for the recruitment of subjects that may result in selection bias.

In an effort to increase sample size and to shorten the time needed to identify a given number of exposed pregnancies, collaborative projects among networks of TIS sites in North America are conducted through the Organization of Teratology Information Specialists (OTIS) (Scialli, 1999) and in Europe through the European Network of Teratology Information Services (Vial *et al.*, 1992; Schaefer *et al.*, 1996). These formal collaborations can add to the variability and possibly the representativeness of subjects in the sample and increase the obtainable sample size by drawing on a larger population of potentially exposed women. However, even these studies, similar to other cohort studies with moderate sample sizes, usually are only suffi-

ciently powered to detect or rule out very large increased risks of specific major congenital anomalies associated with exposures.

The primary strength of TIS studies is the ability to evaluate a spectrum of pregnancy outcomes following a given exposure, including major congenital anomalies, spontaneous abortion and stillbirth, preterm delivery, pre- and postnatal growth deficiency, and, in some cases, longer term child development. In this context, although underpowered to evaluate rare outcomes, these studies can be useful for generating hypotheses that can be tested using other methods. Furthermore, in some OTIS and individual TIS designs, exposed and comparison children are systematically evaluated for a pattern of both major and more subtle minor congenital anomalies (Chambers, 2011). This additional level of scrutiny can increase the sensitivity of this approach for the identification of a unique pattern of effects on fetal development (e.g., a pattern analogous to the anticonvulsant embryopathy) that might not be detectable through any of the other study methods available (Lyons Jones *et al.*, 1989; Chambers *et al.*, 2001; Lyons Jones *et al.*, 2002).

8. *Database linkage studies*, as technological advances permit, can offer many of the advantages of large cohort studies at potentially far less cost. Early efforts along these lines utilized the Michigan Medicaid database, a government health insurance program within which maternal prescription records could be linked to pediatric billing records to identify children born with and without congenital anomalies (Rosa, 1999). Similar approaches have been used successfully elsewhere in North America and Europe. For example, investigators in Denmark have linked prescription database records to hospital discharge and medical birth register records for children with and without congenital anomalies to investigate the safety of a widely used antibiotic (Larsen *et al.*, 2000). In countries where there is universal and standardized healthcare delivery and record keeping, or in countries where healthcare maintenance organizations or other large membership-based providers serve a significant proportion of the population, linked prescription and birth records provide an attractive alternative method for testing hypotheses regarding drug safety in pregnancy. For example, hospital dis-

charge data across the Canadian population have been used to evaluate adverse outcomes of pregnancies complicated by asthma (Wen *et al.*, 2001). This approach has also been used successfully to evaluate pregnancy exposure to clarithromycin using longitudinal claims data for members from 12 geographically diverse United Health Group-affiliated insurance plans (Drinkard *et al.*, 2000). Similarly, information from the Group Health Cooperative of Puget Sound in the USA has been used to examine the association between topical tretinoin (Retin-A) and major birth defects (Jick *et al.*, 1993). The General Practice Research Database in the UK is another potentially fruitful resource (Jick and Terris, 1997; Jick, 1999). Recent efforts to develop algorithms for accurately identifying pregnancies, exposure windows, gestational timing, and pregnancy outcomes utilizing this database hold promise for increased utilization of these existing resources to address hypotheses related to pregnancy exposures (Hardy *et al.*, 2004).

The primary advantages of large-linked databases are the availability of large numbers of subjects, the ability to establish temporal relationships between exposure and outcome by constructing an historical cohort, and the relative ease of access to previously collected medical, administrative, or claims data. This approach also avoids some of the biases involved in studies that rely entirely on maternal report to classify exposure, especially if that information is collected retrospectively.

These strengths must be weighed against the limitations inherent in a study design that does not involve subject contact. For example, these studies usually cannot insure that the medication prescribed was actually taken by the mother, taken in the dose prescribed, or taken during the period critical for the development of any specific birth defect. With respect to specific outcomes, the validity of linked databases may vary by database and by type of outcome (Andrade *et al.*, 2012). To remedy this limitation, some database analytic designs involve the validation of a subset of records through other methods such as chart review or maternal interviews. There are also issues related to the misclassification of outcome depending on the quality of records used to determine or exclude the diagnosis of a congenital anomaly. Again, this limi-

tation is not insurmountable if recognized and if it is possible to incorporate some level of validation (Ehrenstein *et al.*, 2010).

In addition, similar to large cohort studies, even databases containing hundreds of thousands of patient records may have limited power to test drug-specific hypotheses due to relatively small numbers of pregnant women exposed to any particular drug. Furthermore, for low- to moderate-risk teratogens, large-linked databases often do not have immediate access to information on potentially important confounders such as maternal exposure to tobacco, alcohol, vitamins, and over-the-counter medications. However, databases can be a relatively efficient method for surfacing and testing hypotheses related to prescription medications; therefore, these studies hold significant promise for the future.

## **MONITORING FOR PREGNANCY EXPOSURES AND PREGNANCY PREVENTION FOR KNOWN HUMAN TERATOGENS**

For well-recognized potent human teratogens, pharmacovigilance efforts may also encompass the monitoring of unintended pregnancy exposures to evaluate and inform methods for improving pregnancy prevention. An example of one such effort is the STEPS program (System for Thalidomide Education and Prescription Safety), which is intended to prevent pregnancy exposures to thalidomide (<http://www.celgene.com/>). Using a comprehensive system of drug dispensing through registered clinicians and through registered pharmacies, as well as careful education and monitoring of women who are treated with thalidomide and have the potential to become pregnant, this program has to some extent allowed a known high-risk teratogen to be marketed in the USA for the first time.

Similarly, isotretinoin, another high-risk teratogen, has been monitored for many years, initially through the Pregnancy Prevention Program, which was superseded in some regions with the expanded SMART program (System for Management of Accutane Related Teratogenicity). As of March 2006, in the USA, this effort has been increased to

a level in many respects comparable to the thalidomide prevention program. The iPLEDGE risk-management program is aimed at preventing the use of isotretinoin during pregnancy. To obtain the drug, in addition to registering with iPLEDGE, patients must comply with many key requirements that include completing an informed consent form, obtaining counseling about the risks and requirements for safe use of the drug, and, for women of childbearing age, complying with necessary pregnancy testing and birth control methods (<https://www.ipledgeprogram.com/>). As part of iPLEDGE, pharmacovigilance for pregnancies that may occur despite the enhanced prevention program will contribute to the evaluation and improvement of these efforts to maintain access to the drug while preventing these high-risk exposures. No information on the success of this program has been made publicly available as of the writing of this chapter.

Upon the enactment by Congress of the FDA Amendments Act of 2006, the FDA has had the authority to require sponsors to conduct a risk evaluation and mitigation strategy (REMS) to manage risks of certain products (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>). As noted in Chapter 12, a REMS may include a medication guide aimed at providing information directly to patients, a communication plan that may involve targeted education to health providers and patients, and/or elements to assure safe use (ETASU), which may impose restrictions on medication access. The STEPS and iPLEDGE programs are examples of ETASU REMS programs. Other programs that include ETASU elements aimed at minimizing exposure in pregnancy include the programs for bosentan and ambrisentan for pulmonary arterial hypertension, and lenalidomide for multiple myeloma and myelodysplastic syndromes. Other REMS programs, such as those for testosterone gels used to improve and maintain testosterone levels, and dronedarone prescribed for atrial fibrillation, include strong warnings in the patient medication guide to avoid exposure during pregnancy. Many REMS medication guides advise patients to tell their healthcare provider if they are pregnant before taking the medication; however, in most cases, these are for

REMSs aimed at safety issues not related to pregnancy or fetal risks.

## CHALLENGES FOR THE FUTURE

Existing methods of pharmacovigilance for medication-induced birth defects, taken individually or as a whole, are limited in capacity to recognize a potential teratogenic effect with a new pharmaceutical agent or, conversely, to provide reassurance that a new drug does not pose a substantial risk. These limitations are amplified if the drug is infrequently used by women of reproductive age, if the relative risk for congenital anomalies is not high, or if the associated birth defect(s) pattern is not unique, is difficult to diagnose, or is not likely to be recognized at birth. Existing methods also suffer from the need for large enough sample sizes and the costs associated with supporting studies that are adequately powered. One area of opportunity is improvement in the designs of premarketing reproductive toxicity studies. If the cross-species predictive value of these experiments can be increased, then it may be possible in the preclinical setting to accurately identify and avoid human pregnancy exposure to those agents that will be new teratogens (Moore *et al.*, 1995; Lau *et al.*, 2000; Selevan *et al.*, 2000). Another possibility for the future is to take advantage of the efficiency and cost effectiveness of large existing databases to “screen” for possible signals of major teratogenic effects of new and older medications. Potential for building on systems that involve more real-time signal detection for adverse drug events across multiple databases may hold promise in this regard (Beaulieu *et al.*, 2012). When strong signals are identified, other methods, such as case-control surveillance studies or small follow-up studies, might be appropriate for confirmation or refutation.

However, it is important to recognize that no single study design or methodology is sufficient to assure that new teratogens will be identified in a timely fashion or that medications that can be used relatively safely in pregnancy are also identified as quickly as possible. Therefore, a coordinated and systematic approach to evaluating new medications, both on a national and on an international

basis, could contribute to more effective pharmacovigilance for birth defects and provide information that is critically and urgently needed by clinicians and pregnant women (Olsen *et al.*, 2002; Mitchell, 2003; Schatz *et al.*, 2011). The coordinated and integrated use of existing ongoing resources, including adverse event reporting, large databases, population cohort studies, and case-control surveillance, along with the additional complementary information provided by pregnancy registries and small cohort studies, would require substantial efforts toward the harmonization of purposes and methods. However, a comprehensive systematic surveillance system offers far more promise for effective pharmacovigilance than the fragmented and often sporadic methods that are currently in place to evaluate drug safety for pregnant women and their infants. With the large number of prescription and over-the-counter medications used by pregnant women, a teratogen surveillance system that can adequately address these safety issues could substantially reduce the uncertainty around the safety of medications used during pregnancy.

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# Pharmacovigilance in Pediatrics<sup>1</sup>

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## BACKGROUND AND INTRODUCTION TO PEDIATRIC ISSUES

There are two very humane behaviors adults have that can or have resulted in poor outcomes for children. The first behavior is to give children medicines that have been developed for adults. Denying children needed therapy, because it has not been studied in children or has not been produced or marketed in a form which children can or will ingest, may not appear to be reasonable. Therefore, any therapy that becomes available for adults is likely to be used for the same or similar conditions in children, even when we have not studied the product in children, may not have a sound scientific

basis for establishing a dose (besides scaling down the dose on a weight basis), and have no understanding of how children may react differently than adults to the therapy. The second humane behavior is to protect our children from unknown and uncertain situations. This has also included “protecting” them from research even when the research may provide a potentially better therapy or access to a therapy not otherwise available.

As a result, the 20th century is replete with tragic stories of therapeutic misadventures involving children. By the end of the 20th century, children had essentially been left behind in the amazing pharmacologic advances of that era (Shirkey 1968; Wilson, 1999). In addition, if children are not studied in clinical trials, the adverse events defined during the trial are limited to adults. Therefore, most products do not have information on specific pediatric adverse events noted even though the product may be used extensively in the pediatric population. Another problem that is particularly

<sup>1</sup>The views expressed are those of the authors. No official support or endorsements by the US Food and Drug Administration is provided or should be inferred. No commercial interest or other conflict of interest exists between the authors and the pharmaceutical companies.

relevant to pediatric trials, which are often very small in size, is that even adult trials, involving many more patients, are not powered to detect adverse events, and safety profiles are very different for adults versus pediatric patients (Burkart *et al.*, 2011). Therefore, postmarketing safety assessments become even more critical to understanding the pediatric safety profile for a product being administered to children.

The impetus for the formation of the US Food and Drug Administration (FDA) has much to do with pediatric therapeutic disasters. The 1938 Federal Food, Drug and Cosmetic (FD&C) Act was passed after ethylene glycol, a solvent, and raspberry syrup, a sweet-tasting flavoring, were used by the manufacturer's chemist in an effort to market an elixir of sulfanilamide (FFDCA, 1938). The solvent caused renal failure, and many children died because of the chemist's efforts to provide a needed antibiotic to children in a formulation they would take. This act required demonstration of the safe use of a new drug product before marketing. The 1962 Kefauver amendments to the FD&C Act required that a product be proven not only safe, but also effective for the labeled indication (Drug Amendments, 1962). This amendment was partially a response to the thalidomide disaster. Although thalidomide was safe for the mother who took the product, it caused severe limb abnormalities (phocomelia) in the fetus. Another pediatric therapeutic disaster occurred when chloramphenicol therapy caused toxicity and deaths in infants (i.e., gray baby syndrome). This occurred because physicians were not aware that neonates and infants were unable to metabolize chloramphenicol adequately. These examples, which demonstrate the lack of pediatric-appropriate preparations, knowledge regarding teratogenicity, or the understanding of the need for appropriate dosing modifications in certain pediatric subpopulations, highlight the problems that still exist today.

Despite urging in 1977 and 1995 from the American Academy of Pediatrics, Committee on Drugs (1977, 1995) that the continued use of untested therapies in the pediatric population was essentially unethical, as it subjected children to a never-ending experiment where little was learned, most products continued to be developed and studied only in adults. Few studies were being performed to answer

the dosing and safety issues associated with pediatric use of a product (Wilson, 1999).

At the very end of the 20th century, the US Congress passed legislation that changed the world of pediatric drug development (Federal Register, 1992, 1994; FDAMA, 1997; Federal Register, 1998; PREA, 2003; FDAAA, 2007). In 2012 Congress made this legislation permanent. This now means that pediatric product development is no longer an "add-on" or after thought, but part of the routine development of products. In addition, the FDA had put into place a series of efforts to encourage pediatric drug development and assessments. A number of the FDA's regulatory efforts were also incorporated into legislation. The main components of these changes were as follows:

- 1 An incentive of six additional months of marketing exclusivity for products studied in response to the FDA issuance of a document called a Written Request for pediatric studies.
- 2 The requirement that the sponsor of a product being studied in adults, that would have the same use in children, also conduct and submit pediatric studies or a plan with timelines.
- 3 The concept of extrapolation of pediatric efficacy data from adult efficacy data, provided the disease and the response to therapy in children and adults are sufficiently similar to permit this approach, was introduced into regulation. If this approach is utilized to establish efficacy, other studies to define dosing and safety in the pediatric populations are mandated. The FDA published a review of a decade of using this concept in pediatric trials in 2011 (Dunne *et al.*, 2011).
- 4 It has been recognized that most pediatric studies performed for the intent of satisfying requirements for any of the above-mentioned legislative initiatives are not likely to be replicated nor other indications be sought. Therefore, this information should be publicly available. Since 1997, study results from trials conducted in response to the FDA's Written Request are posted in summary form on the FDA's website (FDA, 2012). This summary is made public irrespective of the approval status of the application. This did not occur for pediatric studies conducted in response to legislative requirements until 2007.

An assessment of safety information identified in FDA reviews and compared with published literature found that safety reporting may be biased and more favorable in the peer-reviewed articles (Smith *et al.*, 2008). In 2007, the FDA Amendments Act required information to be placed in labeling for all studies conducted under the legislation and that the complete scientific reviews of the medical officer, pharmacologist, and statistician be made available to the public. The FDA posts these reviews on its website.

5 A specific focus on monitoring postmarketing pediatric adverse events was established in 2002 and expanded in 2007. Many new products have been and will be studied in pediatrics. The adverse events are to be provided to the Office of Pediatric Therapeutics, and a review is to be presented to the Pediatrics Advisory Committee. Their recommendations are obtained on any necessary actions. The review of products assessed under this program and the recommendations by the pediatric advisory committee can be accessed via the FDA's website (FDA, 2013).

### **WHY A SPECIAL FOCUS ON POSTMARKETING SAFETY REPORTING IS NECESSARY FOR PEDIATRICS**

In addition to reasons outlined in other chapters of this book as to why some safety issues are not identified until after a product has been approved and on the market (postmarket), there are seven aspects of pediatric drug development and use that contribute to the probability a safety signal may not be identified in the pediatric population until postmarketing.

- 1 The first of these aspects is the relatively small number of pediatric patients who are often involved in pediatric trials. There are fewer patients affected with pediatric diseases or conditions, and trial designs reflect this pragmatic recognition of what is reasonable to expect versus what may be ideal.
- 2 Children are less frequently involved in early phase 1 pharmacokinetic and safety and phase 2 dose-finding and safety studies. This means

development of larger phase 3 pediatric trials may be based on information obtained in adults and some pharmacokinetic studies in pediatrics.

- 3 There is intrinsic variation that exists across pediatric age groups. Product development programs in pediatrics specifically focus on attempting to identify appropriate changes in dosing due to differences in absorption, metabolism, distribution, and elimination in the various pediatric age groups. As a result of these differences, one subpopulation of pediatrics may be more or less likely to experience higher levels and/or differences in response to a therapy. Again, because the numbers become very limited when dealing with a subpopulation in pediatrics, it becomes even more difficult to ascertain the real frequency of an adverse event prior to its use in a larger postmarketing population.
- 4 There is extensive off-label use of products within the pediatric population. This off-label use encompasses both use in pediatric subgroups that have not been studied for an indication obtained in one pediatric subgroup, and for other indications that have not been studied in any or most pediatric subgroups, but are marketed for adults.
- 5 Children have unique exposures through prenatal (*in utero* exposure) and breast milk. Breast-milk exposures are not routinely evaluated for effects on the child. Animal models are utilized to attempt to determine teratogenicity of a product but have limitations as to identification of long-term outcomes not associated with being a teratogen.
- 6 Because of a lack of pediatric-appropriate formulations, there is frequent use of compounded or extemporaneous preparations that are usually not tested for bioavailability or drug-drug and drug-food interactions and may contain excipients with unknown risks, thereby increasing the potential for errors in dosing, delivery, and adverse events.
- 7 The growing and evolving nature of children requires attention to potential effects on physical growth, puberty, cognition, and other developmental parameters. Most studies in children are directed to defining the safety and efficacy of a product for a condition during a certain age or

development time frame. No one realistically expects that one can study all the possible adverse effects a product used at one stage of development may have on all latter stages of a child's development. Recognizing a product may have delayed effects on growth, puberty, behavior, development, and cognitive abilities, there is a clear need to develop focused, long-term studies and surveillance that involve follow-up directed at answering questions regarding the potential longer term effects of some therapies. All of these pediatric-unique issues increase the need for specific, focused, active postmarketing pediatric surveillance systems.

## **SAFETY REPORTING OF ADVERSE EVENTS REPORTED TO FOOD AND DRUG ASSOCIATION**

The FDA has developed a thorough approach for the review and report of pediatric adverse events. The pediatric-focused safety review includes an analysis of all adverse events reported to FDA's adverse event reporting system (AERS) during the year after the product has been labeled with new data from pediatric studies. This labeling then triggers the mandated safety reviews. In addition, all pediatric serious adverse events and deaths since marketing of the product for adults are assessed and evaluated as appropriate to further enrich the 1-year pediatric assessment (Johann-Liang *et al.*, 2009). An assessment is also made of how much the drug is used in the pediatric population. In addition, published literature, summaries of the clinical, pharmacology, and statistical reviews, the trials conducted for exclusivity, and the product's labeling are reviewed to prepare a safety analysis for the Pediatric Advisory Committee. There have been situations where the above process has led to more questions. Additional studies of the product that have been submitted to the agency are then reviewed and other known studies that have been conducted but *not* submitted to the agency may also be requested for submission and review.

From June 2003 through September 2011, there have been 15 Pediatric Advisory Committee meetings to review the safety analysis of 172 products.

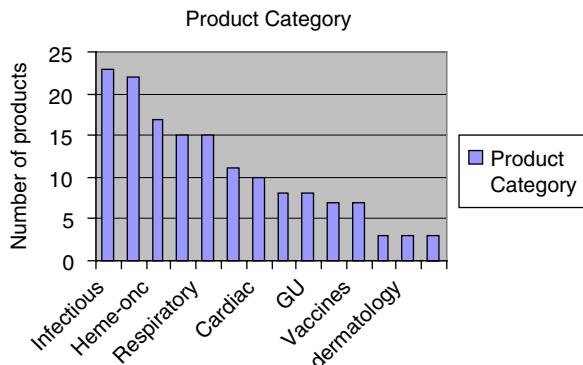


Figure 41.1 Pediatric safety reviews by therapeutic drug categories, June 2003 through September 2011.

Several therapeutic categories of products have been involved (see Figure 41.1). For the majority of products there were no safety signals identified and labeling appeared adequate. However, in 40 (23%) products the committee recommended new labeling changes to better describe safety issues.

## **PEDIATRIC SAFETY REVIEWS BY THERAPEUTIC DRUG CATEGORIES**

Examples of important safety concerns for different drug products that evolved as a result of the mandated pediatric safety reviews are:

- 1 Opioid transdermal systems associated with misuse and deaths or serious adverse outcomes.
- 2 Selective serotonin reuptake inhibitors (SSRIs) associated with neonatal withdrawal syndrome following prenatal exposure.
- 3 Antidepressants and an association with suicidality reports that were only confirmed by the reanalysis of the controlled pediatric clinical trials submitted to the FDA for pediatric exclusivity.
- 4 Stimulants used to treat attention deficit hyperactivity disorder (ADHD) and postmarketing reports of psychiatric and cardiovascular adverse events.
- 5 Non-psychotropic drug products with reported behavioral and neuropsychiatric adverse events: Ditropan and Tamiflu.

- 6 Topical hormonal product with inadvertent secondary exposure to children. Androgel (topical testosterone gel) resulting in severe adverse events in young children, including precocious pubertal development with enlarged genitalia and virilization, advanced bone age, and aggressive behavior. In some cases clitoral reduction surgery occurred.
- 7 Atypical antipsychotics with metabolic and endocrine effects that appear to occur more in children.
- 8 Proton pump inhibitors are used off-label in children <1 year of age. The need to better understand the use, dosing and safety, especially for neonates, infants, and young children.
- 9 As noted in the label, animal studies have shown a linear dose relationship in monkeys between dose and the rate of occurrence of malignancy, and transplant patients have demonstrated that systemic administration has been associated with an increased risk of infections, lymphomas, and skin malignancies.
- 10 Toxicity from active ingredients may occur, especially in young infants. Kaletra oral solution with alcohol and propylene glycol may be associated with neonatal toxicity, especially in preterm neonates.

### **WHY THE PEDIATRIC POPULATION MAY BE MORE VULNERABLE TO EXPERIENCING ADVERSE EVENTS FROM THERAPIES AND WHY THEY MAY GO UNRECOGNIZED**

The areas unique to pediatrics that increase the probability a child may experience either an adverse event or have the adverse event remain unrecognized are of four general types:

- 1 Differences in the disease process and/or physiology of drug disposition because of differences in maturational and developmental stages of the pediatric population.
- 2 Difficulties in determining an exposure in some earlier stage of childhood that has a delayed effect on later development or maturation.

- 3 Formulation issues, which may encompass preparations or medication errors because of extemporaneous or compounded preparations, and exposures to excipients not present in adult preparations.
- 4 Communication or recognition oversights because infants, small children, and mentally disabled children may not be able to articulate what is wrong and/or the carers assume it is part of the normal maladies that beset childhood development.

### **DIFFERENCES IN DISEASE PROCESS AND/OR DRUG PHARMACOKINETICS IN CHILDREN**

Children, by definition, are growing, maturing, developing, and acquiring skills and information. In addition, many enzymatic, endocrine, and metabolic systems and processes have yet to be expressed at the time the child is exposed to an infection or develops a condition and is given a therapy. A disease may not manifest itself in the same way in children as in adults. A high fever in children is more frequently associated with benign processes than a high fever in adults; adults are usually much more symptomatic when exposed for the first time to viral infections, such as hepatitis B. Children have high normal levels of hepatic enzymes and lower levels of creatinine than adults. To recognize the untoward effects of a therapy, one must know what is normal, and not all physicians and carers are aware of all of the differences in pediatric values for various laboratory tests at the different stages of pediatric development. Numerous studies now demonstrate that children at various ages are going to handle a product's absorption, distribution, metabolism, and elimination differently. Trileptal is an example where children younger than 4 years of age have an apparent increased clearance (liters per hour per kilogram) such that they may require twice the dose per body weight compared with adults. There have been a number of products where younger, preschool children have not cleared a product as rapidly as older children, and other products where the younger children have cleared the product more rapidly. Clearly, these differences can result in overdosing and an increase in adverse events or underdosing

and a failure to resolve the condition or benefit from the product, respectively.

#### ASCERTAINMENT OF DELAYED EFFECTS OF DRUGS ON GROWTH AND DEVELOPMENT

Children are maturing and changing over a time spectrum. It is difficult to know if any deviation from the normal process was going to occur independently of any exposure to a therapy. Children are “unfinished” by definition. Attribution of an exposure to a therapy as the cause of a delay/problem in growth, development, or cognitive abilities is often difficult. We know a certain percentage of the pediatric population would experience these problems/delays without any exposure to any therapy. It is difficult to ascertain if the child’s problem would have occurred without the exposure when the “baseline” was not yet established for that particular child. Confounding this issue is the possibility that an exposure in infancy or early childhood may not express the adverse effect until years later, when normally some other maturation event, such as puberty, was to occur. Long-term studies are not usual in pediatrics and are very difficult to “power” because there are so many unknowns for each child and there are many exposures occurring over a long duration of time.

#### PEDIATRIC FORMULATION ISSUES

Formulations are always a difficult pediatric issue. The excipients required to dissolve solids for liquid preparations or the materials used for sweetening or masking of unpleasant tastes may in themselves cause problems. Small amounts of alcohol may be tolerated in older children, but not by infants. Attempts to make pediatric formulations are usually expensive and difficult, and sponsors are not usually enthusiastic to develop these or to market them. Liquid preparations have a shorter shelf life also. Often, pharmacists, carers, and parents devise their own preparations. These preparations have usually not been tested for bioavailability or for interactions with the foods or liquids used to prepare them. Overdosing, underdosing, and an increase in frequency of medication errors

occur because of the lack of age-appropriate pediatric therapies.

#### UNIQUE ISSUES WITH RECOGNITION, COMMUNICATION, AND REPORTING OF ADVERSE EVENTS IN CHILDREN

Reporting of adverse events for pediatrics is “indirect” and generally involves intermediaries such as parents or carers. The younger the child, the fewer ways they can visibly react to an untoward effect of drugs. An infant’s repertoire of reactions is limited to physical expressions such as crying, somnolence, vomiting, and diarrhea, and cardiac and respiratory abnormalities. It is easy to see why only fairly impressive adverse effects would be identified by parents or carers for this population. The younger verbal child has a limited vocabulary to express their discomfort or pain. Because behavior is normally changing, parents may be confused or think a child’s behavior change is normal when it really is a reaction to a therapy. Even teenagers present a challenge, as we know communication with their parents is not always optimal. In addition, they may self-medicate and not want their parents to know they are taking certain drugs. All of these “normal” events or processes that occur in the pediatric population make ascertainment of adverse effects of therapies even more difficult than for the adult population. This is particularly relevant to being able to identify events postmarketing. Parents may not be provided information about what to look for during the usual therapeutic intervention, as they would be during the conduct of a trial.

#### DATA SOURCES FOR POSTMARKETING PEDIATRIC ADVERSE DRUG EVENTS

The main source of pediatric pharmacovigilance data is the spontaneous adverse drug event reports compiled by various regulatory agencies, one of the largest systems being the AERS database maintained by the FDA. AERS contains data for all ages, and FDA staff use the database for postmarketing drug safety surveillance and signal generation. Results of further evaluation of the signals may form the basis for regulatory action to improve

product safety and protect the public health, such as updating a product's labeling information, sending out a "Dear Health Care Professional" letter, or re-evaluating an approval decision. The signals may also generate a hypothesis about a drug and adverse event relationship that should be further assessed in formal epidemiological or clinical studies.

The limitations of these voluntary and spontaneous drug adverse event reporting systems are well recognized and adequately described elsewhere, but there are some unique aspects of use of drugs in pediatrics that contribute to these limitations, especially to underreporting in children. First, healthcare professionals may be less likely to report suspected adverse reactions for drugs that are unlicensed or used off-label (Blumer, 1999; Turner *et al.*, 1999; American Academy of Pediatrics, Committee on Drugs, 2002; Bush, 2003). Second, the practice of polypharmacy in the premature and sick neonate, often with unapproved and off-label drugs, adds another level of complexity that further hampers recognition and reporting by healthcare practitioners and consumers. Third, adverse drug reactions (ADRs) arising from *in utero* or breast milk exposures and manifesting during the neonatal period may be underreported because maternal history of pregnancy drug exposures is poorly documented or their potential contribution to neonatal problems is underappreciated. Fourth, delayed ADRs, especially those with a long latency, such as effects on growth, development, and cognition, are less likely to be recognized and reported. Fifth, possible drug adverse reactions may not be recognized because young children may be unable to describe their symptoms, and intermediaries such as parents and carers may fail to report them. The result is relatively few pediatric reports entering the AERS and a longer time period needed to build an adequate case series of postmarketing reports to perform a pediatric safety analysis.

The premarket evidence base for pediatric drug safety is limited for most approved drugs because few clinical drug development programs have included pediatric patients. Despite the absence of data to guide dosage, dosage frequency, route of administration, or appropriate formulation and evidence of clinical efficacy or safety, drugs are

commonly prescribed off-label to pediatric patients. These off-label uses constitute the collection of "*N* of One trials," outcomes that become the single most important source of information of ADRs in pediatric patients.

In recent years, US legislation and financial incentives to sponsors have led to increased clinical drug studies in children. These studies have resulted in useful data on a drug's pharmacokinetics, safety, and efficacy for pediatric labeling. However, these studies are often short in duration, include a small sample of selected patients, and are typically not powered for safety. Therefore, postmarket reporting of adverse events still continues to be the primary source of safety data for pediatrics. But there is increasing interest in going beyond the postmarketing spontaneous adverse event reports to assess the safety and effectiveness of drugs in the pediatric population.

Although the US requirement is for submission of periodic adverse drug experience reports (PADERs), the FDA grants waivers that allow firms to submit periodic safety update reports (PSURs) in place of PADERs after a new drug's approval for marketing. A separate and detailed safety analysis focused on pediatrics is currently a feature of the PSUR. The PSUR was designed to be a stand-alone document that allows a periodic but comprehensive assessment of the worldwide safety data of a marketed drug or biological product. The PSUR can be an important source of data for the identification of new safety signals, a means of determining changes in the benefit–risk profile, an effective means of risk communication to regulatory authorities, and an indicator for the need for risk management initiatives. Incorporating a requirement for a separate pediatric safety analysis as part of the PSUR submitted by sponsors will facilitate early detection and evaluation of possible safety issues.

In the USA, postmarketing drug adverse events surveillance data are available from sources other than spontaneous reporting systems, such as emergency department (ED)-based systems and epidemiologic data from automated claims databases. The National Electronic Injury Surveillance System (NEISS), which collects data on all injuries from a probability sample of EDs in approximately 100

hospitals, recently evaluated an active drug adverse event surveillance program using ED chart reviews in six sites (CDC, 2005). The results indicated that although the predictive value positive for ADRs was high, the sensitivity was low, suggesting the need for additional training of reviewers and coders in the recognition and reporting of suspected ADRs.

Another source of surveillance information is the Drug Abuse Warning Network (DAWN), whose data-collection procedures were modified in 2003 to include ADRs. This system collects data from a probability sample of short-term, general, non-federal hospitals and from medical examiners/coroners in 300 jurisdictions in 48 metropolitan areas, and it collects data on any drug-related visit irrespective of intent, including drug abuse, misuse, overmedication, intentional/accidental ingestion, and drug adverse reaction. DAWN and other drug adverse reaction data sources, such as the Toxic Exposure Surveillance System run by the American Association of Poison Control Centers, may benefit from an assessment similar to that done for NEISS with a focus on pediatric adverse drug events. All of the above systems have significant shortcomings (i.e., only severe cases are captured in EDs, claims databases collect information only from hospitalized patients enrolled in a particular health plan) and can only serve as a complement to existing postmarketing drug adverse event data systems. Pediatric diagnoses and coding also remain an issue.

Population-based, electronic medical record (EMR) database, and computerized administrative healthcare claims databases linked to drug utilization data and outcomes have been gaining popularity in evaluation of drug safety. Among the EMR databases, the largest and best known internationally is the General Practice Research Database (GPRD) maintained by the Medicines and Healthcare Products Regulatory Agency (MHRA) (Wood and Martinez, 2004). GPRD is a longitudinal EMR database that collects data on patient demographics, prescription drug use, diagnosis, treatment outcomes, and laboratory tests from a voluntary group of general practitioners who provide primary healthcare via the National Health Service through-

out the UK. Although GPRD has been used less in drug safety research in pediatrics than in adults, it has proven to be useful in the assessment of safety signals, drug usage patterns, and quantification of population risk of drugs, including those of rare outcomes. Because the data are collected prospectively and are longitudinally linked, GPRD can be particularly useful in evaluating pediatric drug adverse effects with long latency, such as adverse effects on growth, cognitive development, and neoplasia.

Other population-based databases consist of computerized insurance healthcare claims data which are commonly used for pharmacoepidemiology studies. These are organized at regional or healthcare setting level. The Saskatchewan Health Database (Downey *et al.*, 2000) is a regional database from Canada that contains linked data on prescription drug, hospital services, physician services, and vital statistics for all residents in one province in Canada. Healthcare setting-based databases in the USA are TennCare (state-based Medicaid program), the Kaiser Foundation database, the Harvard Pilgrim healthcare database (health maintenance organizations), HealthCore, databases maintained by Brigham and Women's Hospital system, and the University of Pennsylvania, who were awarded contracts for drug safety research by the FDA in 2010. Important limitations of these databases include the inability to study rare drug adverse events due to the small population size, and inability to study effects of newly marketed drugs due to formulary restrictions. These databases, although designed for administrative purposes, offer many opportunities for pharmacoepidemiology but remain underutilized for pediatric-specific drug safety evaluation and research. Again, pediatric-specific diagnoses and coding are often an issue in the larger databases established for adult populations.

The potential to identify and report suspected drug adverse events could be enhanced by the implementation of the requirement for EMRs for all patients. EMRs can also be useful in preventing serious adverse events by incorporating automated reminders about previous drug reaction history, drug-drug and drug-food interactions, dosage

adjustments, and new safety alerts. Until an EMR for all patients becomes a reality, postmarketing safety assessments will have to employ one or more of the available resources described above.

## **SAFETY SIGNAL DETECTION AND EVALUATION IN THE PEDIATRIC POPULATION**

The “pediatric population” encompasses preterm babies to adult-sized adolescents, and many aspects of drug disposition, efficacy, and safety profile differ over this age range, making attribution of safety data from adults to the pediatric population very problematic. Although drugs are used off-label, most have little or no pharmacokinetic data to support rational dosing in pediatrics. Even for those drugs that have had formal clinical studies in pediatric patients, the premarket safety assessments are limited by small numbers and being inadequately powered studies to evaluate safety. Therefore, postmarketing monitoring of drug safety in pediatrics largely falls on careful evaluation of spontaneous reports and, when possible, data from epidemiologic studies or sponsor conducted phase 4 post-approval studies.

Monitoring of postmarketing data has led to the detection of important drug adverse reactions that are unique to pediatrics. Examples include the use of ciprofloxacin in neonates and its effect on teeth (Lumbiganon *et al.*, 1991), valproic acid and liver toxicity (Dreifuss *et al.*, 1987), isotretinoin and depression/suicide (Wysowski *et al.*, 2001), as well as other examples cited elsewhere in the chapter. Continuous monitoring of spontaneous postmarketing reports supplemented by epidemiological data and data from phase 4 studies with a focus on pediatrics is critical to better define the risks of drugs in the pediatric population.

A pediatric safety signal may arise when the evaluation of spontaneously reported pediatric adverse drug events includes the following findings:

- 1 Serious and unexpected drug adverse events that are unique to pediatrics; that is, not described in the approved product labeling.

- 2 Serious drug adverse events that may be related to a labeled event but differ from the labeled event because of
  - i greater severity (hepatic necrosis vs. increase in liver enzymes or hepatitis in the labeling) and
  - ii greater specificity (cerebrovascular accidents versus cerebral thromboembolism or cerebral vasculitis).
- 3 A new high-risk pediatric subgroup for ADRs is detected arising from off-label use for an unstudied pediatric age group or indication.

Once a potential safety signal is detected, evaluation of the signal for possible causality is challenged by the limitations of passive reporting systems. Both the numerator (underreporting of adverse events) and the denominator (lack of good national estimates of pediatric drug exposures) are uncertain, and usual reporting rates calculated from these data can be misleading and difficult to interpret. The value of these calculations is further reduced by the lack of valid data on background incidence rates against which the calculated reporting rates are compared. Consequently, it is often not possible to measure excess risk unless the reported event of concern has a hard endpoint (e.g., death, liver necrosis) and it has a low background incidence rate in the general pediatric population.

## **ENSURING A FAVORABLE BENEFIT/RISK RATIO FOR MARKETED DRUGS USED IN PEDIATRICS: CHALLENGES FOR SURVEILLANCE OF DRUG ADVERSE EVENTS**

A product may be considered safe if it has an appropriate benefit–risk balance for its intended population and use. However, this balance is not static, as information on the benefits and risks emerges continually during the post-approval phase as more patients are exposed to the drug. These new data can reflect the results of both labeled and off-label uses (used in unapproved age groups and/or for unapproved new indications) which can shift the benefit–risk balance of drugs from favorable to unfavorable. Therefore, new information from

postmarketing surveillance data or studies revealing new safety signals or new benefits (e.g., new indications or pediatric-appropriate formulations) should be incorporated into professional labeling. This continuous process of updating the product labeling with new information will help guide the safe and effective use of products and help to minimize the risks and maximize the benefits of drugs in clinical practice.

The continuous maintenance of a favorable benefit/risk ratio for pediatric patients is challenged by the limitations of postmarketing data on safety as well as the effectiveness of drugs in real-life use. Therefore, multifaceted efforts to ameliorate the shortcomings of our current data systems and process are needed.

- The AERS system has distinct strengths, in that it covers all marketed drug and biologic products and can receive reports from around the world. Although it is the largest database of adverse events, underreporting is considered to be a significant problem. Programmatic enhancements to improve the quality of reports and to encourage reporting of suspected adverse reactions via professional and public outreach efforts are needed. Particularly for pediatrics, data resources to provide accurate estimate of exposed patients (denominator data) are lacking. Without valid and complete data on the numerator (number of patients with adverse events) and better databases and projection methodology to estimate the number of pediatric patients exposed to a suspect drug, it becomes very difficult to quantify the risks of drugs. Ideally, pediatric drug use data will be linked to outcomes data in a defined pediatric population.
- The time has come for initiating pilot programs for active postmarketing drug adverse event surveillance for all marketed drugs and biologics. Such pilot programs should evaluate the feasibility of several promising strategies, including establishing patient exposure registries, healthcare setting-based (health maintenance organization, pharmacy benefit management organizations) or population or community-based sentinel reporting sites. A system of sentinel sites must have the capacity and expertise

to monitor specific populations at risk, such as infants, children, and adolescents, and ascertain adverse events specific to those populations, including growth, neurocognitive development, pubertal development, birth defects, and adverse pregnancy outcomes.

- Post-approval sponsor studies or phase 4 studies should be more aggressively pursued by regulatory agencies when there are potentially serious safety concerns that may affect pediatric patients, as this may represent the only opportunity to have the drug sponsor evaluate drug safety in pediatrics after approval.
- Require the sponsor to submit pediatric-specific safety assessments in the post-approval period. The PSURs would include an analysis to update the benefit/risk ratio for a drug's use for its approved indication in pediatric patients.
- Finally, efforts to mine automated claims databases and the design and conduct of epidemiological drug safety studies need to be encouraged. Of specific relevance to pediatrics will be the design and conduct of epidemiological studies to assess the long-term effect of drug exposures on growth and development.
- Improved pediatric specific coding of both pediatric diagnoses and adverse event reporting.

## NEW OPPORTUNITIES FOR PEDIATRIC SAFETY ASSESSMENT

Compared with earlier years, the last 10 years has seen the largest increase in the type and size of pediatric safety data, which has vastly enhanced our understanding of the safety profile of drugs when used in the pediatric population. However, opportunities to leverage existing data sources and new safety initiatives exist to make even greater strides in generating new safety information for pediatric-age patients.

- 1 *Sentinel Initiative.* This new initiative which was launched in 2008 is envisioned to be a national electronic data system comprised of healthcare data for a hundred million individuals across the United States. The sentinel system will enable the FDA to conduct active surveillance to evaluate medical product safety in real time by querying

diverse automated health care data stemming from electronic health record data, administrative and insurance claims databases and registries. When fully developed, it will have tools and methods related to signal detection, strengthening and validation. Because of its large size and diversity of age groups included in the data system, it will present a significant opportunity for active surveillance of pediatric safety to augment the current surveillance systems. The limitation with sentinel from the pediatric perspective is the fact it is mostly reflective of billing codes and these codes are notoriously problematic for pediatrics in that they lack many pediatric specific diagnostic codes.

**2 Medication Exposure in Pregnancy Risk Evaluation Program.** The FDA has launched a new research infrastructure program to enable the study of the effects of prescription medication during pregnancy on the newborns and infants. The program is a collaboration of the FDA with the HMO Research Network Centers for Education and Research in Therapeutics (CERTs), Kaiser Permanente's multiple research centers, and Vanderbilt University. This system, which will create a linked mother–baby healthcare record, will present unprecedented opportunities to detect and evaluate risks of drug exposures during pregnancy and their effect in the newborn, such as birth defects.

**3 Diseased-based registries.** Single drug exposure registries to detect and evaluate new drug risks and long-latency events, such as cancer events, have suffered from important limitations of sample size, inability to capture information on all concomitant drug exposures, and lack of suitable concurrent controls. To overcome these limitations, increasing focus is being placed on efforts to build disease-based registries. Such an example is a program to create a Juvenile Rheumatoid Arthritis registry being led by Cincinnati Children's Hospital Medical Center to help understand rare and long-term risks of disease-modifying agents, such as anti-tumor necrosis factor agents. Encouraging the formation of disease-based registries in pediatrics will provide additional opportunities for generating more long-term safety data for products approved

for use in pediatrics, especially for chronically used drugs.

- 4 **New Authorities and Postmarketing Studies.** The FDA Amendments Act of 2007 authorized the FDA to require postmarket studies and clinical trials if the FDA becomes aware of new safety information defined as data about a serious risk, or an unexpected serious risk associated with the use of the drug. The purpose of the required postmarketing studies and clinical trials will be to (1) assess a known serious risk related to the use of the drug, (2) assess new signals of serious risk related to the use of a drug, and (3) identify an unexpected serious risk when available data indicate the potential for a serious risk. This authority provides an additional opportunity to better understand the safety of drugs in pediatric patients. For example, the FDA was able to order clinical trials to study the safety of long-acting beta agonists (LABAs) when used in combination with inhaled corticosteroids in the treatment of asthma. In these large safety trials, the use of LABAs plus a corticosteroid will be compared with the steroid alone in patients 12 years and older. One of the trials will study younger patients aged 4–11 years. Results are expected in 2017.
- 5 **CERTs.** The CERTs program at the University of Pennsylvania Center for Pediatric Clinical Effectiveness evaluated data from two large US pediatric hospitalization databases to characterize the patterns and rates of pharmaceutical inpatient dispensing of drugs in the pediatric population (Feudtner *et al.*, 2012). The CERTs program will continue for another 5 years under a new *Agency for Healthcare Research and Quality* (AHRQ) funding of six CERTs sites. Among the six research centers, Cincinnati's Children's Hospital Medical Center will serve as the lead CERTs research center with a primary focus on pediatric healthcare quality and research that presents continuing opportunities for evaluating important pediatric drug safety.
- 6 **FDA's Pharmacoepidemiology Research Program.** The FDA Pharmacoepidemiology Research Program enables the conduct of observational safety studies using existing healthcare databases in six research sites as described earlier in the chapter. Examples of observational safety studies

- in pediatric patients include a recently completed study of the cardiovascular safety of drugs used to treat ADHD in children and young adults (Cooper *et al.*, 2011). A comparative study of the risk of incident type 2 diabetes mellitus and use of second-generation antipsychotic agents in children, adolescents, and young adults aged 6–24 years is ongoing. Both studies were co-funded by the AHRQ and the FDA.
- 7 *MedSun and KidNet pilot studies.* In response to safety concerns and questions about off-label use with products used in children that were raised by the Pediatric Advisory Committee, the FDA is utilizing its Center of Device and Radiological Health's medical surveillance network of US hospitals, MedSun. This ongoing device safety surveillance system has a subnetwork of children's hospitals, KidNet. Pilot studies are underway with a subset of participating pediatric facilities that have pediatric and neonatal ICUs in order to retrospectively collect hospital data to better understand the use and safety for certain drug products of interest.
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# Drugs and the Elderly

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## THE AGEING POPULATION AND CHANGING DEMOGRAPHY

Over the past 100 years there has been a major change to the age structure in Western countries. For example, Americans and UK citizens live far longer than previously. Thus, a person born in the USA at the beginning of the twentieth century could expect to live to around 49 years, while the life expectancy at the end of the century was 76.5 years, a gain of over 27 years (Olshansky *et al.*, 2001). These changes have been brought about by an improved standard of living with better housing, clean water, and immunization programs, together with better medical treatments, especially drugs.

The age structure of the population also continues to change, and these changes are set to continue. It is forecast that the expansion of the elderly population will continue to rise over the next 20 years or more. Current and predicted figures from the USA (US Department of Health and Human

Services, Administration on Aging, 2012) showed that the proportion of the population 65 years and older increased from 4% in 1900 to 12% in 2000 and is projected to be 19% in 2030 and 20% in 2050 (Figure 42.1). The very elderly show similar trends, such that the prevalence of the population 85 years and older increased from 0.2% in 1900 to 1.5% in 2000 and is projected to be 2.3% in 2030 and 4.3% in 2050.

## MEDICINES USE IN THE ELDERLY AND RELEVANCE TO DRUG SAFETY

The prevalence of many diseases is age related, and several may coexist in the same patient. It is therefore not surprising that the elderly are the segment of society who are most exposed to medicines. The great majority of elderly people (up to 90%) in developed countries take at least one medicine daily (Barat *et al.*, 2000). Besides prescribed medicines,

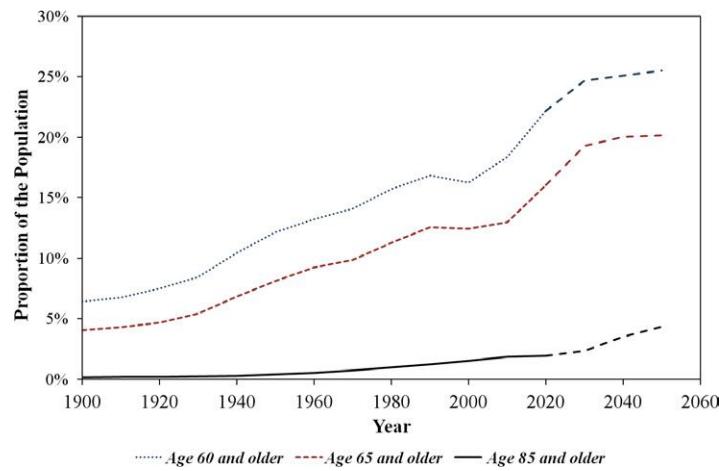


Figure 42.1 Chart of percentage of population aged 60 years and over, 65 years and over, and 85 years and over: from 1900 to projected figures for 2050. Data obtained from US Department of Health and Human Services, Administration on Aging (2012).

elderly people as a group are also high consumers of nonprescription medication. Indeed, it has been estimated that over 50% of elderly people take one or more over-the-counter (OTC) preparations every day (Chrischilles *et al.*, 1992). Those OTC medicines most commonly taken are oral analgesics, vitamins, and tonics, but recently the popularity of herbal medicines has increased (Barnett *et al.*, 2000). Women are particularly likely to consume OTC medicines, and some of these can interact with prescription medicines to cause adverse events. There are two other features that are characteristic of drug therapy in the elderly: polypharmacy (see next section) and long duration. Drug treatment for older people is often for chronic conditions, which means that, once started, medicines tend to be continued for 6 months or longer (Ridout *et al.*, 1986). This problem highlights the need for improvements in repeat prescribing and for regular review of medication in the elderly.

Another particular issue in the treatment of the elderly is often in regard to the extrapolation of evidence gained in the general adult population from clinical trials. Whilst treatment limitation on the basis of age is not advocated, understanding the life expectancy of patients through the application of prognostic tools and specialist judgment may help guide goal-driven decisions about prescribing

(Reuben, 2009). A limited life expectancy affords patients lesser opportunity to be helped by medications that require several years to achieve a clinical benefit, such as statins for primary prevention of cardiovascular disease. Matching a patient's medications to their clinical conditions is the first step in clarifying the possibility of prescribing problems. In the elderly, ensuring appropriate matching of condition and treatment as part of individualized decisions to attain the goals of care is probably more important than simply adhering to generic guidelines and best practices.

## POLYPHARMACY

The evaluation of the harm–benefit balance of drugs taken by the elderly often takes the number of medicines as a starting point. It will be noted that the risk of adverse drug reactions (ADRs) increases with number of medications as does the risk of potential adverse pairwise drug–drug interactions. Polypharmacy – the use of multiple concurrent drugs – has become the norm in many elderly patients, and definitions of polypharmacy have changed considerably over time as the use of several indicated medicines to control chronic medical conditions has become standard. A large

survey of the ambulatory adult population of the USA found that over 90% of patients who were older than 65 years had taken at least one medication during the preceding week, and 12% of the same age group had taken 10 or more different drugs during the same period (Kaufman *et al.*, 2002).

The easiest, and therefore commonest, approach to polypharmacy is to count the number of regular (with or without as required) medications taken by a patient and use a numerical cut-off to define the term (and many different cut-off values have been quoted). However, owing to the change in demographic and usage of medicines, appropriateness of therapy has now become part of many definitions. This requires individual patient's medication to be reviewed and judging medication appropriateness rather than just counting the number of difference medicines (Shah and Hajjar, 2012). Thus, polypharmacy would be alternatively defined as taking at least one medication that is not clinically indicated (*i.e.*, overuse) because of lack of indication, lack of effectiveness, or duplication of another medication on the participant's medication list (Hajjar *et al.*, 2005). This indication-based definition is argued to be more relevant because it takes into account the need for multiple medications to treat multiple comorbidities that elderly patients are likely to have.

There are several perceived reasons for polypharmacy in the elderly. First, as noted previously, the prevalence of many diseases is age related, and several may coexist in the same patient. Second, it may not be possible to achieve an adequate therapeutic response from the use of a single drug. There is an increasing promotion of therapeutic regimens including two or more drugs used in combination for the optimum management of a number of conditions, including diabetes, heart failure, hypertension, and ischemic heart disease (Gurwitz, 2004). Third is the need to counteract or minimize the risk of an adverse drug event (ADE) occurring. The difficulty with this approach is that adverse drug effects may be misinterpreted as a new medical condition and another drug prescribed to treat the observed effects; leading to a "prescribing cascade" (Rochon and Gurwitz, 1997). Finally, in some countries, patients are also being targeted by pharmaceutical companies in so-called "direct-to-

consumer advertising," which is likely to have the effect of increasing polypharmacy in older people.

## INTERACTIONS IN RELATION TO MULTIPLE DRUG PRESCRIBING

ADRs are common in the elderly (see below). This is frequently a consequence of multiple drug prescribing, which leads to the occurrence of drug-drug interactions (Johnell and Klarin, 2007). The risk of potentially inappropriate drug combinations is increased by the greater number of physicians prescribing medications for an elderly patient (Tamblyn *et al.*, 1996). A drug interaction can be defined as a clinically meaningful alteration in the effect of one drug (object drug) as a result of co-administration of another (precipitant drug). Interactions may be pharmacokinetic or pharmacodynamic. Although some drug interactions may be used for therapeutic benefit, interactions may also increase the effects of a drug, leading to toxicity, or inhibit the effects of a drug, leading to a diminished therapeutic benefit.

The elderly are more susceptible to drug interactions due to gradual age-related physiologic changes that affect the pharmacokinetic and pharmacodynamic properties of a variety of medications. These changes may be influenced by genetics, lifelong living habits, and/or the environment. This may contribute to wide interpatient variability and increases the complexity of managing drug interactions in the elderly population.

Knowledge of drug-drug interactions has increased dramatically over recent years, but studies have rarely involved the frail elderly, who are more susceptible to the adverse effects of interacting medications (Hines and Murphy, 2011). There are additional concerns about interactions of drugs with herbal supplements, certain food stuffs, and alcohol, which are also important to consider when prescribing.

## PHARMACOKINETIC INTERACTIONS

Drug-drug interactions may occur through alteration of any of the pharmacokinetic processes:

absorption, distribution, metabolism, or elimination. The clinical significance translating into actual harms varies substantially between these processes. Inhibition or induction of drug metabolism is one of the most important mechanisms for drug-drug interactions. Interactions involving a loss of action of one of the drugs are at least as frequent as those involving an increased effect (Seymour and Routledge, 1998). There are many examples of one drug interfering with the metabolism of another by inhibition of the cytochrome P450 (CYP) enzymes in the liver (Tanaka, 1998). Common inhibitors of one or more CYP isoenzymes include amiodarone, fluconazole, erythromycin, clarithromycin, sulfonamides, ciprofloxacin, omeprazole, and paroxetine. There is increasing evidence that many herbal remedies and other dietary supplements may have pharmacological activity that can lead to potential interactions with drugs when taken together. Many of these interactions have been identified to occur by inhibition of CYP isoenzymes, although the effects of herbal supplements, diet, and food on drug metabolism still requires further study in older persons (Kinirons and O'Mahony, 2004). Liver enzyme induction by one drug may lead to inactivation of a second drug. The delay between the commencement of the enzyme-inducing agent and its full effect can take 7–10 days, making recognition of the interaction more difficult (Seymour and Routledge, 1998). However, in general terms, elderly individuals appear to be less sensitive to drug induction than younger individuals are (Lin and Lu, 1998).

## PHARMACODYNAMIC INTERACTIONS

An antagonistic pharmacological interaction between two drugs may counteract the intended therapeutic effects. For example, co-administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensives may lead to a reduced hypertensive effect due to NSAID-induced sodium retention. One Australian study found that 12% of almost 3000 noninstitutionalized elderly patients were taking NSAIDs and antihypertensive medications simultaneously. Furthermore, NSAID usage was an independent risk factor for hypertension in

this age group (Johnson *et al.*, 1993). Indirect pharmacodynamic effects may occur when one drug's pharmacological effect influences another drug's action. For example, enhanced myocardial depression, hypotension, and atrioventricular block may occur when  $\beta$ -adrenoceptor blockers are administered with verapamil or diltiazem (Edoute *et al.*, 2000).

## DRUG-DRUG INTERACTIONS AND ADVERSE EFFECTS

Despite the many ways in which drug-drug interactions may occur, it is likely that only about 10% of potential interactions result in clinically significant events. However, while death or serious clinical consequences are rare, low-grade clinical morbidity in the elderly may be much more common (Seymour and Routledge, 1998). Nonspecific complaints, such as confusion, lethargy, weakness, dizziness, incontinence, depression, and falling, may indicate an underlying drug-drug interaction. In some cases the cause of the interaction is complex, involving both pharmacokinetic and pharmacodynamic mechanisms. Attempts have been made to highlight the most important drug-drug interactions in the elderly using an expert consensus approach (Malone *et al.*, 2004). Determining from pharmacologic studies which are the important drug-drug interactions can be an important way of prioritizing knowledge about certain drugs/drug classes. A review of drug-drug interactions has shown that many studies concentrate on drugs with narrow therapeutic indices (e.g., warfarin, theophylline, lithium, and digoxin) and that important interactions involve the commonly prescribed drug classes used in the elderly (Hines and Murphy, 2011). The impact of drug-drug interactions in causing actual harm has been demonstrated in several population-based studies (Juurlink *et al.*, 2003; Hanlon *et al.*, 2011).

Methods to prevent adverse drug-drug interactions will be one way to reduce preventable harms in practice. The challenges associated with reducing drug-drug interactions have recently been reviewed by Mallet *et al.* (2007). Alerting prescribers to possible drug-drug interactions using computer-based

alerts is one method that is becoming more widespread as hospital- and community-based practices adopt prescribing software. A study examining the use of such software has identified that in elderly patients ( $\geq 65$  years) 80% had at least one potential drug–drug interaction related to CYP enzyme effects when taking five or more medications (Zakrzewski-Jakubiak *et al.*, 2011). As in other areas of clinical decision support, it is important that alerts offer actionable advice to increase the likelihood of them being accepted in practice; for example, by noting the impact of such an interaction, and how a dosing schedule change, medication substitution, or drug discontinuation is likely to mitigate against such harms.

Other practical ways of reducing the likelihood or impact of adverse drug–drug interactions could be by encouraging full disclosure of all prescription, OTC, and complementary/alternative medicines by patients at each health encounter, by developing comprehensive compendia of clinically important drug–drug interactions, by screening for potential drug–drug interactions when adding a new drug or changing a medication regimen, and, where essential combination treatments are required involving potential drug–drug interactions, for doses or dosage intervals to be adjusted for those medicines with consequent careful patient monitoring (Hanlon *et al.*, 2011).

## ALTERED PHARMACOKINETICS IN THE ELDERLY

Elderly patients may develop drug-related problems even when their medication is confined to a single agent or noninteracting multiple agents. This may relate to pharmacokinetic and pharmacodynamic changes associated with ageing. Such age-related physiological changes may alter the way in which the body handles medication, leading to changes in drug disposition in the elderly patient (Mangoni and Jackson, 2004). Knowledge about pharmacokinetic and pharmacodynamic changes aids the prescriber to make sensible decisions about which drugs to avoid or which drugs can be used (often with caution and appropriate monitoring).

Elderly patients can present changes in all pharmacokinetic processes (absorption, first-pass processes, protein binding, distribution, hepatic and other metabolism, and elimination).

### ABSORPTION

With increasing age a number of changes occur in the gastrointestinal tract that should make the rate and extent of absorption of orally administered drugs less predictable, including a reduction in acid secretion in the stomach, decreased gastric emptying, diminished splanchnic blood flow, and decreased gastrointestinal mobility (Greenblatt *et al.*, 1982; Montamat *et al.*, 1989; Woodhouse, 1994). However, in practice, few drugs have significantly delayed rates of absorption (Greenblatt *et al.*, 1982; Woodhouse, 1994). This is probably because potentially rate-limiting factors in the small intestine (such as surface area and luminal pH) are not altered to a critical degree. A review by Cusack (2004) concluded that studies assessing the extent of absorption by comparing area under the curve after oral and intravenous administration and rate of absorption using  $T_{max}$  corroborate the prevailing opinion that ageing does not affect absorption to a significant degree.

Once drugs are absorbed from the gut, they enter the portal circulation and must pass through the liver before entering the systemic circulation. The bioavailability of most polar or water-soluble drugs is not affected by age because they are not highly extracted by the liver. For many lipophilic drugs, this first pass through the liver is accompanied by pronounced (sometimes over 90%) extraction with only 5–10% of the dose reaching the systemic circulation. Decreased presystemic extraction in the elderly may lead to increased bioavailability of various drugs, but again usually not to a clinically significant extent. The changes may be more marked, however, in the frail and hospitalized elderly (Woodhouse, 1994).

### DISTRIBUTION

Following absorption of a drug, the extent to which it is distributed within the body depends on body composition, plasma protein binding, and blood flow.

## BODY COMPOSITION

With age there is a decrease in lean body mass and body water and a corresponding increase in adipose tissue in relation to total body weight (Novak, 1972). Adipose tissue increases from about 18% to 36% in men and from 33% to 45% in women (Novak, 1972). Therefore, the distribution of lipid-insoluble drugs may decrease in the elderly. This means that plasma concentrations per unit dose are higher. Lipid-soluble drugs such as diazepam are more widely distributed in the elderly and may have prolonged action and a "hangover" effect because of the longer elimination half-life (Macklon *et al.*, 1980).

## PROTEIN BINDING

Serum albumin levels decline with age, but in healthy elderly people this change is minimal. More marked reductions appear to relate to disease, immobility, and poor nutrition rather than age itself (MacLennan *et al.*, 1977). This reduction may result in a decrease in the binding capacity of weakly acidic drugs such as salicylates and phenytoin (Wallace and Verbeeck, 1987). Measurement of the plasma free-drug concentration (which will be increased under these circumstances) may be a better guide to the dose requirements than the total plasma concentration, particularly if the therapeutic ratio is low (Grandison and Boudinot, 2000). However, a raised free fraction will also result in an increased clearance, allowing a new steady state to be achieved with regular dosing. Total plasma drug concentrations may then be lower, but free-drug concentrations will remain the same since these are determined by hepatic or renal clearance of free drug. On the other hand,  $\alpha$ -1-acid glycoprotein increases with age, and basic drugs such as lidocaine display increased protein binding in elderly patients (Cusack *et al.*, 1980).

## METABOLISM

Although some drugs are eliminated directly by the kidneys, many first undergo metabolism in the liver. Clearance of drugs by the liver depends on the activity of the enzymes responsible for biotransformation and on blood flow, which determines the rate of delivery of the drug to the liver. For drugs

that are metabolized relatively slowly by the liver (those with low intrinsic clearance), clearance is proportional to the rate of hepatic metabolism (Woodhouse, 1994). Hepatic mass decreases with age by 25–35%, so the metabolism of such drugs may be reduced (Woodhouse and James, 1990).

Phase 1 oxidative drug metabolism may be reduced in the elderly (O'Malley *et al.*, 1971), but phase 2 reactions are generally thought not to be altered, at least in fit elderly patients. However, in the frail elderly, in those who have suffered injury or have undergone surgery, enzyme activity may be significantly depressed, resulting in higher blood drug concentrations and an increased risk of adverse reactions (Woodhouse, 1994).

Metabolism of a number of drugs, such as the benzodiazepines, may involve phase 1 followed by phase 2 reactions. Diazepam undergoes oxidative (phase 1) metabolism and its elimination is prolonged in the elderly (Belantuono *et al.*, 1980). It is also partly converted to an active metabolite, desmethyldiazepam, which has a half-life of up to 220 h in elderly people. However, other benzodiazepines, such as lorazepam, undergo conjugation reactions in the liver and their metabolism is unaltered by age. These compounds that do not give rise to active metabolites may, therefore, be safer for elderly people to use than the other benzodiazepines.

Age may be only one factor that affects drug metabolism. Cigarette smoking, alcohol intake, dietary considerations, drugs, illnesses, and caffeine intake may be equally important (Montamat *et al.*, 1989). In addition, hepatic blood flow rather than microsomal enzyme activity is the major determinant of total clearance of many drugs that have a very rapid rate of metabolism, and consequently high extraction rates across the liver. Hepatic blood flow is 35% lower in healthy people over 65 years of age than in young people (Wynne *et al.*, 1989). Reductions in systemic clearance of drugs with high hepatic extraction ratios (including presystemic clearance), such as propranolol and morphine, have been reported in the elderly.

## RENAL EXCRETION

Most polar drugs or polar drug metabolites are eliminated by the kidney after filtration at the

glomerulus. In addition, drugs such as the  $\beta$ -lactam antibiotics are actively secreted in the proximal tubules. As part of normal ageing, both renal functional capacity and renal reserve diminish. The structural changes include a decrease in renal weight, thickening of the intrarenal vascular intima, a reduction in the number of glomeruli with increased sclerosis within those remaining, and infiltration by chronic inflammatory cells and fibrosis in the stroma (Muhlberg and Platt, 1999). Altered renal tubular function may also lead to impaired handling of water, sodium, and glucose in old age. There is a steady decline in the glomerular filtration rate by approximately 8 mL/min per decade (Rowe *et al.*, 1976). By the age of 70, therefore, a person may have a 40–50% reduction in renal function (even in the absence of overt renal disease).

Drug elimination may be reduced even in patients with normal serum creatinine concentrations because creatinine production decreases with age. Many drugs that are dependent on the kidney for elimination will accumulate to toxic levels if given in the usual doses to elderly people. In addition, reduced clearance of active metabolites of certain drugs may increase the risk of toxicity particularly in very elderly patients. One example is morphine-6-glucuronide, the active metabolite of morphine (McQuay, 1990). Furthermore, many drugs themselves adversely affect renal function in the elderly; for example, aminoglycosides, diuretics, NSAIDs, and angiotensin-converting enzyme inhibitors. In this way, age-dependent changes in renal function are responsible for altered pharmacokinetics in the elderly, but in many cases the kidneys are the target for the ADRs produced by these changes (Muhlberg and Platt, 1999). Estimation of the creatinine clearance helps determine dosing in the elderly but should be supplemented by therapeutic drug monitoring where available, especially in drugs with a low therapeutic index (Cusack, 2004).

## ALTERED PHARMACODYNAMICS IN THE ELDERLY

Age-related changes in pharmacodynamics may also be relevant. The most important concept in

regard to pharmacodynamics is sensitivity; that is, the measurement of a response to a given dose of drug. Sensitivity is independent of dose- and age-related changes in the pharmacokinetics (Jackson, 1994). It may be difficult to quantify in elderly patients, who may show both increased and decreased responsiveness to medication. The mechanisms include changes to organ systems, such as age-related impairment of homeostatic mechanisms, as well as changes at receptor and cellular level (Jackson, 1994).

Evidence related to age-related changes in pharmacodynamics and their clinical relevance continues to be published (Bowie and Slattum, 2007). Examples of medicines associated with an exaggerated response in elderly patients include central nervous system (CNS)-active drugs (particularly benzodiazepines and psychotropic agents), oral anticoagulants such as warfarin, and opioid analgesics. However, some drugs show a decreased effect in the elderly:  $\beta$ -adrenoceptor antagonists, due to a reduction in receptor numbers/responsiveness, and diuretics, due to an age-related decrease in renal function lowering their effectiveness (Bowie and Slattum, 2007). There is not space here to describe the many more medications that show altered sensitivity in the elderly; and although evidence about mechanisms underlying these alterations has been proposed, there is a need for further data to support the pharmacodynamic alterations that are observed in practice.

## ADVERSE DRUG REACTIONS IN THE ELDERLY

Age-related changes in pharmacokinetics and pharmacodynamics, together with higher disease burdens and specific problems in the elderly (e.g., instability, prostatism, cognitive impairment) place elderly patients at increased risk of experiencing ADEs, including falls, confusion, and urinary retention, with a subsequent worsening of morbidity when such events occur. In addition, the elderly often experience quite nonspecific ADRs that may mimic underlying disease processes, such as generalized functional decline akin to dementia.

## INCIDENCE OF ADVERSE DRUG REACTIONS IN THE ELDERLY

The rates of hospital admissions attributable to or contributed to by ADRs vary between different populations. In the general adult population the incidence of ADRs contributing to hospital admissions has been shown to be around 6.5% (Pirmohamed *et al.*, 2004). ADRs may cause 1 in 30 hospital admissions in the older population based upon data from a large observational study based in 81 Italian academic hospitals as part of the Italian Group of Pharmacoepidemiology in the Elderly (Onder *et al.*, 2002). These data are consistent with estimates noted in the USA (Budnitz *et al.*, 2007) and elsewhere previously (Moore *et al.*, 1998), but rates have been noted to be higher (up to around 10%) in other studies (Kongkaew *et al.*, 2008; Olivier *et al.*, 2009). As with other investigations of ADRs causing hospital admissions, the majority of studies demonstrate reactions that are considered preventable, in that they reflect inappropriate prescribing or inadequate monitoring.

Fewer studies have been done to determine the incidence of ADRs during hospital admission, but the incidence is probably similar to that of ADRs causing hospital admission and may be higher (Leach and Roy, 1986; Davies *et al.*, 2009). The incidence tends to be higher in the elderly than in the general population. In addition, ADRs have been shown to be risk factors for delayed discharge from hospital (Davies *et al.*, 2009), as well as early hospital readmission (Chu and Pei, 1999). Finally, in the outpatient population, ADRs occur with an annual incidence rate of around 5% (Gurwitz *et al.*, 2003).

## FACTORS ASSOCIATED WITH INCREASED RISK OF ADVERSE DRUG REACTIONS

Various risk factors have been identified with ADRs in all settings. These include: prescription of unnecessary or interacting drugs, or drugs with relative or absolute contraindications (Lindley *et al.*, 1992); female gender and increasing age (Hofer-Dueckelmann *et al.*, 2011); self-medication (Olivier *et al.*, 2009); and comorbidity from chronic

diseases (Sikdar *et al.*, 2012). Hajjar *et al.* (2003) identified risk factors for ADRs in older outpatients using a literature search and a two-round Delphi panel. Consensus was reached on nine patient characteristics, including polypharmacy, multiple chronic medical problems, previous ADRs, and dementia.

One of the most important predictors of ADRs is the total numbers of drugs given simultaneously (Leach and Roy, 1986; Olivier *et al.*, 2009). A study in geriatric nursing-home residents has found a positive correlation between the use of nine or more different scheduled medications and the occurrence of ADRs (Nguyen *et al.*, 2006).

Green *et al.* (2007) investigated risk factors for self-reported ADEs in a North American managed care cohort. The number of prescribing physicians was found to be an independent risk factor for ADEs, with each additional provider prescribing medicines increasing the risk by about 30%. The authors of this study suggest that these findings support the hypothesis that lack of communication and coordination between prescribing physicians may adversely impact patient care.

In addition to deficiencies in care that may contribute to harms, developing an understanding of patient risk factors for developing an ADR may also allow providers to target additional resources to those patients who are at increased risk of an ADR. The Italian Group of Pharmacoepidemiology in the Elderly has used their work to compute and validate an ADR risk score in order to identify risk factors for ADRs (Onder *et al.*, 2010). The GerontoNet ADR risk score consists of the following factors: the number of drugs and a history of an ADR as strongest predictors, followed by heart failure, liver disease, presence of four or more comorbid conditions, and renal failure. The Geronto ADR risk score failed to find a clear association between age and ADR risk and also did not report the association between gender and ADRs. However, a study of consecutive inpatients also undertaken in Italy revealed that female gender conferred a doubling of risk of ADRs during the hospital stay and confirmed that the number of medications taken was independently associated with occurrence of ADRs (Lattanzio *et al.*, 2012). The main aim of this study was to identify whether

any individual geriatric conditions were risk factors for ADRs; but after correction for potential confounders, none did so. The only condition-specific characteristic identified as a risk factor was the simultaneous presence of a history of falls and dependency in at least one activity of daily living.

Gender differences in the use of drugs at high risk of ADEs in the elderly have demonstrated that community-dwelling women are more likely to receive such drugs. This gender difference is found to persist even after accounting for prescribing for appropriate indications, and it has been proposed that such sex differences in patterns and correlates of inappropriate prescribing must be addressed to develop effective interventions to reduce inappropriate drug use in the elderly (Bierman, 2007).

Amongst the current literature, therefore, it seems that there are care processes (such as number of different prescribers), medication-related factors (such as number of concurrent medications taken), and patient factors (such as female gender) that may confer risk for the occurrence of an ADR. Some of the heterogeneity between the studies would suggest that these factors are not absolutely consistent in different populations or different care settings, and no doubt further evidence will continue to emerge to clarify common risk factors for ADRs in the elderly. In the meantime, the risk factors should be used to increase vigilance in relevant risky situations to mitigate harms where possible.

By linking deficiencies in the pharmacotherapeutic process to the occurrence of ADRs, effective interventions may be considered. Therefore, making accurate and reliable assessments of the relationship between drug administration and adverse event is necessary, both in terms of causality and preventability, and yet some of the criteria used to make these judgments have been considered to be less suitable in the elderly population (Hamilton *et al.*, 2009). These researchers argue that traditional criteria such as the Naranjo assessment of ADRs can be difficult to interpret in the context of older patients with multiple comorbidities and medications.

Some adverse effects seen in the elderly are fairly subtle, and impairments in terms of body functions and structures, activities, and participation in life

activities have been subsumed under a general term of "functional decline." There are many potential physiologic explanations for the impact of medications on functional outcomes. For example, it has been suggested that specific medications may increase the risk of impaired functional status by adversely affecting such domains as alertness, vision, and muscle strength (Thwaites, 1999).

With medication use being a potentially modifiable risk factor for functional status decline, it is important to understand which drugs or situations are associated with these less specific adverse effects as well as ADRs more generally. A review of studies has determined which medicines are associated with functional status decline (Peron *et al.*, 2011). Benzodiazepines and anticholinergics have been consistently associated with impairments in functional status in the elderly. The relationships between suboptimal prescribing, antidepressants, and antihypertensives and functional status decline were mixed.

Some medicines are much more likely than others to cause problems when prescribed to elderly people. Groups of drugs consistently causing more specific ADRs in this age group are anticoagulants, cardiovascular drugs, NSAIDs, opioid analgesics, and drugs acting on the CNS. Various different studies have supported these drug classes as risk factors for ADRs. The most prevalent medication-related risk factors noted in the Delphi consensus study of ADR risks were opioid analgesics, warfarin, NSAIDs, anticholinergics, and benzodiazepines (Hajjar *et al.*, 2003). Data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project in North America has identified certain medication types associated with the highest rates of adverse events (Budnitz *et al.*, 2011). Warfarin was implicated in about one-third of these hospitalizations, while insulins, oral antiplatelet agents, and oral hypoglycemic agents accounted for another third. The authors conclude that targeting the safe management of antithrombotic and antidiabetic agents would provide the highest potential to reduce harm to elderly patients.

Elderly people are more sensitive to medications that affect CNS function. Drugs of particular relevance in this regard are benzodiazepines, major

tranquillizers, and antidepressants, which are all frequently used by elderly patients. Adverse reactions due to psychotropic drugs have long been recognized to be a cause of hospital admission in the elderly (Williamson and Chopin, 1980); however, this has recently raised particular concern internationally. Behavioral problems in older adults with dementia are the usual indication for psychotropic drugs, but their use has been associated with adverse events (Rochon *et al.*, 2008). Benzodiazepines are also CNS-active drugs associated with adverse events, including impaired cognition, hip fractures, and falls (Tinetti *et al.*, 1988). There are other important effects of drugs on brain function that can cause specific problems, especially when used in patients with cognitive impairment. Anticholinergics, dopamine agonists, opiates, and antidepressants may also all induce delirium as an idiosyncratic effect in the elderly.

## **IDENTIFYING INAPPROPRIATE MEDICATION USE**

Medication selection, it follows, is an important factor influencing the likelihood of ADRs, and prescribing practices change as safer, superior alternatives to existing medications become available. It has been recognized for decades that elderly patients admitted to hospital are often receiving inappropriate or contraindicated drugs (Gosney and Tallis, 1984). In the 1990s, Beers and colleagues developed explicit criteria for potentially “inappropriate medications” in elderly patients, and these criteria were subsequently updated (Fick *et al.*, 2003). Studies have used these criteria to identify the prevalence of the problem and found approximately one in five elderly patients to be on at least one inappropriately prescribed medication (Sloane *et al.*, 2002; Van de Hooft *et al.*, 2005). More criteria continue to be proposed and existing criteria modified for specific situations (see below).

Given such a complex process of decision-making about medicines for elderly patients, it is not surprising that there is much scientific and social debate about the concept of “appropriateness.” Dichotomizing prescribing into good or bad, optimal or suboptimal, appropriate or inappropri-

ate attempts to simplify clinical situations that are often very difficult. Nevertheless, value judgments often have to be made against appropriateness that can be construed as the outcome of a process of decision-making that maximizes net individual health gains sometimes countered by society’s available resources (Buetow *et al.*, 1997). A considerable amount of research has been undertaken to develop reliable and reproducible criteria for appropriateness (or usually inappropriateness) against which clinical situations can be judged.

There are several ways to determine whether patients are receiving potentially inappropriate medicines (PIMs) – either explicit (criteria-based) lists of drugs or drugs for specific indications can be drawn up that are not advised in the elderly, or alternatively an implicit approach is taken where all medications taken can be scored for “inappropriateness” (judgment based). In general, a combination of a structured approach supplemented by clinical judgment is probably regarded as best practice (Spinewine *et al.*, 2007).

When considering the prevalence of PIMs, it is important to understand the context in which the study is undertaken. A systematic review of inappropriate medication use in community-dwelling older people using mostly explicit criteria in their assessments showed a range of between 12 and 62% of inappropriate use across different studies (Guaraldo *et al.*, 2011).

The explicit (criteria-based) measures used to determine PIMs do not consider the characteristics or clinical situation of each patient. The medication appropriateness index is an implicit approach where each medication is scored for criteria such as effectiveness, directions for use, duration, and expense (Hanlon *et al.*, 1992). This index may reduce the potential for drug-related problems, as higher scores for a drug may provide a rationale for changing or stopping particular drugs, and total summative scores for all drugs may provoke a medication use review.

As with medication error audits, many of these measures require careful chart review by trained observers; therefore, it is not surprising that with the use of electronic health records has come the automated detection of PIMs using such records (Buck *et al.*, 2009). Being able to measure the

volume of PIM usage through the use of electronic records has also given rise to a number of quality improvement initiatives to reduce the risk of harm. A study in 99 primary care practices has demonstrated that through performance reporting of inappropriate and rarely appropriate medication choice in elderly patients, together with site visits and network meetings for performance review, academic detailing, and quality improvement planning, there was an improved performance over time across the network (Wessell *et al.*, 2008). Such quality reporting is more easily achievable with the use of electronic medication records and automated reporting – an area that is likely to show further promise with the continued implementation of electronic records over time.

Whilst explicit consensually developed criteria exist for inappropriate prescribing in the elderly (such as the Beers criteria), a number of these are modified for specific studies or different geographical regions. This is not surprising given that some of the criteria rely on dosage, dose frequency, diagnosis, or specific drug forms that are instituted in countries different to the one where the original criteria were developed where prescription habits are rarely the same. Adaptations, therefore, have to be made based around drugs with a similar pharmacological profile to those mentioned in the original criteria but which are available in the country of study (Zhan *et al.*, 2001). For example, a consensus study of nine Japanese experts has, from a selection of 27 medicines or medication classes, developed modified Beers' criteria relevant to their country (Imai *et al.* (2008), quoted in Akazawa *et al.* (2010)). The prevalence of elderly Japanese patients with at least one PIM using the Japanese modified Beers' criteria was 44% in one observational cohort study (Akazawa *et al.*, 2010), which is higher than in other studies. The use of country-specific criteria seems appropriate in some circumstances but does hinder direct comparisons with other countries if specific medication use varies substantially and different inclusion criteria are used for modified indicators (Dimitrow *et al.*, 2011). Many other country-specific explicit criteria are in use, some of which have been developed independently of currently existing criteria (McLeod *et al.*, 1997; Naugler *et al.*, 2000). It is noteworthy that

even where the same criteria are used, substantial differences in PIM use have been found to exist between different countries in Europe (Fialová *et al.*, 2005).

The explicit criteria fall under the umbrella term “drugs-to-avoid criteria.” Attempts have been made to determine the validity of such criteria. In a group of older outpatients taking five or more medications, Steinman *et al.* (2009) evaluated the concordance between the Beers and Zhan criteria compared with an individualized patient assessment by physician and pharmacist reviewers. They found that the drugs-to-avoid criteria had limited power to differentiate between drugs and patients with and without prescribing problems when compared with expert review, thus concluding that such explicit criteria are unsuitable as stand-alone guides of medication quality. The authors of this study acknowledge that as the intended focus of drugs-to-avoid is in detection of medicines whose use is often (or almost always) inappropriate, such criteria will not be able to identify PIMs in all clinical situations. It is suggested that using drugs to avoid criteria to screen lists of patients in order to follow up situations for individual review seems like a sensible and incontestable way to use these criteria in the future.

Medications included within the explicit criteria lists are generally considered ineffective or to have potential risks that exceed the potential benefits. A study to determine how frequently ADEs occur in the acute hospital setting related to Beers' criteria medicines has been undertaken in the USA (Page and Ruscin, 2006). Nearly a third of hospitalized elderly patients in this study suffered from an ADE during admission; however, relatively few were related to the use of Beers' criteria medicines (9.5%). The authors considered that an increased number of medications at admission was a stronger independent predictor for subsequent ADEs during the hospital stay, which may serve as a surrogate for increased disease burden and frailty. It was noted that targeting interventions only at Beers' criteria medications in this acutely ill population would have seemingly done little to reduce the occurrence of ADEs and to minimize drug-related morbidity and mortality. However, other research has suggested that increasing numbers of inappropriate medicines using defined criteria may be associated

with increased risk of ADEs (Chrischilles *et al.*, 2009; Lund *et al.*, 2010).

## OTHER FACTORS ASSOCIATED WITH INAPPROPRIATE MEDICATION USE

Inappropriate medication use is often seen as a prescribing issue, but there are various patient-related factors that may contribute to unnecessary drug use. Concerns and beliefs about medicines have been found to be important in patients' self-reporting of ADEs. However, the role of sociopsychological variables as risk factors for ADEs in the elderly has rarely been considered. A secondary analysis of an internet-based cross-sectional survey of older adults identified a positive association between self-reported ADEs and concerns and beliefs about medicines assessed using the Beliefs about Medicines Questionnaire (BMQ)-specific scale (Shiyanbola and Farris, 2010).

There are perceived differences in the management of elderly patients depending on whether they are dwelling in the community or in full-time care (residential homes or nursing homes). Whether there are differences in the rates of inappropriate drug prescribing between these settings is unclear. A US study of nursing-home residents has found that inappropriate medication prescribing was similar before nursing-home admission among patients with and without dementia (Zuckerman *et al.*, 2005). A study concentrating on patients receiving home healthcare (i.e., provision of organized services to promote continued independent living) – where the prevalence of routine systematic drug utilization reviews is perceived to be lower – has also found a high frequency of PIM use and dangerous drug interactions compounded by polypharmacy (Cannon *et al.*, 2006).

One healthcare sector that has received specific attention is residential care/assisted living. This type of institution often fills the gap between community-dwelling older persons and skilled nursing facilities; but of note, the staff who administer medicines are generally not nurses and, therefore, have minimal or no training in medication administration and effects. A study in the residential care/assisted care setting in North American

using modified Beers' criteria has found that 16% of residents were receiving potentially inappropriate medication (Sloane *et al.*, 2002). Similar risk factors were seen for comparable studies in other settings; but of note, lack of weekly physician visits and moderate licensed nurse turnover were associated with higher rates of PIMs. Professional and consistent staff engagement may, therefore, be beneficial in providing expertise on medicines management in order to reduce inappropriate prescribing in such institutions.

## REDUCING HARMS/MEASURES TO IMPROVE PATIENT SAFETY

A number of different types of interventions directed at patients, providers, or systems of care have been used to reduce the risk of drug-related harm in the elderly (Kaur *et al.*, 2009). These approaches are often specific to this group of patients because of the existence of multiple comorbidities and different settings to other adult patient groups (Loganathan *et al.*, 2011). Interventions that have been proposed include specialized professional input (through geriatric medicine service, multidisciplinary teams, or dedicated pharmacy medication reviews), educational types of intervention (academic detailing, educational outreach), technological approaches (computerized decision support), and multifaceted approaches.

It is perhaps not surprising that in hospitalized patients the care by physicians or units with a specialist interest in elderly care may reduce inappropriate medication use and optimize appropriate medication use, thus leading to lower safety concerns in these patients (Schmader *et al.*, 2004). An area of increasing concern more generally is around the interface between care providers, and this remains an important aspect in the care of the elderly. Ensuring appropriate continuity of care between different care providers should reduce errors, and this is particularly relevant with respect to medication use. Medication reconciliation is a technique for identifying discrepancies in drug regimens prescribed in different care settings or at different time points to inform prescribing decisions and prevent medication errors. This reconciliation

is done to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions. It should be done at every transition of care (including changes in setting, service, practitioner, or level of care) in which new medications are ordered or existing orders are rewritten (The Joint Commission, 2006).

A study of the prevalence of intentional, undocumented intentional, and unintentional medication discrepancies (for both prescription and OTC medications) in elderly patients undergoing acute admission has demonstrated rates of medication discrepancies of up to 40%, with the potential to cause patient distress or clinical deterioration (Villanyi *et al.*, 2011). This is very important as there is good evidence that admission medication changes are associated with ADEs (Boockvar *et al.*, 2011). In some cases, specific interventions have been introduced to correctly manage the medicines that an elderly patient takes when moving between care providers. This can allow errors associated with discrepancies (including ADRs) to be prevented (Boockvar *et al.*, 2006).

Part of the reconciliation process is in determining what the indications are for each drug, and this can help in the decision-making process about medication inappropriateness. Unfortunately, medication histories in charts are often inaccurate and incomplete. The use of medications without a clear reported indication is of particular concern and has been associated with inappropriate use and polypharmacy. In a hospital-based study it was found that nearly 70% of patients admitted to a medical ward had more than one unspecified medication listed in the admission note (Slain *et al.*, 2008). Based on these results, the authors suggest that healthcare professionals must be careful to obtain and document complete medication histories with matching indications – an essential prerequisite of reconciliation.

Discrepancies not only exist between the interfaces of care, they are also common in the community. When reconciling medicines it is recommended that several sources of information are used to inform the medication lists for patients. One of the principal processes is involvement of the patient in confirming details of medication taken, and yet in elderly patients this is not always reliable.

A study assimilating prescription information from a community pharmacy, the primary care physician, and the patients themselves looked at elderly outpatient consultations and found that in a majority of cases (94%) at least one discrepancy between the medication lists of the patients, general practitioner, or pharmacy was present (Tulner *et al.*, 2009). An evaluation of the impact of such discrepancies was also undertaken and discovered that medication discrepancy adverse patient events occurred in a quarter of patients where the medication had not been appropriately described in the referral letter. It is probably reasonable to assume that medication lists supplied from primary care practitioners are incomplete or incorrect, and that additional information from the community pharmacy and patient is useful.

One area of further concern, as well as hospital admission and discharge, is the transition into full-time nursing care facilities. A study in North Carolina studying medication error incidents in nursing homes identified that 11% of the incidents occurred during patient transition from either home or another care facility (Desai *et al.*, 2011). The incidents involving patient transfer were more likely to cause harm than all other incidents. The study found that staff communication, order transcription, medication availability, pharmacy issues, and name confusion were particularly important contributors to medication errors during transitions. It is acknowledged that transitional care for nursing-home residents usually involves communication about complex medication regimens to address their high burden of comorbidities and that care should be taken to reduce avoidable harms in such circumstances.

A number of quality improvement initiatives have been described which intend to reduce inappropriate polypharmacy and intervene if there are other potential medication problems. Drug regimen (drug utilization) reviews by pharmacists have been described as a way to achieve such medicines optimization (Christensen *et al.*, 2004). Drug utilization reviews are one way to assess a medication list using knowledge of the patient to determine the potential for inappropriate medication use and then initiate an intervention if required – such as contacting the prescribing physician. Whilst this is an activity that

has been proposed to occur prospectively with patients on a regular basis, Starner *et al.* (2009) demonstrated that a retrospective drug utilization review (RetroDUR) – where prescribers were mailed when any patients receiving PIMs were identified from an administrative claims database – can lead to a reduction in PIMs prescribing in elderly subjects.

Intervention studies to reduce polypharmacy are relatively uncommonly reported despite the fact that it is relatively clear that healthcare professionals should be aware of the risks and fully evaluate all medications at each patient visit to prevent inappropriate polypharmacy from occurring (Hajjar *et al.*, 2007). Drug utilization reviews whilst identifying new risks from PIMs may paradoxically increase (or not impact) polypharmacy if one improves both unnecessary use and underuse simultaneously, as no difference in overall medications use will result.

Supporting elderly patients to manage their own medicines appropriately may pre-empt potential drug-related problems such as nonadherence, unintentional overdose, and other errors leading to harms. A number of tools have been devised to test the ability of patients to understand their medication regimen. It has been proposed that elderly patients, especially those with memory loss, should be routinely evaluated for their ability to manage their own medications. The Medication Management Ability Assessment (MMAA) (Patterson *et al.*, 2002) and the Drug Regimen Unassisted Grading Scale (DRUGS) (Edelberg *et al.*, 1999) are standardized tools used to assess medication management skills in elderly patients. A study investigating these tools against cognitive function and self-reported drug problems has shown a positive association between worse performance using these tools and lower cognitive scores (Hutchison *et al.*, 2006).

With the advent of electronic prescribing or computerized physician order entry (CPOE) systems, there is the potential to aid prescribers' practice through clinical decision support (Venot, 1999). Rules, alerts, and reminders can be associated with the prescribing stage within the electronic record that can draw upon knowledge bases that contain information on dosing, drug–drug interactions, and contraindicated medicines specifically relevant

to elderly practice. A systematic review of computerized decision-support interventions related to elderly patients has confirmed their effectiveness in improving medication prescribing in older adults, but noted that at present few studies reported actual clinical outcomes related to changes in medication prescribing (Yourman *et al.*, 2008).

An evaluation of computerized decision support used in an emergency department which identified nine potentially inappropriate medications using hard-coded rules and directed prescribers toward the use of potentially safer substitute therapies has been undertaken (Terrell *et al.*, 2009). As with many decision-support rules, acceptance of such recommendations was not universal, and only 43% of 114 alerts were heeded, which led to a nonsignificant reduction in odds of inappropriate medications being prescribed when compared with a control group of prescribers who did not receive the computerized alerts.

An inpatient study in an academic medical center in the USA has investigated the rates of prescribing of PIMs before and after the CPOE with computerized decision-support system was deployed (Mattison *et al.*, 2010). Prescribers received alerts requiring responses before confirming their orders. Each alert contained an explanation for the warning and a list of conditions that could place a patient at increased risk; when appropriate, the alert advised an alternative medication or dose reduction. The study showed a highly significant reduction in the rate of PIMs after the implementation of decision-support warnings, thus supporting the notion that information technology interventions may improve the quality of prescribing in the elderly.

Various research approaches have been used in attempts to improve prescribing practices among physicians in multiple clinical care settings. These include interventions to improve education of the healthcare staff providing patient care, to utilize computerized decision-support systems, to use clinical pharmacy interventions, to use a multidisciplinary approach, and to use a multifaceted approach (Marcum *et al.*, 2010). The conclusions of these various interventions have produced mixed results, leading to a lack of clear guidance about the optimal effective intervention to improve prescribing in such populations. As with most applied

health research, many interventional studies have reported on changes in rates of inappropriate prescribing as a surrogate of likely morbidity and mortality, whereas few actually report harms such as ADE rates or death.

## QUALITY ISSUES AND MEDICINES OPTIMIZATION IN THE ELDERLY

Good-quality care for the elderly involves optimizing the use of medicines and the provision of high-quality pharmaceutical care. The Institute of Medicine's definition of quality care has been adapted to define quality medication use as "the degree to which medication use for individuals and populations increases the likelihood of desired health outcomes and is consistent with current professional knowledge" (Institute of Medicine, 1990). Quality problems related to medication use can be broadly classified as underuse (failure to provide a medication when it could have produced a favorable outcome for a patient), overuse (when a medication is provided under circumstances in which the potential for harm exceeds the possible benefit or when there is no clear benefit), and misuse (when an appropriate medication has been selected but a preventable problem occurs that precludes the patient from realizing the full potential benefit of that medication) (Roth *et al.*, 2008).

Medication underutilization, or the omission of a potentially beneficial medication indicated for disease management also needs to be considered in elderly patients. Whilst undoubtedly discrimination on the basis of age for potentially beneficial drugs is wrong, the causes for underutilization must be understood if initiation of underutilized drugs to inappropriate patient situations is to be avoided. Analysis of medicine underutilization should be considered in addition to PIMs, as undertreatment has previously been shown to be a problem of equivalent magnitude to that of medication overuse in long-term care settings of elderly residents (Sloane *et al.*, 2004).

In general terms, using criteria to detect inappropriate omissions where a healthcare professional matches a list of chronic medical disorders against evidence-based medications to establish

whether a relevant drug is missing should benefit many patients. However, efforts to avoid harms should take into consideration increased multiple disease severity and disability when starting seemingly indicated medicines and involve liaison with other providers where necessary to make sure that the benefit-harm balance remains positive (Wright *et al.*, 2009). At present, there is no strong evidence that applying medication underutilization interventions to large populations of elderly patients will be beneficial, and these criteria seem more likely to be helpful to guide physicians in individualized care decisions.

Ensuring that medicines are managed appropriately for elderly patients is illustrated by attempts to formalize such an approach. A conceptual framework comprising 10 sequential steps has been proposed (Scott *et al.*, 2012). The steps are to: (1) ascertain all current medications; (2) identify patients at high risk of or experiencing ADRs; (3) estimate life expectancy in high-risk patients; (4) define overall care goals in the context of life expectancy; (5) define and confirm current indications for ongoing treatment; (6) determine the time until benefit for disease-modifying medications; (7) estimate the magnitude of benefit versus harm in relation to each medication; (8) review the relative utility of different drugs; (9) identify drugs that may be discontinued; and (10) implement and monitor a drug minimization plan with ongoing reappraisal of drug utility and patient adherence by a single nominated clinician. It is noteworthy that these steps do not include an evaluation of underutilization of medicines as previously described.

The optimization of drug prescribing in the elderly was highlighted in the UK by the introduction of the National Service Framework in Older People (Department of Health, 2001). This noted several important areas where drug prescribing to older patients can be improved, including the linking of prescribing and clinical data to identify, and thereby reduce, ADRs. As quality issues have become a central concern in healthcare, the development of measurable indicators that indicate quality of care have also been proposed. Such indicators allow the benchmarking against other healthcare organizations and allow for performance management of care processes. One such set

of indicators are the ACOVE (Assessing Care of Vulnerable Elders) quality indicators, which identify medications that should be avoided and whether the medications prescribed for patients with specific diagnoses were appropriate for their conditions (Higashi *et al.*, 2004). The American Geriatrics Society has also defined quality indicators for medication use in vulnerable elderly individuals. These quality indicators focus on performing routine drug regimen reviews, patient monitoring (e.g., of warfarin use, renal function), and identifying drugs to be avoided in this age group.

## CONCLUSION

For decades, elderly patients were excluded from many trials of drugs from which they may benefit. In an era of evidence-based medicine, better quality evidence of the benefits and harms of medicines in these age groups is now available, but not for all diseases nor often for the very elderly. Valuable contributions can be made by studying drug utilization over time, investigating variations in pharmacokinetics and pharmacodynamics with age, and applying pharmacovigilance principles, in addition to simply extending the age range of clinical trials. Challenges exist in translating research into meaningful endpoints and coping with modern-day therapeutic complexities in order for clinicians and the patients we care for to make valid decisions about whether to take medications or not. We all need to be ready for this challenge in our increasingly ageing population.

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## **Part IV: PHARMACOVIGILANCE AND DRUG/SYSTEM ORGAN CLASSES**

### **Special Product Classes**

**43**

# **Anesthetic Adverse Drug Reactions**

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### **INTRODUCTION**

Anesthesia requires the exposure of a patient to a mixture of drugs in a short space of time. The main groups of drugs selectively used for anesthesia include the intravenous anesthetic agents, the gases and volatile inhalational agents, neuromuscular blocking drugs, and selected benzodiazepines and analgesics. For these groups, allergic reactions can be a source of adverse events. In the UK, the incidence and severity of anaphylactic reactions are unclear. A report of suspected anaphylactic reactions associated with anesthesia from the Association of Anaesthetists of Great Britain and Ireland and British Society for Allergy and Clinical Immunology (AAGBI and BSACI, 2003) from January 1, 1995, to June 22, 2001, identified from Medicines and Healthcare Regulatory Agency (MHRA) figures a total of 361 (36 fatal) reactions described as anaphylactic shock, anaphylactic reaction, or anaphylactoid reaction compared with 2074 (76

fatal) for all reported reactions. Hence, 361 of 2074 (17%) of all reported allergic drug reactions occur in the context of anesthesia, and 10% are fatal compared with 4% for all drugs. It is possible that the intravenous route for many anesthetic agents predisposes patients to these reactions, and more than 90% of reports occurred immediately or soon after induction of anesthesia. The MHRA yearly average for reported suspected anaphylactic reactions related to anesthesia is 55 per year compared with 319 for all drugs. Unfortunately, there is no denominator data to calculate the frequency of allergic reactions. However, the report by the AAGBI and BSACI (2003) estimates that in the UK there are 500 anaphylactic reactions annually by using epidemiological data from France and Australia. Previous estimates for the UK ranged from 350 to 5000 patients per year (Clarke and Watkins, 1993).

Anesthetists are also working in intensive care units (ICUs) where similar drugs to those used during surgery are continued for longer periods.

A recent USA national survey compiled from data in 1998 identified the sedative agents most often used for over 72 h to be opioids and benzodiazepines. If mechanical ventilation was maintained, then neuromuscular blocking drugs were also administered, such as vecuronium and pancuronium (Rhoney and Murry, 2003). Less than half the units in this survey used protocols, and drug selection was based on physician preference. In the UK in a similar survey, the most commonly used drugs for sedation were opioids (e.g., alfentanil and morphine), benzodiazepines (e.g., midazolam), and propofol (Murdoch and Cohen, 2000). Neuromuscular blocking agents were rarely used, but of those that were atracurium was the commonest. For children, propofol was still being used despite reports of adverse drug effects in this situation. A review of the risks involved in patient care using long-term anesthetic infusions has identified the following adverse effects (Riker and Fraser, 2005):

- propofol infusion syndrome (see below);
- propylene glycol intoxication (Cawley, 2001);
- prolonged QTc intervals with analgesics and antipsychotics (Glassman and Bigger, 2001);
- interference with bone healing with nonsteroidal anti-inflammatory drugs (Reuben *et al.*, 2005); and
- delirium/withdrawal after opioid combinations with benzodiazepines (Korak-Leiter *et al.*, 2005).

## HISTORICAL PERSPECTIVES

In 1954, a paper on the deaths associated with anesthesia and surgery identified an overall anesthetic mortality of 1 in 1560; but when the neuromuscular blocking drug curare (tubocurarine) was administered, the mortality rate was up to six times higher than those who did not receive the drug (Beecher and Todd, 1954). In hindsight, it was the anesthetic management that was at fault and not an adverse drug event. The introduction of the drug had created a scenario where airway management became a critical issue. Nevertheless, this report highlights the importance of drug postmarketing surveillance of morbidity and mortality to

improve patient safety during anesthesia and critical care.

In the UK in the late 1970s, Lunn and Mushin identified the pharmacological causes of anesthetic deaths as being caused by drug overdose, drug interactions, and genetic susceptibility, such as malignant hyperthermia (Lunn and Mushin, 1982). It was recognized in the Lunn and Mushin report that almost all the reactions reported the use of suxamethonium. This association was considered to reflect the situation where patients were requiring emergency surgery and were likely to be critically ill. Hence, the causation of the reaction was likely to be multifactorial rather than a direct consequence of suxamethonium use.

The incidence of drug usage is critical to reporting systems and is often an unknown quantity. It was in the 1970s and early 1980s that collaborations developed to identify the problems associated with allergies to anesthetic drugs in the Australian continent and Europe. Over the past 30 years as a result of these initiatives, regular reports and significant advances in the identification and management of anaphylactoid reactions have occurred (Mertes and Laxenaire, 2002). Historically, many drugs have been withdrawn in the UK or their use curtailed because of adverse effects. These include

- althesin, because of allergic phenomenon with an incidence of 1 in 11 000–19 000 (Clarke and Watkins, 1993);
- methoxyflurane, because of renal toxicity (Reichle and Conzen, 2003); and
- halothane, because of hepatic dysfunction (Reichle and Conzen, 2003).

## ANAPHYLACTIC REACTIONS

In Australia, the reported incidence of anaphylactic reactions was between 1 in 10 000 and 1 in 20 000 anesthetics (Fisher and Baldo, 1994). Since 1984 in France, there has been an epidemiological study of suspected anaphylactic reactions occurring during anesthesia. Initially, routine allergic assessments focused on IgE-dependent immune mechanisms. These investigations were skin tests combined with the identification of specific antibodies in the

serum. A spectrum of tests has now been described starting at the time of the event with estimation of plasma histamines (these are of low specificity), tryptase (with a half life of 2 h and occasional false-negative tests), and specific IgE and skin tests 6 weeks later (Mertes and Laxenaire, 2002; AAGBI and BSACI, 2003).

The most common drugs implicated in these types of reactions were the neuromuscular blocking agents with an incidence of 1 in 6500 anestheties compared with an overall incidence of 1 in 13 000 (Laxenaire, 1999). The specific substances identified in this multicenter outpatient study as possible causes of allergic phenomena and that were associated with positive allergy tests were neuromuscular blocking drugs (62%), latex (17%), antibiotics (8%), hypnotics (5%), colloid solutions (3%), and opioids (3%). Anaphylactic reactions to local anesthetic drugs are considered to be rare. The AAGBI and BSACI (2003) report was unable to identify allergic reactions to inhalational agents, but a few have been reported in the UK (Table 43.10) through yellow forms onto the database of the MHRA.

Fisher and colleagues have identified the presenting clinical features of anaphylaxis during anesthesia in 555 patients (Whittington and Fisher, 1998). In order of frequency, they are: no pulse, difficulty inflating the lungs, flushing, oxygen desaturation, cough, rash, dysrhythmias, urticaria, and edema. The cardiovascular system is most often destabilized, and cardiovascular collapse may be the only feature, leading to misdiagnosis. Many factors can influence severity of the reaction. These are asthma, beta-adrenergic blockade, and neuraxial anesthesia, where there may be compromise of the sympathetic nervous system. During the reaction there was cardiovascular collapse (88%), bronchospasm (37%), cutaneous signs such as erythema, urticaria, rash (in over 70%), edema (33% including generalized and pulmonary), and gastrointestinal effects (7%). The wide range of clinical symptoms and signs may generate diagnostic difficulties given the timing of the event and the range of drugs used. The recommendations of the AAGBI and BSACI (2003) include immediate management (depending on the severity), immediate and late investigations, and centralized reporting.

A diagnosis of an anaphylactoid reaction to anesthetic drugs may be difficult to establish. First, many drugs are often delivered simultaneously; second, skin testing may not be sensitive; and third, the heterogeneous nature of the signs may delay or obscure the diagnosis. An important observation has been that the severity of the reaction does not establish the diagnosis. Although most anaphylactic reactions were severe (88%) and often life threatening (65%), some cases were only mild (Mertes *et al.*, 2003) and may be indistinguishable from anaphylactoid reactions without adequate diagnostic investigation.

The allergic reaction can be activated by the binding of antigens to the drugs. For neuromuscular blocking drugs, the main antigenic determinants are substituted ammonium ions. Most neuromuscular blocking drugs contain two similar quaternary ammonium ions, and the distance between them is relevant to the chemical structure of the antibodies. Flexibility in the molecule also confers sensitivity to these effects, as demonstrated by suxamethonium compared with pancuronium. For thiopentone, two antigenic determinants have been identified, one on position 5 of the pyrimidine ring nucleus and the other in the thiol region (Baldo *et al.*, 1991). It should be recognized that antibodies to neuromuscular blocking drugs can persist for a long time.

The risk factors for allergic reactions have been listed as gender, age, atopy, and allergy history (Mertes and Laxenaire, 2002). Reactions to anesthetic drugs are more common in females than males even when the gender ratio of anesthetized patients is taken into account. Age was only identified as a factor for latex allergies, but allergies to anesthetic drugs overall are reported at all ages from neonates to the very elderly. Atopy has long been considered a risk, especially where there is a risk for histamine release; for example, neuromuscular blocking drugs (such as atracurium and mivacurium) or where drugs have a food component. For example, the propofol formulation contains egg lecithin and soybean oil, so its use is contraindicated in patients with hypersensitivities to these components (Hofer *et al.*, 2003). Interestingly, Mertes and Laxenaire (2002) consider that previous drug exposure does not appear to be a risk, but a

Table 43.1 A summary of the data analysis prints for the available intravenous induction agents.

	Total reactions	Total reports	Fatalities (% of reports)
Methohexitone	213	137	21 (15%)
Thiopentone	541	278	51 (18%)
Etomidate	217	141	5 (4%)
Propofol	2777	1500	80 (5%)
Ketamine	136	76	3 (4%)

documented reaction to a specific anesthetic drug, particularly the muscle relaxants, is a positive risk factor. In addition, the high incidence of cross-reactions leads to a recommendation of caution between muscle relaxants (Matthey *et al.*, 2000). Their advice in the context of a previous allergy to a neuromuscular blocking drug is to check for cross-reactivity before anesthetic administration. There is no evidence for generalized screening before surgery, but, given the importance of a positive history of adverse drug reaction, primary prevention and accurate documentation are essential.

Although the majority of adverse drug reactions to anesthetic drugs occur at the time of anesthesia, there are many reported delayed reactions after general anesthesia. These include exfoliative dermatitis, Stevens–Johnson syndrome, and other events (Fisher and Baldo, 1993).

## INDIVIDUAL AGENTS

### THE INDUCTION AGENTS

The available UK data for thiopentone, methohexitone, etomidate, propofol, and ketamine were obtained from voluntary reports of suspected adverse drug reactions entered from yellow forms onto the Adverse Drug Reactions On-line Information Tracking (ADROIT) database of the MHRA. They are summarized from data analysis prints and include the reactions reported up to January 2004. In the interpretation of the data, the causation of the event cannot be determined; comparative relationships between drugs may be misleading because both numerator and denominator data are not available, yet, despite biases and other factors, the

pattern of results provides a direction that can be exploited in the design of prospective studies.

For each drug, the total number of reactions for the single drug are listed, the number of reported cases, and the number of fatalities (Table 43.1). A multiple drug category is listed in the data analysis prints that include the induction agents, but it contains very small numbers of reactions, so these have not been analyzed here. The data contain more reactions than cases since one patient may suffer more than one reaction; for example, one patient who has an allergic reaction may have urticaria, bronchospasm, and hypotension, a total of three reactions. The fatalities for each agent reported as a percentage of the number of reported cases are listed in magnitude from thiopentone at 18% to etomidate and ketamine at 4% (Table 43.1). Table 43.2 summarizes the category classifications for the reactions. Table 43.3 summarizes the detailed diagnoses of the fatalities and the number of reported cases in that diagnostic category. One of the limitations of this data set is in the diagnostic classification; for example, “sinus bradycardia” and “bradycardia” are both reported separately yet are essentially the same.

The majority of reactions were expected; that is, cardiovascular, respiratory, and allergic. Thiopentone, methohexitone, and propofol are implicated in allergic reactions though their incidence is not known. Althesin is no longer marketed because of the high incidence of allergic reactions (Clarke and Watkins, 1993). Etomidate demonstrated a profile lacking allergic phenomena. However, many more reactions reported with etomidate related to central nervous system excitation, with convulsions in the majority of reactions (Table 43.4). Involuntary muscle movements can be severe, and epileptiform

Table 43.2 The number of total reactions (R) to the intravenous induction agent indicated and the fatalities (F) in that category.

Category	Thiopentone		Methohexitone		Etomidate		Propofol		Ketamine	
	R	F	R	F	R	F	R	F	R	F
Cardiovascular	168	16	35	14	26	3	599	45	26	2
Cerebrovascular	2	2	1	0	0	0	4	2	0	0
Congenital	0	0	0	0	0	0	3	0	0	0
Metabolic	1	0	0	0	4	0	46	2	2	0
Hearing	3	0	0	0	0	0	6	0	1	0
Eye	0	0	4	0	1	0	38	0	4	0
Allergies	86	19	19	2	8	0	100	12	0	0
Adrenal insufficiency	0	0	0	0	5	0	0	0	0	0
Gastrointestinal	11	0	16	0	5	0	44	1	14	0
General	35	0	25	0	13	0	257	0	16	0
Hemopoietic	1	0	0	0	1	0	15	2	0	0
Hepatobiliary	10	2	7	2	2	0	36	3	0	0
Infections	0	0	0	0	0	0	3	0	0	0
Injuries/overdose	0	0	0	0	0	0	9	0	2	1
Musculoskeletal	4	2	4	0	5	0	98	0	0	0
Neurological	14	1	24	1	62	0	788	1	19	0
Peripheral vascular	9	0	4	0	20	0	22	0	0	0
Pregnancy	0	0	0	0	0	0	4	1	0	0
Psychiatric	2	1	3	0	7	0	58	3	31	0
Renal	12	0	0	0	3	0	41	0	0	0
Respiratory	99	8	22	2	20	2	282	8	13	0
Skin	83	0	48	0	35	0	321	0	8	0
Surgical	1	0	0	0	0	0	0	0	0	0
Total	541	51	217	5	2777	5	136	80	13	0

Table 43.3 Data from the drug analysis print on single drug reports for intravenous agents submitted up to January 2004.

Reaction	Thiopentone		Methohexitone		Etomidate		Propofol		Ketamine	
	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal
<i>Cardiovascular</i>										
Sudden death (unexplained)	1	1					6	5	1	1
Cardiac arrest	22	9	16	12	5	2	63	17		
Electromechanical dissociation					4		1			
Cardiac failure	3	1					7	3		
Bradycardia							104	6		
Sinus bradycardia					4		4	1		
Extrasystoles									1	1
Ventricular fibrillation							6	2		
Acute cardiac failure	9	2	4	1			23	4		
Coronary artery occlusion							1	1		
Myocardial ischemia							3	1		
Myocardial infarction					1	1	5	1		
Cardiorespiratory failure	1	1					2	2		
Pulmonary edema	4	2	1	1						
Pulmonary hypertension							1	1		
<i>Cerebrovascular</i>										
Cerebral hemorrhage		1					1	1		
Brain stem ischemia	1	1								
Cerebral embolism							1	1		
<i>Others</i>										
Metabolic acidosis							19	2		
Hepatic failure							2	1		
Hepatic necrosis	2	2	2	2			2	2		
Gastrointestinal bacterial overgrowth syndrome							1	1		
Malignant hyperthermia	2	2								
Coagulation disorder							3	1		

Table 43.3 (Continued)

Reaction	Thiopentone		Methohexitone		Etomidate		Propofol		Ketamine	
	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal
Disseminated intravascular coagulation							1	1		
Coma	4	1								
Suicide/nonaccidental overdose	1	1					3	3	1	1
Cerebral edema							2	1		
Motor neurone disease			1	1						
Intrauterine death							1	1		
<i>Respiratory disorders</i>										
Anoxia			1	1					3	1
Acute respiratory distress syndrome										
Pneumothorax	2	1								
Respiratory failure	2	1								
Respiratory depression	5	3								
Bronchospasm	76	3	13	1	14	1	155	6		
Exacerbation of asthma										
Laryngeal edema							7	1		
<b>Total (non-allergies)</b>	<b>136</b>	<b>32</b>	<b>38</b>	<b>19</b>	<b>21</b>	<b>5</b>	<b>430</b>	<b>68</b>	<b>3</b>	<b>3</b>
<i>Allergies</i>										
Anaphylactic reaction	54	14	9	1			42	8		
Anaphylactic shock	1	1					7	1		
Anaphylactoid reaction	24	4	7	1			39	3		
<b>Total (allergies)</b>	<b>79</b>	<b>19</b>	<b>16</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>88</b>	<b>12</b>	<b>0</b>	<b>0</b>
<b>Total</b>	<b>215</b>	<b>51</b>	<b>54</b>	<b>21</b>	<b>21</b>	<b>5</b>	<b>518</b>	<b>80</b>	<b>3</b>	<b>3</b>

Each fatal reaction is one patient's report, but the total number of reactions may be more than the number of patients. The list selects the categories where fatalities have occurred.

electroencephalographic activity has been demonstrated on induction of anesthesia, leading to the avoidance of etomidate for patients with epilepsy (Holdcroft *et al.*, 1976; Krieger and Copperman, 1985). Peripheral vascular thrombotic events, of which none were fatal, were also commonly

reported (Table 43.4). They may be related to the formulation of the drug in propylene glycol. Part of the evidence that led to etomidate being withdrawn from use as a sedative in an ICU setting are recorded in Table 43.2 in the category of adrenal insufficiency. The main evidence came from

Table 43.4 Neurological and peripheral vascular reactions reported in the etomidate data analysis print ( $n = 217$ ).

Reaction	Number
<i>Neurological</i>	
Convulsions	22
Grand mal convolution	21
Myoclonic seizure	7
Loss of consciousness	2
Chorea	2
Extrapyramidal disorder	2
Dyskinesia	1
Focal convulsion	1
Hypoesthesia	1
Paresthesia	1
Hypotonia	1
Muscle rigidity	1
<i>Peripheral vascular</i>	
Venous thrombophlebitis	12
Vein thrombosis	2
Venous thrombosis	2
Vasculitis	1
Arterial thrombosis	1
Thrombosis	1
Vasodilation	1

a published prospective study that demonstrated direct adrenal suppression (Fellows *et al.*, 1983). Even a bolus dose can delay a rise in serum cortisol following surgery by up to 6 h. A prolonged infusion can cause similar effects that are not responsive to adrenocorticotropic hormone (Ledingham *et al.*, 1983). A call to abandon the use of etomidate in ICUs was made a few years ago (Annane, 2005), but this may not be so easy because other sedatives also have adverse effects when used for long-term infusions.

Propofol has a remarkable safety profile. Dose-dependent hypotension is a common complication leading to the large number of reports of cardiovascular adverse events. Clinically, these are particularly frequent in volume-depleted patients. Hypertriglyceridemia and pancreatitis are uncommon complications (Possidente *et al.*, 1998), and hepatobiliary fatalities are recorded in Table 43.3. For propofol, the event that limits its use in children

in the ICU is highlighted in the "metabolic" column of Table 43.2 (see below for adverse drug reactions in children) and has been called the propofol infusion syndrome. It is not confined to children, having been identified in an adult (Perrier *et al.*, 2000). Propofol is the only intravenous agent associated with infections (Webb *et al.*, 1998). The main reason for this is its formulation. At room temperature, propofol is an oil and insoluble in water. The present formulation consists of 1% or 2% (w/v) propofol, 10% soybean oil, 2.25% glycerol, and 1.2% egg phosphatide. Disodium edetate (ethylenediaminetetraacetic acid (EDTA)) or metabisulfite is added to retard bacterial and fungal growth. Allergic complications, including bronchospasm, have been reported with the formulation containing metabisulfite (Han *et al.*, 2001).

Fatal reports of allergic reactions are recorded in Table 43.3. The severity of these events is striking, but the vagaries of the reporting system should be considered. For example, in Table 43.2 in the large category of "skin" manifestations there are likely to be some mild allergic reactions. The incidence of allergic reactions to thiopentone has been estimated as 1 in 30 000 (Clarke and Watkins, 1993). Specific antibody binding tests for thiopentone have been developed to exclude cross-sensitivity to other anesthetic agents.

There are a small number of reported fatal reactions to ketamine in the data analysis prints, and this confirms the safety of the drug in critically ill patients. Cardiostimulatory events may cause cardiovascular compromise as a result of increases in catecholamines (Zsigmond and Kelsch, 1974). Emergence reactions are psychomimetic; for example, patients describe body detachment, floating experiences, or experience frank delirium. Long-term psychometric reactions have been reported. Following drug use, the incidence of emergency reactions ranges from 5% to 30% and increases with age, female sex, and large doses (Hejja and Galloon, 1975).

## NEUROMUSCULAR BLOCKING DRUGS

The 21 French centers contributing to data from anesthetic outpatient allergy clinics in 1990–1991

Table 43.5 A summary of the data analysis prints for the neuromuscular-blocking drugs and neostigmine.

	Total reactions	Total reports	Fatalities (% of reports)
Suxamethonium	741	399	53 (13%)
Vecuronium	178	101	6 (6%)
Rocuronium	140	80	2 (3%)
Atracurium	680	355	17 (5%)
Cisatracurium	26	13	1 (8%)
Gallamine	32	15	2 (13%)
Tubocurare	52	22	1 (5%)
Pancuronium	73	45	6 (13%)
Neostigmine	48	45	3 (7%)

reported in 1993 that an immune mechanism had been demonstrated in 813 of 1585 patients, and of these the muscle relaxants were involved in 571 (70.3%) cases (Laxenaire, 1993). Those most often involved were suxamethonium (43%), vecuronium (37%), pancuronium (13%), alcuronium (8%), atracurium (7%), and gallamine (6%). The high percentage of suxamethonium reactions observed in this study was not explained by its rate of use because the drug accounted for 9% of the drug market. Neither was the rate for vecuronium easily explained, because in a previous study the adverse drug reactions to vecuronium had been <20% and vecuronium use had not increased dramatically. One explanation was that vecuronium had replaced suxamethonium, and thus a change in usage had occurred, perhaps in a more vulnerable patient population. Another explanation was cross-reactivity between different muscle relaxants.

In France from 1994 to 1996, the frequency of allergic reactions to neuromuscular blocking drugs was highest with vecuronium, followed in descending order by atracurium, suxamethonium (succinyl choline), pancuronium, rocuronium, mivacurium, and gallamine (Laxenaire, 1999). In this French group of patients, there was a female-to-male ratio of 2.5, and cross-reactivity between drugs was common (70%).

Data analysis prints (Tables 43.5, 43.6, and 43.7) record fatalities and allergies in the atracurium, pancuronium, vecuronium, and tubocurarine groups. Fatalities would not present to outpatient allergy clinics, and so these data are useful in iden-

tifying the potential severity of reactions, albeit not in patients investigated for allergy. Cardiovascular and respiratory events are also commonly reported.

## INHALATIONAL AGENTS

The results of the data analysis prints for halothane, methoxyflurane, trichloroethylene, isoflurane, sevoflurane, enflurane, desflurane, and nitrous oxide have been summarised in Tables 43.8, 43.9, and 43.10. Table 43.9 summarizes a predominance of reports relating to the hepatobiliary system, and halothane, isoflurane, desflurane, isoflurane, enflurane, methoxyflurane, and trichloroethylene are all listed as single agents associated with the report. The fatalities associated with these effects are described in more detail in Table 43.10, where hepatic failure and hepatic necrosis predominate.

Halothane is well recognized to cause hepatic damage because it is metabolized to a large extent in the body. The other inhalational agents, though, are not without effect on the liver; this activity may be in proportion to the amount metabolized to the particular metabolic pathways; for example, acetylation and types of metabolites formed. For example, the fatalities associated with isoflurane indicate that hepatocellular damage is occurring (Reichle and Conzen, 2003).

Nephrotoxicity has been reported for methoxyflurane, enflurane, isoflurane, and sevoflurane. Hepatic defluorination with renal toxicity from inorganic fluoride is considered to be the main cause of methoxyflurane effects. Renal effects

Table 43.6 The number of total reactions (R) to the neuromuscular or antagonist drug indicated and the fatalities (F) in that category.

Category	Atracurium		Cisatracurium		Gallamine		Pancuronium		Rocuronium		Suxamethonium		Tubocurarine		Vecuronium		Neostigmine	
	R	F	R	F	R	F	R	F	R	F	R	F	R	F	R	F	R	F
Cardiovascular	184	8	10	1	12	1	15	1	44	1	266	20	16	0	67	3	13 <sup>d</sup>	3
Cerebrovascular	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Congenital	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Metabolic	6	0	0	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0
Hearing	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Eye	3	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	1	0
Allergies	100	6	5	0	8	0	10	2	41	0	160	16	7	1	22	1	1 <sup>a</sup>	0
Gastrointestinal	2	0	0	1	0	0	0	0	1	0	7	0	0	0	3	0	5	0
General	35	0	1	0	4	0	17	1	8	0	47	5	4	0	14	0	8	0
Hemopoetic	4	0	0	0	0	0	0	0	1	0	3	1	0	0	0	0	0	0
Hepatobiliary	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2	0
Injuries/ poisoning	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Investigation/ procedure	0	0	0	0	0	0	0	0	0	0	2	0	0	0	2	0	0	0
Musculoskeletal	9	0	1	0	0	0	0	0	3	1	36	4	0	0	5	0	0	0
Neurological	32	0	2	0	0	0	11	0	3	0	21	0	2	0	14	0	6	0
Peripheral vascular	10	0	0	1	0	0	0	1	0	0	6	0	4	0	1	0	0 <sup>a</sup>	0
Psychiatric	3	0	0	0	0	0	0	0	0	0	3	1	0	0	2	1	1	0
Renal	4	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1	1	0
Respiratory	134	2	6	0	5	1	12	2	20	0	123	6	10	0	25	1	3 <sup>b</sup>	0
Skin	138	0	1	0	1	0	7	0	16	0	48	0	9	0	21	0	5 <sup>c</sup>	0
Surgical/ medical interventions	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Total	680	17	26	1	32	2	73	6	140	2	741	53	52	1	178	6	48 <sup>e</sup>	3

<sup>a</sup>plus 1 from a mixture with multiple constituents.

<sup>b</sup>plus 2 from a mixture with multiple constituents.

<sup>c</sup>plus 3 from a mixture with multiple constituents.

<sup>d</sup>plus 9 from a mixture with multiple constituents.

<sup>e</sup>plus 17 from a mixture with multiple constituents.

Table 43.7 Data from the drug analysis print on single drug reports for neuromuscular-blocking agents or their antagonists submitted up to January 2004.

Reaction	Atracurium		Cisatracurium		Gallamine		Pancuronium		Rocuronium		Suxamethonium		Tubocurare		Vecuronium		Neostigmine		
	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	
<i>Cardiovascular</i>																			
Sudden death unexplained	2		2														1	1	
Acute circulatory failure																	29	3	
Cardiac failure																	1	1	
Cyanosis																	23	1	
Electromechanical dissociation																			
Hypotension																			
Myocardial infarction																			
Myocardial ischemia																			
Cardiac arrest	25		3														52	10	
Bradycardia	28		3														33	2	
Ventricular fibrillation																	5	1	
<i>Cerebrovascular</i>																			
Brain stem ischemia	1		1														13	1	
General																	3	1	
Collapse																	3	2	
Hyperpyrexia																	6	2	
Pyrexia																	1	1	
Hematological																			
Disseminated intravascular coagulation																			

(Continued)

Table 43.7 (Continued)

Reaction	Atracurium		Cisatracurium		Gallamine		Pancuronium		Rocuronium		Suxamethonium		Tubocurare		Vecuronium		Neostigmine	
	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F
<i>Musculoskeletal</i>																		
Malignant hyperthermia																		
Myoglobinuria																		
Psychiatric																		
Suicide																		
<i>Respiratory disorders</i>																		
Respiratory gas exchange disorder																		
Pneumonia																		
Bronchospasm	96	2			3	1	6	1										
Apnea																		
Laryngeal edema																		
<b>Total (non-allergies)</b>	152	11	1	1	6	2	11	4	3	2	337	37	0	0	18	5	4	3
<i>Allergies</i>																		
Anaphylactoid reaction	30	2							3	1			10	1				
Anaphylactic reaction	71	4							6	1			41	4				
Anaphylactic shock													100	9	6	1	11	1
<b>Total (allergies)</b>	253	17	1	1	6	2	20	6	9	2	0	0	159	16	6	1	11	1
<b>Total</b>	253	17	1	1	6	2	20	6	3	0	2	53	6	1	1	29	6	4

Each fatal reaction (F) is one patient's report, but the total number of reactions may be more than the number of patients. The list selects the categories where fatalities have occurred.

Table 43.8 A summary of the data analysis prints for nitrous oxide gas and the inhalational anesthetic agents.

	Total reactions	Total case reports	Fatalities (% of reports)
Halothane	822	548	211 (39%)
Desflurane	37	19	8 (42%)
Isoflurane	165	101	9 (9%)
Sevoflurane	136	84	3 (4%)
Enflurane	165	103	5 (5%)
Methoxyflurane	5	3	0 (0%)
Trichloroethylene	11	8	3 (38%)
Nitrous oxide	83	55	13 (24%)

Each fatal reaction is one patient's case report, but the total number of reactions may be more than the number of cases.

reported in the data analysis prints are small (Table 43.9) and may reflect appropriate use of the inhalational agents and risk avoidance measures.

Long-term exposure to clinically effective concentrations of nitrous oxide may cause megaloblastic bone-marrow depression and neurological symptoms. These effects occur from an interaction with vitamin B12 resulting in selective inhibition of methionine synthase, a key enzyme in methionine and folate metabolism. The reporting of such effects in the data analysis prints is not identifiable (Table 43.9).

## LOCAL ANESTHETICS

Table 43.11 shows the results of the UK data analysis prints for the local anesthetics lidocaine, bupivacaine, levobupivacaine, ropivacaine, procaine, and prilocaine. For levobupivacaine, adverse drug reaction data collection is limited by recent licensing, and hence a shorter period for reporting reactions. In addition, specific reactions to local anesthetic drugs have been reported:

- nerve toxicity with hyperbaric lidocaine delivered intrathecally through a microcatheter during long-term use;
- reduced metabolic breakdown (e.g., by drugs altering plasma cholinesterase activity or CYP450 enzymes) can allow toxic concentrations of local anesthetic drugs to build up;
- reduction of liver blood flow (e.g., by hypotension) will decrease the hepatic clearance of amide local anesthetics.

Lidocaine data (Tables 43.11, 43.12, and 43.13) are divided into three categories because lidocaine has a different toxicity profile when combined with a vasoconstrictor, such as epinephrine (adrenaline) or phenylephrine. In anesthesia, lidocaine with and without epinephrine is usually available, whereas for dental procedures the preference is for lidocaine with phenylephrine. Hence, the reported reactions may reflect the context of use and the drug delivery systems. For example, dental syringes are volume limited. Lidocaine can be readily absorbed from tissues leading to systemic absorption and toxicity. This can be prevented by constricting local blood vessels to prevent uptake into the circulation. Hence, a higher total dose of lidocaine can be administered. For example, the reports of overdose with lidocaine in Tables 43.12 and 43.13 do not occur with the lidocaine and vasoconstrictor mixture. However, a lidocaine and epinephrine mixture has been associated with cardiovascular and fatal reactions, presumably because of systemic absorption of the epinephrine. The concentration of epinephrine with lidocaine in the past was high, and sometimes a mixture was prepared at the bedside by a medical practitioner. Mistakes in dilution used to be a risk, and nowadays a solution pre-prepared should be used with a concentration of 1 in 200 000.

What these data do not identify is the co-administration effects of volatile anesthetic agents such as halothane with lidocaine solutions containing epinephrine. In this situation, the volatile anesthetic agent can sensitize the myocardium and this leads to dysrhythmias.

Table 43.9 The number of total reactions (R) to the gas or inhalational anaesthetic drug indicated and the fatalities (F) in that category.

Category	Halothane		Desflurane		Isoflurane		Sevoflurane		Enflurane		Methoxyflurane		Trichloroethylene		Nitrous oxide	
	R	F	R	F	R	F	R	F	R	F	R	F	R	F	R	F
Cardiovascular	62	20	27	7	28	0	24	2	13	1	0	0	1	1	22	10
Cerebrovascular	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Congenital	6	0	0	0	0	0	0	0	2	0	0	0	0	0	5	0
Metabolic	8	0	0	0	2	0	0	0	0	0	0	0	0	0	1	0
Hearing	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Eye	3	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Allergies	2	1	0	0	2	0	2	0	2	0	0	0	0	0	0	1
Endocrine	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Gastrointestinal	38	0	0	0	4	0	6	1	7	0	0	0	0	0	3	0
General	90	1	2	0	14	0	16	0	0	0	0	0	0	0	9	0
Hemopoietic	7	0	0	0	2	0	0	0	2	0	0	0	0	0	4	0
Hepatobiliary	505	182	1	0	48	6	32	3	1	0	0	4	1	9	2	0
Infections	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Injuries	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Musculoskeletal	11	3	0	0	16	0	11	0	0	0	0	0	0	0	1	0
Neurological	22	0	0	0	17	0	59	0	0	0	0	2	0	0	9 <sup>b</sup>	0
Peripheral vascular	0	0	1	0	1	0	0	0	0	0	0	1	0	1	0	0
Pregnancy	1	0	1	0	1	0	0	0	0	0	0	0	0	0	4 <sup>c</sup>	0
Psychiatric	7	0	0	0	3	0	0	0	4	0	0	0	0	0	1	0
Renal	19	2	0	0	4	0	0	0	2	0	3	0	0	0	1	0
Respiratory	12	1	1	0	11	1	0	0	13	1	0	0	3	1	5 <sup>a</sup>	0
Skin	23	0	2	0	12	0	0	0	1	0	0	0	0	0	7	0
Surgical	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	822	211	37	8	165	9	30	3	165	5	5	11	3	83 <sup>d</sup>	13	

<sup>a</sup>Plus 1 from a mixture with multiple constituents.

<sup>b</sup>Plus 4 from a mixture with multiple constituents.

<sup>c</sup>Plus 3 from a mixture with multiple constituents.

<sup>d</sup>Plus 10 from a mixture with multiple constituents.

**Table 43.10 Data from the drug analysis print on single drug reports for the gas and inhalational agents submitted up to January 2004.**

Reaction	Halothane		Desflurane		Isoflurane		Sevoflurane		Enflurane		Methoxyflurane		Trichloroethylene		Nitrous oxide		
	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	
<i>Cardiovascular</i>																	
Acute circulatory failure	4	3	2	2													
Pulmonary edema	6	3															
Cardio-respiratory failure									2	2							
Cardiac arrest	19	13	1	1													
Myocardial infarction																	
Myocardial ischemia					4	4											
Ventricular fibrillation	3	1															
<i>Cerebrovascular disorders</i>																	
Cerebral thrombosis	1	1															
<i>Gastrointestinal</i>																	
Mesenteric occlusion									1	1							
<i>General</i>																	
Hyperpyrexia <sup>a</sup>	3	1															
Hepatobiliary Hepatic function abnormal	31	1															
Hepatitis	72	14															
Hepatic coma	7	4															
Hepatic failure	37	30															
Hepatic necrosis	53	50															
Hepatocellular damage	10	1															
Reye's syndrome	1	1															
Jaundice																	

(Continued)

Table 43.10 (*Continued*)

		Halothane		Desflurane		Isoflurane		Sevoflurane		Enflurane		Methoxyflurane		Trichloroethylene		Nitrous oxide		
Reaction		T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	
<i>Infection</i>																		
Septicemia																		
Musculoskeletal																		
Hyperthermia	5	3																
malignant <sup>a</sup>																		
Renal disorders	11	2																
Respiratory disorders	1	1																
Respiratory arrest																		
Respiratory failure																		
Anoxia																		
Adult respiratory distress syndrome																		
Total (non-allergies)	544	210	37	8	8	7	3	3	13	5	0	0	3	3	14	12		
Allergies	1	1																
Anaphylactoid																		
Anaphylactic																		
Total (allergies)	1	1	0	0	2	2	0	0	0	0	0	0	0	0	1	1	1	1
Total	545	211	37	8	10	9	3	3	13	5	0	0	3	3	15	13		

Each fatal reaction (F) is one patient's report but the total number of reactions (T) may be more than the number of patients. The list selects the categories where fatalities have occurred. (Similar symptoms but classified in different classes.

Table 43.11 A summary of the data analysis prints for the local anesthetic agents.

	Total reactions	Total case reports	Fatalities (% of reports)
Lidocaine	936	815	23 (3%)
Lidocaine with epinephrine	443	231	2 (1%)
Lidocaine with phenylephrine	5	3	0 (0%)
Bupivacaine	375	222	23 (10%)
Levobupivacaine	19	9	0 (0%)
Ropivacaine	32	19	2 (11%)
Procaine	15	13	0 (0%)
Prilocaine	295	204	0 (0%)

Each fatal reaction is one patient's case report but the total number of reactions may be more than the number of cases. No data is presented for multiple constituents.

The reactions for bupivacaine also demonstrate cardiovascular events; they reflect myocardial bupivacaine toxicity that may be refractory to treatment (Table 43.9). Accidental intravenous injection of bupivacaine can lead to fatal cardiac arrhythmias, particularly in association with a Bier's nerve block (intravenous regional anesthesia). The first alert of this scenario was published in 1983. Subsequently, intravenous regional anesthesia with bupivacaine has not been recommended. The preferred drug is prilocaine, which is less toxic (Table 43.11 shows no deaths) but which in infants may induce methemoglobinemia.

### ANALGESICS, SEDATIVES, AND THEIR ANTAGONISTS

Tables 43.14, 43.15 and 43.16 show a selection of adverse effects from opioid and nonsteroidal anti-inflammatory analgesics, sedatives, and antagonists that are used mainly during anesthesia. The risks associated with their long-term use in the ICU are described in the "Introduction" section. In this situation their side effects can be more severe.

### SPECIFIC PROBLEMS

#### ANESTHETIC ADVERSE DRUG REACTIONS IN CHILDREN

A systematic review has found that 9% of children experience an adverse drug reaction while in hospital

(Impicciatore *et al.*, 2001). Fatal reactions reported through ADROIT data from 1964 to 2000 for children aged 16 and less identified 18 deaths out of 331 related to anesthetic drugs. Ten of these were from the use of inhalational anesthetic agents alone and 13 were in association with propofol. Of those where propofol was suspected, 12 were related to its use as a sedative agent. In the data analysis prints (Table 43.2) the reaction is peculiar to propofol but the ages of the patients are not given. The clinical symptoms and signs of the reaction were first described as hyperlipidemia, hepatomegaly, metabolic acidosis, and multiorgan failure (Parke *et al.*, 1992). Despite the propofol infusion syndrome being described in 1992, further fatalities have been reported. The syndrome presents after prolonged propofol infusion with severe metabolic acidosis unresponsive to maximum therapy (Cannon *et al.*, 2001). Acute renal failure can then result from rhabdomyolysis, and myocardial dysfunction with bizarre, wide QRS complexes developed without hyperkalemia. The death of the patient is usually from myocardial collapse with severe metabolic acidosis and multisystem organ failure (involving the renal, hepatic, and cardiac systems). Thus, recognition of the context in which the risk of adverse events increases is essential in risk prevention. However, despite the risk of propofol infusion syndrome being identified in 1992, propofol infusions are still used in children. The main indication is for short-term sedation in children requiring procedures. However, more than 1 in 10 intensivists would use propofol for prolonged

Table 43.12 The number of total reactions (R) to the local anaesthetics indicated, when administered as single constituent products, and the fatalities (F) in that category.

Category	Lidocaine		Lidocaine+epinephrine		Lidocaine+phenylephrine		Bupivacaine		Levobupivacaine		Ropivacaine		Procaine		Prilocaine	
	R	F	R	F	R	F	R	F	R	F	R	F	R	F	R	F
Cardiovascular	125	8 <sup>a</sup>	70	2	1	0	72	15	5	0	4	1	4	0	21	0
Cerebrovascular	1	1	0	0	0	0	4	1	0	0	0	0	0	0	0	0
Congenital	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ear	9	0	3	0	0	0	1	0	0	0	0	0	0	0	6	0
Eye	14	0	11	0	0	0	13	0	0	0	0	0	1	0	3	0
Metabolic	4	1	2	0	0	0	2	0	0	0	0	0	0	0	4	0
Allergies	45	4	17	0	0	0	16	0	0	0	0	0	0	0	12	0
Gastrointestinal	50	0	38	0	0	0	11	0	0	0	2	0	0	0	21	0
General	126	0	97	0	0	0	32	0	0	0	4	0	2	0	39	0
Hemopoetic	2	1	1	0	0	0	2	0	0	0	0	0	1	0	0	0
Hepatobiliary	2	0	1	0	0	0	3	0	0	0	0	0	0	0	0	0
Infections	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Injuries/ overdose	7	2	0	0	0	0	5	0	1	0	0	0	0	0	2	0
Musculoskeletal	10	0	10	0	0	0	14	0	0	0	3	0	0	0	5	0
Neoplasm	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Neurological	133	1	75	0	1	0	129	2	11	0	7	0	2	0	47	0
Peripheral vascular	7	0	1	0	0	0	1	0	0	0	0	0	1	0	0	0
Psychiatric	0	0	25	0	0	0	5	0	0	0	2	0	0	0	0	0
Pregnancy	1	0	2	0	0	0	3	2	2	0	0	0	0	0	0	0
Respiratory	70	1	14	0	1	0	27	2	2	0	6	1	1	0	0	0
Skin	169	1	76	0	2	0	31	0	0	4	0	3	0	0	0	0
Total	815	20 <sup>a</sup>	443	2	5	0	375	23	19	0	32	2	15	0	204	0

<sup>a</sup>Plus 3 from multiple constituent products (2 cardiovascular; 1 anaphylactic).

**Table 43.13** Data from the drug analysis print on single drug reports for local anesthetic agents submitted up to January 2004.

Reactions	Lidocaine <sup>a</sup>		Lidocaine+epinephrine		Lidocaine+phenylephrine		Bupivacaine		Levobupivacaine		Ropivacaine	
	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F
<i>Cardiovascular</i>												
Sudden death unexplained	1	1							1	1		
Pulmonary embolism	1	1							1	1		
Cardiac arrest	6	3							15	9		
Bradycardia	12	1							2	1		
Electromechanical dissociation									3	2		
Cardiorespiratory failure											1	1
Acute circulatory failure	4 <sup>a</sup>	1 <sup>a</sup>			4	1						
Left ventricular failure	1 <sup>a</sup>	1 <sup>a</sup>			1	1						
Myocardial infarction	1	1									1	
Ventricular fibrillation	2	1							3	1		
Cerebrovascular disorders											2	
Cerebral hemorrhage												
Ruptured cerebral aneurysm												
Metabolic												
Diabetic ketoacidosis	1											
Hematology												
Thrombocytopenia	1											
Injury												
Overdose	3											

(Continued)

Table 43.13 (Continued)

Reactions	Lidocaine <sup>a</sup>				Lidocaine+epinephrine				Bupivacaine				Levobupivacaine				Ropivacaine			
	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F		
<i>Infection</i>																				
Septicemia																	1	1		
<i>Neurology</i>																				
Convulsions																	28	1		
Grand mal																	25	1		
Convulsion																				
Spinal claudication																				
Renal disorders																				
Renal failure																				
Pregnancy																	2	2		
Stillbirth																				
<i>Respiratory disorders</i>																				
Respiratory arrest																	5	1		
Anoxia																	2	1		
<i>Asphyxia</i>																				
Respiratory failure																	1	1		
Skin																				
Angioedema																				
Total (non-allergies)	42 + 5 <sup>a</sup>		16 + 2 <sup>a</sup>		0		0		0		0		0		0		2	2		
Allergies																				
Anaphylactic shock	5		1																	
Anaphylactoid	13		2																	
Anaphylactic	17		1 + 1 <sup>a</sup>		5		0		0		0		0		0		69	23		
<b>Total (allergies)</b>	<b>35</b>		<b>4 + 1<sup>a</sup></b>		<b>5</b>		<b>0</b>		<b>0</b>		<b>0</b>		<b>0</b>		<b>0</b>		<b>0</b>			
<b>Total</b>	<b>77 + 5<sup>a</sup></b>		<b>20 + 3<sup>a</sup></b>		<b>5</b>		<b>2</b>		<b>0</b>		<b>0</b>		<b>0</b>		<b>0</b>		<b>2</b>	<b>2</b>		

Each fatal reaction (F) is one patient's report, but the total number of reactions may be more than the number of patients. The list selects the categories where fatalities have occurred.

<sup>a</sup>Lidocaine as a constituent of a preparation containing multiple chemical agents; for example, lidocaine+epinephrine.

Table 43.14 A summary of the data analysis prints for selected analgesic agents and the benzodiazepine, midazolam, and its antagonist.

	Total reactions	Total reports	Fatalities (% of reports)
Alfentanil	155	83	4 (5%)
Fentanyl	695	356	26 (7%)
Ketorolac	251	152	5 (3%)
Naloxone	52	34	1 (3%)
Remifentanil	90	43	4 (9%)
Midazolam	659	355	26 (7%)
Flumazenil	35	20	4 (20%)

sedation in pediatric intensive care while monitoring for adverse events (Festa *et al.*, 2002). The maximum infusion dose that was considered dangerously high was  $\geq 10\text{ mg/(kg h)}$  for more than 72 h. The propofol infusion syndrome is a rare complication first reported in pediatric patients and believed to be due to decreased transmembrane electrical potential and alteration of electron transport across the inner mitochondrial membrane. For

the safe use of propofol infusions, there should be clear indications and contraindications, a maximum dose rate, and period of infusion and identified minimum monitoring requirements.

#### CENTRAL ANTICHOLINERGIC SYNDROME

Acetylcholine is one of the central neurotransmitters on which drugs used in anesthesia act. Anesthetic drugs can block cholinergic transmission to induce the clinical picture of central anticholinergic syndrome, similar to atropine intoxication. The signs are agitation, convulsions, hallucinations, disorientation, and central nervous system depression, such as stupor, coma, and respiratory depression (Schneck and Rupreht, 1989). Drugs that induce this reaction include opioids, benzodiazepines, phenothiazines, ketamine, etomidate, butyrophenones, propofol, nitrous oxide, halogenated inhalational agents, and H<sub>2</sub>-receptor blocking drugs such as cimetidine. The anticholinesterase physostigmine is used to alleviate symptoms because it readily crosses the blood-brain barrier, thus enhancing cholinergic effects. It does not reverse analgesia.

Table 43.15 The number of total reactions (R) to the analgesic, sedative, or antagonist drug indicated and the fatalities (F) in that category.

Category	Alfentanil		Fentanyl		Ketotolac		Naloxone		Flumazenil		Remifentanil		Midazolam	
	R	F	R	F	R	F	R	F	R	F	R	F	R	F
Cardiovascular	51	0	135	12	30	0	12	1	14	4	42	2	89	13
Cerebrovascular	0	0	2	0	0	0	0	0	0	0	0	1	1	0
Congenital	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Metabolic	0	0	11	0	1	0	0	0	1	0	2	0	2	0
Hearing	0	0	3	0	1	0	0	0	0	0	0	0	2	0
Eye	3	0	21	0	8	0	0	0	0	0	0	0	10	0
Allergies	13	2	41 <sup>a</sup>	6	12	0	3	0	1	0	3	0	14	2
Endocrine	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Gastrointestinal	3	0	45	0	36	2	7	0	2	0	2	0	26	0
General	13	0	96	0	16	0	6	0	4	0	15	0	96	0
Hemopoetic	0	0	1	0	6	0	0	0	0	0	0	0	7	0
Hepatobiliary	0	0	8	1	8	0	0	0	0	0	1	1	21	1
Infections	0	0	0	0	1	0	0	0	0	0	1	0	2	0
Injuries/ poisoning	1	0	10	0	3	0	0	0	0	0	0	0	2	0
Investigation/ procedure	1 <sup>b</sup>	0	1b	0	0	0	0	0	0	0	0	0	2	0
Musculoskeletal	3	0	8	0	4	0	3	0	0	0	0	0	14	1
Neoplasm	0	0	1	1	1	0	0	0	0	0	0	0	0	0
Neurological	23	0	83	1 <sup>c</sup>	23	0	8	0	5	0	7	0	117	1
Peripheral vascular	0	0	10	0	2	0	1	0	1	0	0	0	12	0
Reproduction/ pregnancy	0	0	1	0	0	0	2	0	0	0	0	0	1	0
Psychiatric	1	0	51	2	13	1	2	0	2	0	9	1	76	1
Renal	0	0	6	0	5	0	0	0	0	0	0	0	2	0
Respiratory	34	2	81	3	26	1	0	0	3	0	5	0	79	7
Skin	9	0	79 <sup>d</sup>	0	44	0	7	0	2	0	3	0	83	0
Surgical/ medical interventions	0	0	0	0	11	0	0	0	0	0	0	0	0	0
Total	135	4	695 <sup>d</sup>	26	251	5	52	1	35	4	90	4	659	26

<sup>a</sup>Plus 1 from a mixture with multiple constituents.<sup>b</sup>Reported as "difficult anesthetic."<sup>c</sup>Plus 3 from a mixture with multiple constituents.<sup>d</sup>Plus 7 from a mixture with multiple constituents.

Table 43.16 Data from the drug analysis print on single drug reports for analgesic agents or their antagonists submitted up to January 2004.

Reaction	Alfentanil		Fentanyl		Ketorolac		Naloxone		Remifentanil		Midazolam	
	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F
<i>Cardiovascular</i>												
Sudden death unexplained			3	3							3	3
Acute circulatory failure		9	1						1	1	2	2
Cardiorespiratory failure		1	1								3	1
Myocardial infarction											25	1
Hypotension									3	1	11	6
Cardiac arrest												
Ventricular fibrillation												
Gastrointestinal												
Gastrointestinal hemorrhage												
<i>General</i>												
Drug interaction potentiation												
Hepatobiliary												
Heaptic necrosis	1	1							1	1	1	1
Heaptic failure												
Musculoskeletal												
Hyperthermia malignant <sup>a</sup>												
Neoplasm												
Carcinomatosis	1	1										
Malignant neoplasm progression												
<i>Neurological</i>												
Cerebral edema	1	1										
Coma											6	1
<i>Psychiatric</i>												
Anorexia nervosa												
Suicide	2	2										
Drug misuse												
<i>Respiratory disorders</i>												
Adult respiratory distress syndrome									1	1	1	1
Aspiration											5	1
Respiratory failure	4	3									5	1
Respiratory arrest											23	3
Respiratory depression											1	1
Asphyxia												
Laryngeal edema	1	1										
<b>Total (non-allergies)</b>	2	2	51	20	9	5	2	1	6	4	88	24
<i>Allergies</i>												
Anaphylactoid reaction	9	1	13	2							3	1
Anaphylactic reaction	1	1	20	4							3	1
Anaphylactic shock												
<b>Total (allergies)</b>	10	2	33	6	0	0	2	1	6	4	6	2
<b>Total</b>	12	4	84	26	9	5	2	1	6	4	94	26

Each fatal reaction (F) is one patient's report but the total number of reactions may be more than the number of patients. The list selects the categories where fatalities have occurred.

<sup>a</sup>Similar symptoms but classified in different classes.

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# Pharmacoepidemiology as Part of Pharmacovigilance for Biologic Therapies

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## INTRODUCTION

Biologic therapies are medicines that are derived from living cells through recombinant DNA technology. Compared with small-molecule therapies that have a long history, biologics are a relatively new addition to the therapeutic armamentarium, tracing their roots to the 1980s.

In this chapter, we begin by describing some fundamental differences, from a drug safety and risk management perspective, between biologics and small molecules. We then consider the contribution of pharmacoepidemiologic studies to pharmacovigilance for four biologic therapies: two for which there is a decade or more of market experience (EpoGen® (epoetin alfa (EPO)) and Enbrel® (etanercept)) and two that have only recently been approved (Prolia® and XGEVA®; different doses and schedules of denosumab). The former two therapeutics came to market prior to the Food and Drug Administration Amendments Act of 2007

(FDA, 2011a), when the agency acquired authority to mandate postmarket studies, including pharmacoepidemiologic studies. For Prolia and XGEVA, the development of a pharmacoepidemiologic study of prespecified adverse events of interest was an important part of the regulatory approval negotiations. Such requirements have become more commonplace for new therapies, and we will underscore issues of feasibility, study design, and bias that must be considered for valid analyses among patients treated in routine clinical practice.

## SAFETY MONITORING FOR BIOLOGICAL TREATMENTS

Despite some differences, the basic principles of safety monitoring for biologics are similar to those for nonbiologic drugs. The International Conference on Harmonization (ICH) guidelines outline the criteria that apply generally across drugs (ICHM3),

apply specifically for biologics (ICH S6 and its 2011 addendum (R1)) (FDA, 2011b), and apply for compounds administered to patients with diseases for which there is no current adequate treatment (typically oncologic disorders) (ICH S9, 2008).

The specific properties of biologics dictate a somewhat different focus for safety assessment compared with nonbiologics. The relevant considerations are best detailed by stage of development.

## PRECLINICAL SAFETY ASSESSMENT

There are four main differences between small molecules and biologics in safety assessment during the preclinical phase. First is the selection of an appropriate species for toxicology and pharmacology studies. For small molecules, it is typical to study rodent and nonrodent species. However, targets for biologic therapies may not be expressed in rodents. Toxicology studies, therefore, are often conducted in nonhuman primates (usually cynomolgus monkeys), and often one species will suffice. Supportive studies may be conducted; for example, pharmacology studies or knockout mice studies.

A second difference is the duration of therapeutic action. Monoclonal antibodies and other biologic products generally have a prolonged half-life in comparison with small molecules. In addition, there is often a lag time for a pharmacodynamic effect. This is in contrast to small molecules, where there is typically a more direct relationship between pharmacokinetics (PK) and pharmacodynamics (PD).

Third, the toxicities observed for biologics are typically extensions of the desired pharmacologic effects. “Off-target effects” are of more concern for small molecules.

Fourth, the toxicology profile for a biologic may be unrevealing. An example would be Enbrel, where no adverse effects were observed in nonclinical toxicology studies.

## CLINICAL DEVELOPMENT PHASE

During clinical development, biologics are usually administered to humans via the intravenous or sub-

cutaneous route (current formulations are not amenable to enteral absorption). Accordingly, investigators focus on the potential for infusion-associated toxicities and injection-site reactions. The objectives of first in human studies include safety, tolerability, PK, and PD evaluations. In initial human testing, dosing is escalated carefully to a supra-therapeutic dose under controlled conditions to understand the dose (and concentration)–effect relationship. In contrast to small molecules, most biologics, such as monoclonal antibodies, have long half-lives and extended durations of action. Accordingly, the concentration–time profile can be relatively flat and the time of maximum concentration not well characterized for subcutaneous administration. Toxicities of small molecules may relate to the time and extent of maximum concentration, whereas with a large molecule administered subcutaneously the toxicity is more likely to relate to a time above a pharmacologically active concentration and the trough or minimum concentration becomes a more relevant PK variable.

Most biologics are metabolized via proteolytic degradation. It is unusual to see drug–drug interactions. Liver dysfunction does not typically alter PK, and renal dysfunction does not alter PK for biologics of molecular weight greater than serum albumin, such as monoclonal antibodies. Smaller therapeutic proteins that are filtered through the glomeruli may need dose or schedule adjustment in patients with renal failure (e.g., Kineret® (anakinra)).

A further difference between biologics and small molecules is the higher frequency of antibody-mediated immune responses. These responses range from a clinically insignificant laboratory test result to a severe adverse outcome. As a precaution, subjects’ baseline blood samples are usually tested prior to investigational product administration to confirm a lack of prevalent antibodies to the investigational product. If there is a positive binding antibody, further testing will be conducted for evidence that the antibodies can neutralize the investigational product (neutralizing antibody). The consequences can be more severe if the investigational product is a therapeutic protein with a sufficiently similar sequence homology to an

endogenous protein. An example of this phenomenon is pure red cell aplasia (PRCA), which can occur in patients treated with erythropoiesis-stimulating agents. Neutralizing antibodies affect endogenous erythropoietin, causing severe anemia instead of treating the anemia. A further example occurred with a therapeutic protein that stimulated release of platelets. It was similar enough to the endogenous protein thrombopoietin and resulted in thrombocytopenia due to neutralizing antibodies (Li *et al.*, 2001).

In general, large clinical trials (for both biologics and nonbiologics) provide an estimate of frequency of common drug-related adverse effects or adverse reactions. Uncommon or rare adverse effects are detected when sufficient numbers of subjects have been exposed to the therapeutic of interest. These events may not be detected until after a drug is marketed.

## POSTMARKETING PHASE

Postmarketing surveillance for unusual or unrecognized safety signals is similar for small molecules and biologics. This includes follow-up of spontaneously reported adverse events, composition of periodic reports, and surveillance of the medical literature. In contrast to biologics, small molecules tend to have more drug withdrawals related to hepatic toxicity, QT prolongation, or drug interactions (Giezen *et al.*, 2008). Adverse drug reactions for biologics are often related to immune function and may be more complex. For example, PRCA associated with the biologic Eprex was ascribed to either an adjuvant effect of the stopper (leachate) on the syringe (Boven *et al.*, 2005) or a change in excipient. Manufacturing changes and directions from regulators to alter the route of administration to intravenous (from subcutaneous) stopped these product-related adverse immunologic effects in patients.

These considerations, then, provide context for the types of issues that arise or are required to be evaluated by regulators for biologic therapies, and may be best addressed in pharmacoepidemiologic studies.

## EPOGEN AND ERYTHROPOIESIS-STIMULATING AGENTS (ESAS): ESTIMATING THE MORTALITY RISK RELATED TO HIGHER ESA DOSES AS USED IN THE ROUTINE CLINICAL MANAGEMENT OF ANEMIA FOR PATIENTS RECEIVING HEMODIALYSIS

In postmarketing pharmacoepidemiologic studies designed to examine potential adverse effects of therapies, confounding-by-indication or time-dependent confounding can be an important source of systematic error (bias), which, if not handled appropriately in the design and/or analysis, can produce spurious results. However, the use of more sophisticated analytic techniques that can address these biases, coupled with the application of study designs tailored to address specific types of research questions, can help minimize these sources of bias and provide potentially more valid estimates of treatment effects. This is illustrated in the recent body of nonexperimental evidence describing the mortality risk related to greater doses of erythropoiesis-stimulating agents (ESAs).

The first ESA, EPO, received FDA approval in 1989 and was adopted widely by the nephrology community for the treatment of anemia in patients with chronic kidney disease (CKD) requiring and not requiring dialysis (USRDS, 1995). Patients with late-stage CKD, particularly those receiving dialysis, do not produce adequate endogenous erythropoietin and, therefore, become severely anemic (Eschbach and Adamson, 1985). ESAs are biologics administered intravenously or subcutaneously to raise and maintain hemoglobin (Hb) levels to a desired level in order to reduce the need for red blood cell transfusions, which carry important risks for CKD patients (Hakim *et al.*, 1987; Hardy *et al.*, 2001; Dodd *et al.*, 2002; Pomper *et al.*, 2003; Cardarelli *et al.*, 2005; Opelz, 2005; Twomley *et al.*, 2006; Shander and Sazama, 2010; Ibrahim *et al.*, 2011; Vraets *et al.*, 2011; Amgen, 2012).

In 1998, the Normal Hematocrit Cardiac Trial was published showing that hemodialysis patients with heart failure or ischemic heart disease randomized to treatment with EPO to a Hb target of  $14 \pm 1$  g/dL, compared with  $10 \pm 1$  g/dL, had an increased risk of mortality or non-fatal myocardial

infarction (Besarab *et al.*, 1998). In 2006, two randomized controlled trials (RCTs) were conducted to evaluate whether treatment with EPO (Singh *et al.*, 2006) or epoetin beta (Drueke *et al.*, 2006) to a Hb target of  $\geq 13$  g/dL, compared with lower targets of 11.3 g/dL and 10.5–11.5 g/dL, respectively, would improve cardiovascular (CV) outcomes or death in non-dialysis CKD patients. The first showed an excess of events in the high target arm (Singh *et al.*, 2006) and the other showed no benefit (Drueke *et al.*, 2006). Combined, these studies raised concerns about high ESA doses because patients randomized to the higher Hb targets required higher ESA doses, on average. This was further supported by a simple post-hoc analysis of one of the RCTs that showed the higher doses required to achieve the higher targets were associated with elevated risk of CV events and mortality (Szczech *et al.*, 2008).

The safety concerns raised by these RCTs were incorporated into product labeling, but it was unclear whether these risks were applicable to current clinical practice, since the Hb target range in ESA labeling at that time was 10–12 g/dL (the Hb range in the current US package insert is lower). In 2004, however, two noninterventional database studies using Medicare hemodialysis data showed an association between higher average monthly EPO doses and elevated mortality risk (Cotter *et al.*, 2004; Zhang *et al.*, 2004). Patients in the highest dose quartile had a mortality hazard ratio (HR) of 2.7 ( $p < 0.0001$ ) compared with patients in the lowest quartile. While these studies had significant design and analysis limitations, the potential association warranted further investigation.

In 2005, the drug's sponsor initiated a multifaceted pharmacoepidemiologic program to investigate whether higher EPO doses in clinical practice increase the risk of mortality in dialysis patients. Five organizations participated as research centers: four academic institutions and Amgen, Inc. The collaborating institutions had unrestricted access to the data, collaboration across institutions was encouraged, and there were no restrictions on publication.

Evaluating whether higher EPO doses increase mortality risk in dialysis patients is complicated (Bradbury *et al.*, 2009a). EPO doses are generally administered at thrice weekly dialysis sessions and

are titrated to achieve a desired Hb concentration. If Hb concentrations increase above the desired level, the dose is reduced; if Hb drops below the desired level, the dose is increased. A patient's Hb response and EPO dose requirements can be affected by intravenous iron administration (Coyne *et al.*, 2007; Ibrahim *et al.*, 2009), inflammation (Gunnell *et al.*, 1999; Bradbury *et al.*, 2009b), malnutrition (Kalantar-Zadeh *et al.*, 2009), hospitalization events (Solid *et al.*, 2007), and vascular access problems (Roberts *et al.*, 2004). Moreover, dialysis patients frequently have chronic comorbidities: 50% heart disease, 50% diabetes, 85% hypertension, and 10% cancer; require extensive clinical management (approximately 10 medications, on average); and are hospitalized twice a year, on average (USRDS, 2010). The elements of this clinical picture are prognostic and contribute to declining Hb levels, which in turn leads to increases in EPO dose requirements over time. Thus, confounding-by-indication is complicated further by the time-dependent nature of anemia management with EPO dosing (Bradbury *et al.*, 2009a). Consequently, in noninterventional database research, specialized analytic techniques are required to address time-dependent confounding and confounding-by-indication.

Between 2007 and 2011, 10 studies were published from the research initiative (Table 44.1). In 2008, the first publication demonstrated that the original database findings were reproducible, but that the dose–mortality effect estimates were substantially attenuated in time-dependent models. Two studies focused on the short-term mortality risk (90–180 days) related to EPO dose escalations among patients at low Hb concentrations (patients typically receiving the highest doses), one of which used an instrumental variable approach (Bradbury *et al.*, 2009c,d). Both found that higher dose escalations were not associated with elevated mortality risk, even at the highest maintenance doses. Two studies used marginal structural models (MSMs) to address the question (Wang *et al.*, 2010; Weinhandl *et al.*, 2011). The first showed that the elevated mortality risk observed for patients in the highest EPO dose category (versus the lowest) decreased significantly and monotonically with greater confounding control. The dose–mortality association

Table 44.1 Recent studies of ESA dose and risk of mortality in US patients receiving hemodialysis (HD).

Data source	Sample size	Design specifics	Analytic approach	Summary of findings	Reference
Amgen research initiative publications Large dialysis provider	22 955	<ul style="list-style-type: none"> <li>Population: prevalent HD patients (2000–2002); 9-month baseline period</li> <li>Exposure: mean monthly EPO dose (3-month baseline period and monthly over time)</li> <li>Clinical characteristics: assessed at baseline and over time</li> <li>Outcome: all-cause 1-year mortality</li> </ul>	<ul style="list-style-type: none"> <li>Cox proportional hazards regression</li> <li>Effect of baseline EPO dose on mortality risk, with/without adjustment for baseline characteristics</li> <li>Effect of time-dependent (TD) EPO dose (lagged) on mortality risk; additional adjustment for time-varying Hb</li> <li>Patient factors controlled for: demographics, dialysis care metrics, laboratory parameters, comorbidities, medication use, and comorbidities</li> </ul>	<ul style="list-style-type: none"> <li>[Unadjusted] baseline model (HR = 1.31 per unit, 95% CI: 1.26–1.36)</li> <li>[Adjusted] baseline model (HR = 1.21 per unit, 95% CI: 1.15–1.28)</li> <li>[Adjusted] TD analysis of 1-month lagged EPO dose (HR = 0.93, 95% CI: 0.92–0.95) and 2-month lagged EPO dose (HR = 1.01, 95% CI: 0.99–1.03)</li> </ul>	Bradbury <i>et al.</i> (2008)
Large dialysis provider	6033	<ul style="list-style-type: none"> <li>Population: prevalent HD patients with Hb &lt; 11 g/dL for three consecutive months (2000–2002)</li> <li>Exposure: geometric mean EPO dose titration over 3 months</li> <li>Clinical characteristics: Assessed before exposure assessment</li> <li>Outcome: all-cause 6-month mortality</li> </ul>	<ul style="list-style-type: none"> <li>Cox proportional hazards regression</li> <li>Effect of EPO dose change on mortality risk; analyses also stratified by tertile of the maintenance dose</li> <li>Patient factors controlled for: demographics, dialysis care metrics, laboratory parameters, medication use, and comorbidities</li> </ul>	<ul style="list-style-type: none"> <li>Monthly dose increases &gt;12.5% not associated with elevated mortality risk:</li> <li>&gt;12.5–25%, HR = 0.94 (95% CI: 0.76–1.16)</li> <li>&gt;25.0–37.5%, HR = 0.89 (95% CI: 0.69–1.13)</li> <li>&gt;37.5%, HR = 0.86 (95% CI: 0.69–1.08)</li> </ul> <p>Similar results observed in stratified analyses</p>	Bradbury <i>et al.</i> (2009c)

(Continued)

Table 44.1 (Continued)

Data source	Sample size	Design specifics	Analytic approach	Summary of findings	Reference
Large dialysis provider	32 734	<ul style="list-style-type: none"> <li>Population: Prevalent HD patients with Hb &lt;11 g/dL (2000–2002)</li> <li>Exposure: percentage change in EPO dose following Hb &lt;11 g/dL; percentage of patients in each facility with dose change &gt;25%</li> <li>Facility exposure: centers with &gt;75% of dose changes &gt;25% (versus ≤75%)</li> <li>Clinical characteristics: assessed before exposure assessment</li> <li>Outcome: all-cause 3-month mortality</li> </ul>	<ul style="list-style-type: none"> <li>Patient-level analysis using general linear regression</li> <li>IV analysis using two-stage least-squares regression</li> <li>Patient factors controlled for: demographics, dialysis care metrics, laboratory parameters, medication use, and comorbidities</li> </ul> <p>RD = −0.4 per 100 (95% CI: −3.2–2.4)</p>	<ul style="list-style-type: none"> <li>Patient characteristics differed substantially by dose, but not by facility titration practices</li> <li>Patient-level analysis: highest dose quintile associated with elevated mortality risk: risk difference RD = 1.5 per 100 (95% CI: 0.8–2.2)</li> <li>IV analysis: highest dose not associated with elevated mortality risk: RD = −0.4 per 100 (95% CI: −3.2–2.4)</li> </ul>	Bradbury <i>et al.</i> (2009d)
USRDS	269 717	<ul style="list-style-type: none"> <li>Population: incident dialysis patients (1997–2006)</li> <li>Exposure: facility-level ESA and iron management by Hb categories</li> <li>Clinical characteristics: assessed at start of dialysis</li> <li>Outcome: all-cause 1-year mortality</li> </ul>	<ul style="list-style-type: none"> <li>Estimated associations between facility-level ESA and iron dosing and mortality risk using Cox proportional hazards regression</li> <li>Analyses conducted by Hb categories</li> <li>Patient factors controlled for included demographics, laboratory parameters, and comorbidities</li> </ul>	<ul style="list-style-type: none"> <li>ESAs use significantly greater (four- to five-fold) at lower Hb concentrations</li> <li>Higher facility-level ESA use among patients with Hb &lt;10 g/dL not associated with elevated mortality risk: HR = 0.94 (95% CI: 0.90–0.97)</li> <li>Higher facility-level ESA use among patients with Hb 11–&lt;12 g/dL associated with elevated mortality risk: HR = 1.07 (95% CI: 1.03–1.12)</li> </ul>	Brookhart <i>et al.</i> (2010)

USRDS	137918	<ul style="list-style-type: none"> <li>Population: prevalent dialysis patients (2000–2004)</li> <li>Exposure: deciles of ESA dose by Hb level</li> <li>Clinical characteristics: assessed throughout study period</li> <li>Outcome: all-cause mortality throughout follow-up</li> </ul>	<p>Weinhandl <i>et al.</i> (2011)</p> <ul style="list-style-type: none"> <li>Estimated dose-mortality association using history-adjusted inverse probability of treatment weight (IPTW)           <ul style="list-style-type: none"> <li>Treatment weights constructed using clinical characteristics evaluated over time at each exposure assessment</li> </ul> </li> <li>Patient factors controlled for included demographics, dialysis care metrics, medication use, laboratory parameters, and comorbidity</li> </ul>	<ul style="list-style-type: none"> <li>ESA use significantly greater at lower Hb concentrations</li> <li>In patients with <math>\text{Hb} &lt; 10 \text{ g/dL}</math>, highest dose decile not associated with elevated mortality risk: <math>\text{HR} = 0.71</math> (95% CI: 0.48–1.05)</li> <li>In patients with <math>\text{Hb} 10\text{--}11 \text{ g/dL}</math>, highest dose decile associated with elevated mortality risk: <math>\text{HR} = 1.74</math> (95% CI: 1.05–2.89)</li> <li>In patients with <math>\text{Hb} 11\text{--}12 \text{ g/dL}</math>, highest dose decile not associated with elevated mortality risk: <math>\text{HR} = 1.11</math> (95% CI: 0.80–1.53)</li> <li>In patients with <math>\text{Hb} \geq 12 \text{ g/dL}</math>, highest dose decile associated with modest elevation in mortality risk: <math>\text{HR} = 1.30</math> (95% CI: 0.98–1.74)</li> </ul>
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(Continued)

Table 44.1 (Continued)

Data source	Sample size	Design specifics	Analytic approach	Summary of findings	Reference
<i>Non-Amgen research initiative publications</i>					
USRDS 18 454		<ul style="list-style-type: none"> <li>Population: patients 65+ years, on dialysis ≥3 months (2003–2004)</li> <li>Exposure: average weekly dose (by month)</li> <li>Clinical characteristics: assessed throughout follow-up</li> <li>Outcome: all-cause 9-month mortality</li> </ul>	<ul style="list-style-type: none"> <li>Cox proportional hazards regression</li> <li>Estimated dose-mortality association using IPTW modeling</li> <li>Treatment weights constructed using clinical characteristics at exposure assessment</li> <li>Patient factors controlled for included demographics, facility characteristics, medication use, Hb levels, and comorbidity</li> </ul>	<ul style="list-style-type: none"> <li>In unweighted models, highest dose category (&gt;40 000U/week) associated with elevated mortality risk: HR = 1.26 (95% CI: 1.1–1.44)</li> <li>In IPTW models, highest dose category not associated with elevated mortality risk: HR = 0.91 (95% CI: 0.67–1.22)</li> </ul>	Zhang <i>et al.</i> (2009)
USRDS 35,593		<ul style="list-style-type: none"> <li>Population: patients 65+ years, on dialysis ≥3 months (2004–2005)</li> <li>Exposure: cumulative dose over successive months of follow-up</li> <li>Clinical characteristics: assessed throughout follow-up</li> <li>Outcome: all-cause 9-month mortality/ composite of mortality and CV endpoints</li> </ul>	<ul style="list-style-type: none"> <li>Estimated association between cumulative dose and mortality association using IPTW modeling; analyses stratified by diabetes status</li> <li>Patient factors controlled for included demographics, facility characteristics, medication use, Hb levels, and comorbidity</li> </ul>	<ul style="list-style-type: none"> <li>Among diabetics, highest dose category (&gt;40 000U/week) associated with elevated mortality risk: HR = 1.32 (95% CI: 1.11–1.58); risk of composite: HR = 1.26 (95% CI: 1.06–1.50)</li> <li>Among nondiabetic patients, highest dose category (&gt;40 000U/week) not associated with elevated mortality risk: HR = 1.06 (95% CI: 0.88–1.28) or risk of composite: HR = 1.10 (95% CI: 0.92–1.32)</li> </ul>	Zhang <i>et al.</i> (2011)

USRDS: United States Renal Data System.

was not observed in models with the most comprehensive confounding control (Wang *et al.*, 2010). The other MSM study stratified on Hb concentration and observed no excess mortality risk for patients receiving the highest doses while at Hb <10 g/dL, but a modest increase in mortality risk for patients receiving the highest doses at Hb >12 g/dL (HR 1.30, 95% confidence interval (CI) 0.98–1.74) (Weinhandl *et al.*, 2011). Another used multilevel modeling and a split-sample design to examine mortality risk related to facility EPO and iron dosing practices at different Hb concentrations among incident patients (Brookhart *et al.*, 2010). This study found that patients receiving care in facilities with the highest EPO use had lower mortality risk at Hb below 10 g/dL, but elevated mortality risk at Hb above 11 g/dL. A similar pattern was observed for iron use. Finally, three methods publications were produced (Joffe *et al.*, 2010, 2012; Kilpatrick *et al.*, 2013) that discuss strengths and limitations of these advanced methods, which may be useful to researchers.

During this period, two MSM analyses were published by the investigators who originally reported the excess risk related to EPO dose. The first found no excess mortality risk related to higher EPO doses (Zhang *et al.*, 2009). The second found a modest dose–mortality association among patients with diabetes (HR 1.32, 95% CI 1.11–1.58), but no elevated risk among nondiabetic patients (Zhang *et al.*, 2011).

Since the original database reports in 2004 linking EPO dose and mortality, 8 of 10 published studies that directly evaluated the dose–mortality question have found that the elevated risk was largely, if not completely, attributable to residual confounding. The finding of excess mortality risk for patients receiving higher doses at higher Hb concentrations did not comport with a dose effect, considering that the doses received by those patients were, on average, one-fifth as great as the doses received by patients at low Hb concentrations. This finding did suggest that the excess risk observed in those patients was more likely related to higher Hb concentrations, a finding consistent with the results from the anemia management RCTs (Besarab *et al.*, 1998; Drueke *et al.*, 2006; Singh *et al.*, 2006).

## **ENBREL (ETANERCEPT): PHARMACOVIGILANCE FOR A TUMOR NECROSIS FACTOR INHIBITOR**

Enbrel is a dimer of two molecules of the extracellular portion of human p75 tumor necrosis factor (TNF) receptor fused to the Fc portion of a type 1 human immunoglobulin (IgG<sub>1</sub>). Etanercept acts primarily by binding and neutralizing TNF. Therefore, it has application in clinical settings in which TNF plays a major pathogenic role.

Enbrel was first approved in the USA on November 2, 1998, and is currently marketed in all major geographies for use across five distinct clinical populations: adults with moderate to severe rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, adults with psoriatic arthritis (PsA), ankylosing spondylitis (AS), and adults with moderate to severe plaque psoriasis (PsO). Enbrel is an example of a product where safety has been managed using a full armamentarium of pharmacovigilance practices, including (1) routine pharmacovigilance, (2) postmarketing commitments following approval for new indications, (3) risk evaluation and mitigation strategy programs, and (4) postmarketing requirements.

## **ROUTINE PHARMACOVIGILANCE**

The Enbrel pharmacovigilance program includes the evaluation and follow-up of reported adverse events and ongoing surveillance of safety information from the medical literature. Additional pharmacovigilance occurs through the monitoring of all biologics in the class and, in the case of Enbrel, these TNF class findings have driven most of the label changes, rather than the Enbrel-specific pharmacovigilance (FDA, 2012).

## **POSTMARKETING COMMITMENTS AND POSTMARKETING REQUIREMENTS**

In addition to the systematic examination of spontaneous reports, six major commitments and one requirement were designed to examine the postmarketing safety of Enbrel, including open-label

follow-up to assess long-term safety, clinical trials, prospective observational research, pregnancy registries, and, most recently, a requirement to systematically assess spontaneous reports of malignancies in pediatric and young adult patients for 10 years.

At the time of approval in 1998, Immunex, now a wholly owned subsidiary of Amgen, committed to the systematic 3-year follow-up of etanercept-treated RA patients enrolled in open-label extension studies. This follow-up progressed for a period of 10 years, although the original commitment was for 3 years. In addition, the evaluation of the potential association of Enbrel with lymphoma in adult RA patients included data from this open-label extension study, as well as data from EU registries and the RADIUS II observational study. Of particular interest was the finding that the incidence of lymphoma in this patient population did not increase over time with increasing exposure to etanercept (Gibofsky *et al.*, 2011; FDA, 2012).

In 1999, a phase 4 clinical trial was initiated to evaluate the safety and efficacy of Enbrel in children with systemic-onset juvenile rheumatoid arthritis (JRA). Patient recruitment was slow, likely due to the potential for assignment to placebo, given that the therapy was commercially available. Consequently, the FDA released Amgen from this commitment (FDA, 2012).

In 2000, an open-label, multicenter, registry study was initiated to determine the long-term safety of etanercept administered with or without other disease-modifying anti-rheumatic drugs (DMARDs) in pediatric subjects with polyarticular course or systemic JRA compared with a control cohort of similar subjects receiving methotrexate (with or without other DMARDs). Overall, the safety profiles of the subjects were similar, with no significant difference in exposure adjusted rates of adverse events, including infections, between the arms (Lovell *et al.*, 2003).

In 2006, a prospective, multicenter, surveillance study was initiated in the USA and Canada with 2500 adult patients with chronic plaque psoriasis who were treated with commercial etanercept to estimate the incidence of serious adverse events, including malignancies and serious infections. In a 3-year interim analysis, the observed numbers of patients experiencing lymphoma, serious infec-

tions, and malignancies was not higher than expected compared with rates derived from a large US administrative health claims database (Yong *et al.*, 2011a, 2012). Given the lack of an internal comparator group, however, conclusions about the safety of Enbrel are limited. In addition, only 34% of enrolled subjects remained on Enbrel through follow-up. While the study was designed as a 5-year follow-up of patients exposed to Enbrel, another question of relevance is the safety outcomes of patients who have taken Enbrel for 5 years. This kind of question is more easily answered within an electronic data system.

To focus on potential adverse effects during pregnancy, regulators required the establishment of a prospective, observational study of pregnancy outcomes among Enbrel users. In response, Amgen designed a registry consisting of three cohorts of women:

- 1 women with RA, JRA, AS, PsA, or PsO who are exposed to etanercept in the first trimester of pregnancy;
- 2 women with RA, JRA, AS, PsA, or PsO who have not used etanercept or any TNF antagonist during pregnancy (i.e., primary comparison group); and
- 3 women who do not have RA, JRA, AS, PsA, or PsO and have used any TNF antagonist in pregnancy (i.e., secondary comparison group).

For major birth defects, an additional comparison will be made with an external source of population-based rates – the Metropolitan Atlanta Congenital Defects Program (MACDP). This post-marketing commitment has experienced difficulty enrolling subjects and an alternative design using an administrative database with follow-up of pregnancy outcomes is being considered.

In January 2012, the FDA issued a postmarketing requirement to systematically assess spontaneous reports of malignancies in pediatric and young adult patients for a period of 10 years. To date, annual assessment reports have been submitted covering 2010 and 2011 data.

The key learnings from these studies, in addition to the contextualization of the label changes made as a result of spontaneous report analyses, include

(1) the difficulty in recruiting children for a randomized, placebo-controlled clinical trial when commercial product is available, (2) the difficulty in recruiting for a pregnancy registry in general, and especially when the study calls for a comparison cohort, and (3) the value of large administrative databases to serve as an external source of information regarding drug exposure and safety outcomes to complement routine pharmacovigilance and data from controlled clinical trials.

### **PROLIA: ASSESSING LONG-TERM SAFETY OF DENOSUMAB FOR THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS**

Osteoporosis is a chronic disease characterized by low bone mass and compromised bone strength, which predisposes those affected to increased fracture risk. Postmenopausal women are at particularly increased risk, with one in two women over age 50 expected to develop an osteoporotic fracture in their lifetime (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). Osteoporotic fractures commonly occur at the spine, hip and wrist. Such fractures, especially hip fractures, can have devastating consequences; approximately 24% of hip fracture patients die within 1 year (NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001). Based on the World Health Organization definition of osteoporosis (WHO, 1994), worldwide prevalence has been estimated at 200 000 000 (Reginster and Burlet, 2006).

Several pharmacologic agents are available for the prevention and/or treatment of osteoporosis. The newest among them, denosumab, is a fully human monoclonal antibody to RANK ligand (RANKL) (Boyle, 2003). In blocking RANKL, denosumab inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. Prolia (denosumab 60 mg administered every 6 months) has been approved in various countries and regions for treatment of postmenopausal osteoporosis (PMO) in women at high or increased risk for fracture.

A comprehensive Prolia risk management plan was proactively developed by Amgen with input from the FDA. During review of the marketing authorization application, regulatory agencies raised potential or theoretical safety considerations based on mechanism of action, biological plausibility, clinical trial evidence, and/or findings from studies of other anti-resorptive agents (potential “class” effects). One component of the postmarketing program is a prospective database study of unprecedented size and scope: a multinational 10-year open cohort study of more than 20 000 000 women. Adverse events of interest include osteonecrosis of the jaw (ONJ), atypical femoral fracture (Shane *et al.*, 2010), fracture healing complications, hypocalcemia, serious infection, dermatologic adverse events leading to hospitalization or ER visit, acute pancreatitis, hypersensitivity leading to hospitalization or ER visit, and new primary malignancy (excluding nonmelanoma skin cancer). Incidence rates of these events of interest are to be compared between women exposed to Prolia and those exposed to bisphosphonate, which currently are the most commonly used class of osteoporosis medications.

The feasibility of this database study was assessed extensively. The most important study design issues that were considered included:

- *Statistical power.* Use of administrative data systems was considered more practical than a prospective registry because of the infeasibility of recruiting large, representative populations of women to detect increases in relative risk for rare events (expected incidence <1/50 000 person-years), such as ONJ, atypical femoral fracture, and hypocalcemia.
- *Patient burden.* Studies using administrative data minimize burden to patients and healthcare providers by utilizing routinely collected and stored data.
- *Data adequacy.* Data systems had to be accepted sources for monitoring drug safety. Availability of diagnosis, procedure, and medication codes to enable identification of women with PMO was critical. Comorbidity data to facilitate valid comparisons of Prolia with comparator patients had to be accessible. The ability to

conduct long-term follow-up for a significant portion of the patient population facilitates capture of events occurring only with long-term therapy or that have long induction or latency periods, as well as obviating concerns about bias due to differential loss to follow-up; for example, by poor adherence to medication. Lastly, the data resource infrastructure needed to be sufficiently flexible to address *de novo* concerns arising after Prolia approval.

- *Ascertainment of events.* Because the events of interest may be difficult to assess using standardized coding systems, validated ascertainment algorithms with good sensitivity and positive predictive value had to be in place. In addition, medical charts needed to be accessible for review to augment analyses based on diagnosis and procedure codes or to confirm events.
- *Drug exposure assessment.* Plans for ascertaining Prolia exposure needed to be comprehensive from initial product launch when nonspecific J codes for biologics (used in the USA to identify drugs administered other than orally) are used in advance of product-specific codes, which become available later. Exposure assessment must be unbiased with respect to presence/absence of events of interest.

There were also design and analytical challenges arising from the study design and external landscape into which Prolia was introduced. First, confounding by indication for treatment was expected to be an important bias to address when comparing risk of certain events across medication exposure cohorts. Factors potentially affecting the likelihood of receiving Prolia, compared with other osteoporosis medications, include age, severity of osteoporosis, comorbidities, and concurrent and past medications. Since Prolia is approved for treatment of postmenopausal women with osteoporosis at high or increased risk of fracture, but not for prevention of osteoporosis, large proportions of new Prolia users may have been previously treated with bisphosphonates. When comparing event incidence in Prolia versus bisphosphonate users, one must account for such previous exposure, which may confound the risk of on-study events.

Depending on the nature of the putative relationship between exposure and events of interest, time at risk may include on-treatment periods only or both on-treatment and post-treatment periods. The latter is important for events such as malignancy, which may be associated with longer induction or latency periods. The length of post-treatment period considered to be time at risk should be defined according to the potential induction-latency period for the event of interest (Rothman, 1981).

A fundamental design principle to increase validity of pharmacoepidemiologic studies involves structuring subject comparisons where comparability, other than for primary exposures, can be assumed. This can be complicated in analyses of data from clinical practice settings, especially with an open cohort and long follow-up. If one expects limited switching between medications during follow-up, use of propensity scores (Rosenbaum and Rubin, 1984) based upon baseline covariates could help achieve balance in baseline characteristics between treatment cohorts. However, if patients are likely to switch medications, drug exposure must be considered a time-varying covariate to take into account therapy changes over time and methods accounting for changing likelihood of Prolia exposure over time must be considered. Analyses stratified by cumulative doses received could also explore effects of long-term exposure on event risk.

The impact of potential biases inherent in studies of prevalent users can be minimized using a new user design (Ray, 2003), which excludes patients switching from other therapies. Prolia initiators would be compared with new users of other osteoporosis medications. However, because Prolia may often be prescribed as a second-line medication, a new user design might include only a small number of patients. Alternatively, one could consider a “new switcher” design (Schneeweiss, 2010), where analyses would compare users of osteoporosis therapies that switch to Prolia with those that switch, for example, to an intravenous (IV) bisphosphonate.

The above issues illustrate challenges inherent in the design of an appropriate pharmacoepidemiologic study to assess the long-term safety of a novel, first-in-class therapy. The 10-year study duration

generates additional issues to be considered; for example, changes over time in physician prescription patterns, treatment landscape, and patient case-mix in addition to complexities due to approvals in new countries and for new indications. Such changes may suggest the need for reevaluation of the study analytic plan. However, ensuring transparency between the study sponsor, study investigators, and regulatory agencies is crucial in obtaining valid study results.

### **XGEVA: PHARMACOEPIDEMIOLOGIC RESEARCH RELATED TO DENOSUMAB FOR THE PREVENTION OF SKELETAL-RELATED EVENTS IN PATIENTS WITH BONE METASTASES FROM SOLID TUMORS**

Bone metastases and their clinical sequelae are frequent and debilitating complications in patients with advanced cancer (Viadana *et al.*, 1973; Coleman, 1997, 2006; Carlin and Andriole, 2000). Bone metastases are characterized by markedly increased osteoclast activity and are associated with significant skeletal morbidity (i.e., skeletal-related events (SREs), including fractures, radiation to bone, spinal cord compression, and surgery to bone) (Roodman, 2004; Yonou *et al.*, 2004; Coleman, 2006). Until recently, IV bisphosphonates were the only approved treatment to prevent SREs. On an annual basis, the bisphosphonate dose is approximately 10 times the dose in PMO, reflecting the heightened bone resorption associated with bone metastases.

Efficacy results from three phase 3 active comparator studies with denosumab (120 mg every 4 weeks) against the standard of care (zoledronic acid, IV, 4 mg, adjusted for renal function, Q4W) showed a consistent and robust treatment effect of denosumab across solid tumors for reduction of SREs (Stopeck *et al.*, 2010; Fizazi *et al.*, 2011; Henry *et al.*, 2011). The results for all SRE endpoints, whether from the individual studies or the integrated analysis, demonstrated either superiority or directionally favorable efficacy for denosumab. XGEVA (denosumab 120 mg SQ Q4W) was approved in the USA (2010), Canada (2011), and

Europe (2011) to prevent SREs in patients with bone metastases from solid tumors.

An important adverse event focus during the clinical trial program was ONJ, which has been reported among 1–10% of patients treated with IV bisphosphonates for the SRE indication (Migliorati *et al.*, 2010). ONJ is a recently appreciated clinical entity, defined as an area of exposed alveolar or palatal bone associated with nonhealing after 8 weeks of appropriate care in a patient without prior history of radiation to the head, face, or mouth (Khosla *et al.*, 2007; Ruggiero *et al.*, 2009). Research suggests a strong association of ONJ with suppression of bone turnover (Van den Wyngaert *et al.*, 2006; Cartsos *et al.*, 2008; Ruggiero *et al.*, 2009). In the pooled analysis of the denosumab phase 3 SRE studies, at 3 years follow-up, the proportion of subjects with positively adjudicated ONJ was 1.8% and 1.3% among subjects who received denosumab and IV zoledronic acid, respectively ( $p = 0.13$ ) (Saad *et al.*, 2012). Most cases were mild to moderate in severity; only 0.4% in each treatment group were grade 3 or more in severity.

The postmarketing program for XGEVA is multifaceted, including:

- continued assessment of patients in ongoing and additional clinical trials;
- follow-up of spontaneous reports of adverse events;
- a survey of physicians' understanding of recommendations related to ONJ prevention provided in the denosumab prescribing information; and
- a voluntary clinical study of cancer patients with ONJ who will be followed for up to 5 years to further understand the disease's natural history.

The program also includes a trinational Nordic prospective study of cancer patients treated with XGEVA or zoledronic acid. The study will focus on ONJ and infections leading to hospitalization for three treatment cohorts: naive XGEVA patients, naive zoledronic acid patients, and patients who switch from bisphosphonate treatment to XGEVA.

There are important differences between PMO and advanced cancer patients that resulted in a much different study design for the XGEVA versus the Prolia prospective study. First, cancer patients

with bone metastases have a short life expectancy, precluding a focus on outcomes with extended induction-latent periods (Chia *et al.*, 2010; Norgaard *et al.*, 2010; Yong *et al.*, 2011b). Second, incidence of ONJ and infections are much higher among cancer patients than among PMO patients. Thus, the study size required in the advanced cancer population is much smaller than required for PMO patients.

Issues of noncomparability across treatments and other biases are especially marked in the advanced cancer setting. XGEVA is not toxic to the kidneys, while zoledronic acid is contraindicated for patients with severe or worsening renal impairment. Accordingly, switching between treatments is expected to be predominantly from zoledronic acid to XGEVA. This pattern of switching can cause exposure misclassification because ONJ can develop months after treatment ends. There is also the potential for a new adopter physician bias (e.g., information bias) with a novel therapy like XGEVA, whereby early adopting physicians are more comprehensive about referral for dental evaluation, resulting in more complete ascertainment of ONJ cases.

These issues of noncomparability, differential crossover, and information bias are not readily amenable to study design or analytic remedies. Therefore, the analysis approach chosen was to calculate incidence proportions (IPs) by treatment cohort, without explicit statistical comparison across treatments. This analysis has as its primary utility providing a real-world counterpart to the clinical trial results for XGEVA. This addresses a recognized limitation of clinical trials: they often underrepresent specific patient groups and occur in a more controlled environment than routine clinical practice (Schneeweiss and Avorn, 2005). The cohort-specific IP also addresses directly a question of primary interest: what percentage of patients is likely to get the benefit of therapy without the adverse event of ONJ (viz. 1 – IP)?

A key concern in the Nordic study is to detect ONJ as completely as in the clinical trial program. For that purpose, a collaboration was developed with dental researchers at centers where virtually all suspected cases of ONJ would be evaluated and thereby establish a trinational database of known

ONJ cases for linkage with the treatment cohorts. Potential cases identified will be adjudicated as in the clinical trial program. The establishment of this database will enable naturalistic studies of the clinical course of ONJ. Much remains to be learned about ONJ, including elucidation of risk factors that could serve as a basis for preventive activities.

## **PHARMACOEPIDEMOLOGY AND THE PHARMACOVIGILANCE OF BIOSIMILARS**

With the expiration of patents for some of the first approved biologics, biologic drug manufacturers are seeking to market follow-on products designated as “biosimilars.” As defined in United States Affordable Care Act of 2009, a biosimilar, or follow-on biologic, is “highly similar to an approved reference product notwithstanding minor differences in clinically inactive components.” Unlike generic copies of small-molecule drugs, biosimilars are complex proteins derived from unique cell lines and proprietary manufacturing processes. Since EU biosimilar legislation was passed in 2004, regulatory bodies around the world have debated the concept of biosimilarity and criteria for the structural components, clinical profile, approval, utilization, and safety monitoring for such products.

The FDA recognized the complexity of pharmacovigilance for biosimilars, and in their draft guidance, released in February 2012, a two-step approach to postmarketing safety monitoring was recommended. First, safety and effectiveness concerns associated with the reference product and its class should be considered to establish a baseline for class-based safety monitoring. Then, a biosimilar applicant should provide adequate mechanisms to differentiate adverse events associated with the proposed product from those associated with the reference product. Further, additional investigations must be designed to identify adverse events associated with the proposed product that have not been previously associated with the reference product. This consideration is especially important because rare adverse events may not be observed in a biosimilar’s clinical trial program and may only be seen in the postmarketing environment.

Therefore, regulatory agencies generally mandate a molecule-specific postmarketing evaluation program for biosimilar approvals. Such pharmacoepidemiology studies in the postmarketing monitoring of biosimilar safety will facilitate the characterization of comparative safety profiles and are likely to improve safety signal detection over standard voluntary methods of postmarketing pharmacovigilance.

## CONCLUSIONS

Pharmacovigilance and risk management for biologics is largely focused on outcomes related to the on-target effects of these therapies, whether observed during the drug development clinical trial program or theoretical. Pharmacoepidemiologic research has come to play an important role to investigate issues that may arise during routine practice for marketed products and as part of the approval process and risk management plans for newer therapies.

The evolution of electronic data systems has made it feasible to study very rare adverse events, and in some instances to have surveillance programs that cover an entire indicated population in specific countries. Pharmacoepidemiologic studies utilizing these resources have the flexibility to address prespecified and emerging issues as long as exposed patients can be identified without bias related to the outcome(s) of interest, acceptable algorithms can be developed to identify relevant adverse events, and issues of confounding by indication and information bias can be addressed adequately. Even in instances where comparative analyses seem untenable due to uncontrollable biases, single-arm analyses of the frequency of specific adverse events in treated patients can often provide information that is helpful in assessing whether risks in routine clinical practice are similar to those seen in clinical trial programs.

Results from pharmacoepidemiologic studies that utilize data systems or other noninterventional approaches are generally not accepted as providing definitive evidence to support causal interpretations. However, with rapid advances in epidemiologic methods, as in the example of the research

program around EPO dose and mortality discussed in this chapter, such studies can provide convincing evidence with respect to whether an appreciable risk exists in real-world clinical practice.

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# Surveillance for Medical Devices: USA<sup>1</sup>

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## INTRODUCTION

The world of medical devices encompasses a wide variety of products, from single-use disposable to short- or long-term implantable, to multiple-use durable capital equipment, from products that are used to monitor to those used to diagnose or treat, and from products that deliver their effect through

electronic means to those who do so via mechanical or chemical means. In addition, all these products involve both the user and the patient (at times the same) and are used in a variety of settings (e.g., from hospital to home care). The Center for Devices and Radiological Health (CDRH) is that part of the US Food and Drug Administration (FDA) that helps ensure that the world of medical devices (see Addendum for definition) intended for human use is safe and effective and helps reduce unnecessary exposure to radiation from medical, occupational, and consumer products. The industry that CDRH regulates had a US market valued at \$98 billion in 2007 and is projected to be over \$120 billion in value by 2013 (US Department of Commerce, Bureau of the Census, 2007). There were approximately 5300 medical device companies in the USA in 2007, approximately 73% of whom had fewer than 20 employees, with 15% having as many as 100 employees (US Department of Commerce, Bureau of the Census, 2007).

<sup>1</sup>The opinions or assertions presented herein are the private views of the author and are not to be construed as conveying either an official endorsement or criticism by the US Department of Health and Human Services, the Public Health Service, or the US Food and Drug Administration.

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The FDA's mandate is carried out through both premarket product evaluation and postmarket oversight that continues over the lifetime of the product, from early design to widespread use, and, ultimately, to obsolescence. At major junctures of a product's life cycle, the FDA must weigh the product's benefits and risks. Central to this risk management function is the FDA's decision for marketing, one that must ensure that beneficial medical products are available (and labeled with adequate information on their benefits and risks) while protecting the public from unsafe products or false claims (FDA, 1999). Once marketed, a product's continued safety and effectiveness must be ensured not only by oversight on the part of industry and the FDA, but most importantly by healthcare providers' and patients' appropriate product selection and use based on the product's labeling.

## PREMARKET OVERVIEW

The FDA provides reasonable assurance that the product will be useful while not posing unacceptable risks to patients once device marketing begins. Operationally, this goal is accomplished through the FDA's use of regulatory controls and the classification process. General controls include device labeling, registration and listing, premarket notification, good manufacturing practices, and records and reports. Premarket notification requires any manufacturer intending to market a medical device to submit an application at least 90 days before beginning commercial distribution. The FDA then determines if the device is substantially equivalent to a predicate device (meaning as safe and effective and for the same intended use). (New intended uses or significant changes in technology are potential reasons that a device may not be found substantially equivalent. In these cases, a premarket approval (PMA) submission may be required – see below.) Class I devices (such as heating pads or dentures) are those for which these controls alone are sufficient to assure the FDA of a product's safety and effectiveness.

Special controls are used *in addition to* general controls for higher risk Class II devices (such as hospital beds or surgical staplers). These controls

include patient registries, guidances, and standards. Guidance documents are nonbinding and assist industry in preparing regulatory submissions and FDA staff in the review process. They may interpret regulatory requirements, provide information on application content requirements for a specific device type, or convey guidance to sponsors on the development of preclinical and clinical data. Standards (both national and international), on the other hand, are developed through accredited standards development organizations with full participation of the government, industry, and academia. Most pertain to test methods for device evaluation or material specifications for type and quality of materials used in manufacturing. Manufacturers may declare conformity to FDA-recognized standards in a new device application.

When there is insufficient information to determine that general and special controls alone will reasonably assure safety and effectiveness, a product may be placed into Class III pending one other condition. The product must either be life sustaining, life supporting, or for use of a substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury – Section 513 (a)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act). *In addition to* general and special controls, all Class III products (such as deep brain stimulators and cochlear implants) require the submission of clinical data in support of premarket submissions, known as PMA applications (in contrast to premarket notifications noted above).

## POSTMARKET SURVEILLANCE CONTEXT

For the majority of marketed products, no, or very limited, clinical data are required. Of 783 Class I device regulations (each of which typically pertains to more than one device), 730 (93%) are exempt from premarket notification. Similarly, of the 898 Class II device regulations, 75 (8%) are exempt. For the Class I and II products requiring premarket notification, many applications do not include clinical data. Even when clinical trial information is provided (for Class III devices), these data have some of the same inherent limitations noted in drug

trials – that is, limited size, duration, and select patient population (e.g., restrictions in age, gender, disease complexity). In addition, investigators in premarket device clinical trials tend to be those physicians at the “cutting edge” of product development and who are most familiar with the device’s characteristics and application. Thus, limited information may be generated on human factor concerns such as optimal design for ease of use, optimal use environment (e.g., free of electromagnetic interference), labeling that anticipates less sophisticated use or that minimizes maintenance error, or the consequences of reuse on device performance and safety. Once in the marketplace, devices are likely be used by a wide array of physicians and other clinicians of varying skill levels, training, and experience. In addition, less stringent diagnostic and other criteria may be applied reflecting either non-optimal product choice or off-label use, the latter a hallmark of the evolving practice of medicine.

Since no device is free from adverse events and product problems, and since premarket clinical data are limited, postmarket oversight is needed as a “safety net” to ensure the continued safety and effectiveness of marketed products. Postmarket oversight refers to both postmarket surveillance as well as postmarket enforcement. The former refers to the systematic process of adverse event/product problem reporting, monitoring, and evaluation as well as the subsequent, more formal, observational assessments of device use and potential patient risks and benefits. The latter refers to investigations of a device firm’s compliance with statutory and regulatory requirements. Both processes are integral to product development and evolution. This chapter will focus on the FDA programs constituting postmarket surveillance.

## GOALS

As with drugs, the goals of device postmarket surveillance are: (1) identification of previously unknown or not well-characterized adverse events/product problems (“signals”); (2) identification and characterization of subgroups at risk or at benefit; (3) collection and evaluation of information on issues not directly addressed in premarket

submissions (e.g., long-term effectiveness or changes in use environment, from professional to home use); and (4) development of a public health context to interpret these data. This process ultimately aims to disseminate information regarding newly emerging device problems to appropriate stakeholders (particularly health professionals and the public), incorporate the information into the device approval process, and provide findings to the device industry to aid in product corrections and improvements. The principal postmarket “tools” utilized by the FDA to achieve these goals are: (1) adverse event/product problem reporting – through the Medical Device Reporting (MDR) system and MEDWatch, the Medical Device Safety Network (MedSuN), and international vigilance; (2) mandated postmarket studies (including condition of approval and Section 522 studies); and (3) applied epidemiology.

## ADVERSE EVENT/PRODUCT PROBLEM REPORTING

### MEDICAL DEVICE REPORTING AND MEDWATCH

The FDA monitors postmarket device-related adverse events (AEs)/product problems, through both voluntary and mandatory reporting, to detect “signals” of potential public health safety issues. Voluntary reporting to the FDA began in 1973 and presently continues under MEDWatch (Kessler, 1993), a program created in 1993 to encourage voluntary reporting by all interested parties (but principally among healthcare professionals) as a critical professional and public health responsibility.

It was not until 1984 that the FDA implemented mandatory reporting through the MDR regulation. This regulation required device manufacturers and importers to report device-related deaths, serious injuries, and malfunctions to the FDA. Additional legislative initiatives in the 1990s resulted in significant changes to mandatory reporting. Under the Safe Medical Devices Act of 1990, universal reporting of AEs by user facilities (hospitals, nursing homes, ambulatory surgical facilities, outpatient diagnostic and treatment facilities, ambulance

services, and healthcare entities) and distributors was enacted. Under the FDA Modernization Act of 1997 (FDAMA, Section 213 of the Act), and in response to experience with distributor and user facility reporting, the US Congress mandated that distributor reporting be repealed and that universal user facility reporting be limited to a “subset of user facilities that constitutes a representative profile of user reports.” The conceptual framework for these “sentinel sites,” collectively referred to as the Medical Device Safety Network (MedSun), is discussed below.

To better understand reporting of AEs under the current MDR regulations governing mandatory reporting (Title 21 Code of Federal Regulations (CFR) Part 803), requirements should be noted and terms defined. Manufacturers and importers are currently required to submit reports of device-related deaths, serious injuries, and malfunctions. User facilities are required to report deaths to the FDA and deaths and serious injuries to the manufacturer. Serious injuries are defined as life-threatening events – events that result in permanent impairment of a body function or permanent damage to a body structure, and events that require medical or surgical intervention to preclude permanent impairment or damage. Malfunctions are defined as the failure of a device to meet its performance specifications or otherwise perform as intended. The term “device-related” means that the event was or may have been attributable to a medical device, or that a device was or may have been a factor in an event, including those occurring as a result of device failure, malfunction, improper or inadequate design, poor manufacture, inadequate labeling, or use error. Guidance is issued to reporting entities as needed to more clearly define the reporting of specific events; for example, implant failures.

Since its inception in 1973, the FDA's database of voluntary and mandatory reports of device AEs has received close to 2 million individual reports and currently averages approximately 350 000 individual reports per year, with mandatory reports accounting for about 97% of the total. The reports are submitted on the same standardized voluntary and mandatory forms used to submit drug-related events and capture information on device specifics

(e.g., brand name, model number), event description, pertinent dates (e.g., event date), and patient characteristics. The reports are also coded (either by reporters or internally) using a coding thesaurus of patient and device problem codes. Manufacturers also supply methods, results, and conclusion codes relevant to their report investigation. To enhance report handling and signal detection, the FDA has established methods of triage:

- emergency reports (e.g., a cluster of deaths or serious injuries in a dialysis facility) are handled under FDA-wide standard operating procedures;
- predesignated high-priority reports are reviewed within 24 h of receipt and include, among others, reports of pediatric death, exsanguination, explosion/fire, or anaphylaxis;
- other individual reports (account for about 38% of all reports) are reviewed within 5–15 work-days of receipt;
- autoscreen reports (account for about 3%) are those that are computer-screened (by predesignated device and event) where events are considered to be familiar, but text may be particularly valuable in assessing event or events that are coded inconsistently; 10% of screened reports are later individually reviewed; and
- summary reports (account for about 59%) capture well-characterized and well-known device events and amount to a quarterly submission by manufacturers of line-listed data. The data elements per event include the manufacturer, model-specific device, event and receipt dates, and patient and device problem codes. A system has been developed to perform automated numerator-only trend analyses looking for month-to-month variation, monthly moving averages, and 12-month trends.

When potential hazards are detected (either based on internal individual or aggregate review) or upon notification by the manufacturer (under voluntary recalls), denominator data can be obtained from manufacturers upon request. The denominator data most appropriate to the analysis tend not to be generic higher order data (such as number manufactured of that brand during the past year) but

typically are model specific, many times lot specific (and thus time specific), and may be subgroup specific (e.g., pediatric use). Complicating the selection of appropriate denominator data are the myriad types of devices (e.g., single-use disposables to multicomponent durable medical equipment) and the inherent difficulties in assessing potential population exposure (e.g., factoring in multiple uses, average shelf-life, component replacement).

Staff, predominantly nurses and engineers, review the individual reports from a variety of perspectives, including the potential for device failure (e.g., poor design, manufacturing defect), use error (e.g., device misassembly, incorrect clinical use, misreading instructions), packaging error, support system failure, adverse environmental factors, underlying patient disease or co-morbid conditions, idiosyncratic patient reactions (e.g., allergy), maintenance error, and adverse device interaction (e.g., electromagnetic interference) (ECRI, 1998). Since many devices involve complex human interaction, great emphasis is placed on human factor considerations. Simply put, these considerations ask: (1) To what extent did sub-optimal device design, packaging, or labeling induce human error? (2) To what extent was anticipated use (and abuse) of the product factored into device design, packaging, or labeling?

Several immediate actions, aside from routine requests for follow-up information, may be taken by the staff in the context of the “signal escalation” process, including:

- Recommending internal expert safety meetings. These may lead to recommendations for meeting with the company to explore issues further, additional postmarket study, or public notification.
- Recommending directed inspections of manufacturers. These may lead to (a) label changes, including those affecting device instructions or training materials, (b) product modification/recall, and (c) rarely, product seizure or injunction.
- Alerting regulatory authorities outside the USA through the international vigilance program (see below).

Other internal uses of the AE data are widespread, including: input into premarket review (by

providing human factor insights and information on product experience in the general population); input into recall classifications (involving a hazard evaluation based on AE data); monitoring of recalls (and assessing reports in similar products); input into product reclassifications and exemptions from premarket notifications (based, in part, on a product’s safety profile); use in, and initiating of, standards efforts that establish device performance; educating the clinical community through newsletters, literature articles (peer-reviewed and professional and trade journals), and teleconferences; and as a general information resource for healthcare providers and the general public.

An example of reports of AEs typifies the system in action. In June 2002, the FDA received reports of bacterial meningitis in patients with cochlear implants for treatment of hearing loss. Early speculation by manufacturers and implanting surgeons implicated the implant positioner (a Silastic® wedge that is inserted next to the implanted electrode to facilitate transmission of the electrical signal by pushing the electrode against the medial wall of the cochlea). The one manufacturer that made implants with a positioner voluntarily withdrew their product both in Europe and the USA in July 2002. Other manufacturers, however, notified the FDA of additional cases of meningitis, principally in children. A nationwide collaborative investigation was begun by the FDA and the Centers for Disease Control and Prevention (CDC) that involved several thousand implanted children. These children were found to have far greater risk of developing pneumococcal meningitis than children in the general population did, and those with positioners had over four times the risk of developing meningitis than the recipients of other cochlear implant types (Reefhuis *et al.*, 2003). Throughout this process, the FDA posted periodic updated public health notifications on its website to keep the public informed (FDA, 2002–2003). In addition, the CDC Advisory Committee on Immunization Practices added cochlear implant recipients to the list of high-risk patients needing routine immunizations (CDC, 2003).

As is typical of passive surveillance systems (including those for drugs), the FDA’s system has

notable weaknesses as well as strengths. Among the former are:

- data may be incomplete or inaccurate and are typically not independently verified;
- events are underreported – causes include lack of detection and/or attribution of device to event, lack of knowledge about reporting system, liability concerns, perceived lack of utility in reporting, and limited feedback;
- data reflect reporting biases driven by factors such as event severity or uniqueness, familiarity with reporting, or publicity and litigation;
- determination of incidence and prevalence is not possible due to underreporting and lack of appropriate denominator data; and
- causality cannot be inferred from any individual report. (In addition, devices are often not returned to manufacturers for assessment – for a variety of reasons – and, therefore, failure analyses of data are often inadequate or lacking.)

The system strengths are:

- it provides a nationwide safety surveillance from a variety of sources, thus providing insight into AEs related to “real-world” use;
- it is relatively inexpensive considering the scope of surveillance;
- data collected are uniform in terms of a standardized form with prespecified data elements;
- it is one of only a few means to detect rare AEs; and
- it is accessible and the information is open to the public.

#### MEDICAL DEVICE SAFETY NETWORK (MEDSUN)

Recognizing the need for user facility reporting but also the difficulties behind universal reporting, the US Congress mandated under FDAMA 1997 that reporting be limited to a “subset of user facilities that constitutes a representative profile of user reports....” Since 2002, the FDA has been collecting data about problems with the use of medical devices from a sample of hospitals via MedSun. By mid 2005, this interactive Internet-based reporting program expanded to approximately 350 hospitals

nationwide. The program’s principal objective was to increase the utility of user facility reporting by recruiting a cadre of well-trained and motivated facilities and establish a collaborative effort to better understand device use in its natural clinical environment. It is envisioned that, in addition to enhancing the detection of emerging device problems, the network acts as a two-way communication channel between the FDA and the clinical community and serves as a setting for applied clinical research on device issues. To succeed, the effort must train staff in the recognition and reporting of AEs, assure confidentiality to reporters, minimize burden of participation, and provide timely feedback. To achieve its mission, MedSun staff have initiated a variety of efforts within the network: monthly newsletters (highlighting device reports, FDA actions, and other notable safety initiatives by other agencies); webinars on safety issues of general interest; device safety exchanges (highlighting best safety practices and safety solutions); and surveys on high-profile safety concerns. Currently, approximately 4000 AE reports are submitted annually via MedSun.

#### INTERNATIONAL VIGILANCE REPORTING

A process for the global exchange of vigilance reports between national competent authorities (NCAs), previously established under the Global Harmonization Task Force, is now under the auspices of the International Medical Device Regulators Forum ([www.imdrf.org](http://www.imdrf.org)). Approximately 30 NCAs are currently involved. Standardized reports on potentially high-risk issues for which action is to be taken are submitted electronically to a shared list server. General and specific criteria for categorizing issues as high risk have been established and include the equivalent of US Class I and high-level Class II recalls, and all public health notifications. The FDA’s Office of International Programs facilitates communications of confidential information that is not in the public domain.

#### DEVICE IDENTIFICATION

The US FDA Amendments Act of 2007 directed the FDA to issue regulations establishing a unique

device identification (UDI) system for medical devices (<http://www.fda.gov/UDI>). When implemented, this new system will generally require: (1) the label of a device to bear a unique identifier (as well as the device itself, for certain device categories); (2) the unique identifier to be able to identify the device through distribution and use; and (3) the unique identifier to include both a “static” component (i.e., manufacturer, make, model) and a “dynamic” component (e.g., the lot or serial number).

In conjunction with this initiative, the FDA is leading an effort to develop and implement a national strategy for the best public health use of health-related electronic data incorporating UDIs. Health-related data (from large data sources such as health insurers and integrated health systems, registries, and other sources) contain a wealth of public health information that could be harnessed to contribute to understanding device safety and effectiveness. Currently, however, these data generally cannot be used to identify specific device exposures in patients. This is not the case for drug exposure, where the regular documentation of national drug code (NDC) numbers allows for robust analysis of pharmaceutical safety and effectiveness. Absent such information for devices, a vast amount of potentially useful data regarding patient safety and outcomes remains untapped.

The incorporation of the UDI into various health-related databases will greatly facilitate many important public health-related activities, including: (1) reducing medical errors; (2) reporting and assessing device-related AEs; (3) tracking of recalls; (4) assessing patient-centered outcomes and the risk–benefit profile of medical devices in large segments of the US population; and (5) providing an easily accessible source of device identification information to patients and healthcare professionals.

One of the approximately dozen attributes that will be linked to the UDI (such as the brand name) will be the global medical device nomenclature (GMDN) code. The GMDN, developed through a major international standards effort, was created largely via the merging and evaluation of six extant naming systems (including the one used by the FDA) (<http://gmdnagency.com>). Currently, the GMDN has over 19 000 primary terms that abide

by specified naming rules and conventions as well as definition structure and content (e.g., incorporating intended use). The GMDN is based on the level of specificity of the “device group,” which is best described by way of example; that is, pacemaker, cardiac, implantable, or gastroduodenoscope, flexible, fibroscopic. It is meant for use by regulatory agencies, but has the potential for wider applications alongside the UDI (e.g., inventory control or marketing).

## **MANDATED POSTMARKET STUDIES**

Another “tool” that the FDA uses to achieve its surveillance and risk assessment goals is mandated postmarket studies, conducted under either PMA conditions of approval (for Class III products) or FDAMA (Section 522) authorities. A sponsor may be required to perform a post-approval study as a condition of approval for a PMA (Title 21 CFR Part 814(a)(2)). The study questions may relate to longer term performance of an implant, or focus on specific safety issues that may have been identified during review of the product for which additional information is felt to be needed, postmarket. Results from these studies may be included as revisions to the product’s labeling (including patient- and clinician-related material). Current study status, study protocol outlines, and basic study results are posted on the FDA’s website ([http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma\\_pas.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm)).

In addition to the PMA authority for Class III products, the FDA may, under Section 522, impose postmarket study requirements on certain devices. The latter provision, originally mandated in 1990 under Safe Medical Devices Act, allows the FDA, under its discretion and for good reason, to order a manufacturer of a Class II or Class III device to conduct a postmarket study if the device: (1) is intended to be implanted in the human body for more than 1 year; (2) is life sustaining or life supporting (and used outside a device user facility); (3) is expected to have significant use in pediatric populations; or (4) failure would reasonably be likely to have serious adverse health consequences. Although this discretionary authority overlaps the PMA

post-approval authority for some products (e.g., PMA Class III implants), it effectively extends FDA authority to cover non-PMA products as well; that is, those subject to premarket notification. Unless there are unusual circumstances, the Section 522 authority is typically reserved for the latter.

Prior to issuing an order, the FDA will discuss the public health concern with the firm. The concern may arise from questions about a product's long-term safety, about performance of a device in general use or involving a change in user setting (e.g., professional to home use), or notable AEs. Upon receiving an order, the firm has up to 30 days in which to submit their study plan and, by statute, studies are limited to 3-year patient follow-up (or longer if (1) agreed to by the firm or (2) if the device is expected to have significant pediatric use). FDA regulations clearly specify, among other items, the requirements for a study plan, conduct, and follow-up (Title 21 CFR Part 822).

The FDA has issued guidance covering various aspects of the Section 522 Program, including the process for evaluating candidate issues for study, study plan elements, criteria used to note study status, and types of study approaches (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm268064.htm>). With regard to the latter, the possible study approaches vary widely (designed to capture the most practical, least burdensome approach to produce a scientifically sound answer) and include: nonclinical testing of the device; enhanced surveillance; observational studies; and, rarely, randomized controlled trials. Current study status is posted on the FDA's website (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pss.cfm>).

Generally speaking, these mandated postmarket studies (both via PMA conditions of approval and Section 522) require the participation of both firms and the clinical community. Problems, however, may arise in the conduct of these studies if, for instance, it is difficult to recruit physician investigators or accrue patients or if industry lacks incentive. These issues particularly resonate with rapidly evolving technologies, where rapid device evolution may make studies of prior models obsolete by the time they are completed. Recent efforts have focused on utilizing existing and/or developing data

source infrastructures to conduct these mandated studies. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS; [www.intermacs.org](http://www.intermacs.org)) is one example of such a data source that has been used by industry to fulfill post-approval study requirements for ventricular assist devices.

Although there may be difficulties in study conduct, an example of a Section 522 study reveals the authority's public health importance and its risk assessment role. In 1991, FDA scientists demonstrated that it was possible for polyurethane to break down under laboratory conditions to form 2,4-toluenediamine (TDA). TDA had been shown to be an animal carcinogen. Prior to this it was thought that breakdown could only occur at very high temperatures and pH extremes. The firm that manufactured polyurethane foam-coated breast implants ceased sales in 1991 and agreed to a clinical study under Section 522. The study involved comparing TDA levels in urine and serum samples from women with and without the implants. Although minute amounts of TDA were found in the majority of women with the implants, the increase in cancer risk was determined to be vanishingly small (1 in 1 million) (Hester *et al.*, 1997; DoLuu *et al.*, 1998). The FDA issued a public health correspondence (FDA Talk Paper) on the results and their reassuring implications (FDA, 1995).

## APPLIED EPIDEMIOLOGY

Postmarket surveillance and risk assessment would not be complete without epidemiology, a discipline that provides the means and methods to further elucidate a device's postmarket safety and effectiveness in a population context. Through employing methods of observational (as opposed to experimental) study, epidemiologists help refine AE signals, characterize subgroups at risk, test hypotheses, and evaluate device performance and use. The epidemiology program serves a vital postmarket function at the FDA and works to inform CDRH and FDA device policy, address relevant scientific questions, assess the effectiveness of regulatory approaches, provide risk assessments, develop new

postmarket surveillance and other data resources, and provide important public health information (e.g., through peer-reviewed publications). Importantly, the program has oversight of both post-approval studies (i.e., those as a condition of approval of PMA products) and Section 522 studies. It is now the program's responsibility to help design, implement, track, and oversee completion of these studies of high-risk devices and public health issues. To accomplish this, the program works collaboratively with product manufacturers and the premarket staff.

To accomplish its overall mission, the epidemiology program makes use of a variety of data sources. There has been growing interest over the past decade to develop and use national registries, such as the American College of Cardiology (ACC) registries ([www.ncdr.com](http://www.ncdr.com)) and Society of Thoracic Surgeons (STS) registries ([www.sts.org](http://www.sts.org)). FDA collaborative work continues on development of an atrial fibrillation registry (Al-Khatib *et al.*, 2010) and in use of ACC's ICD registry (Wei *et al.*, 2011). In addition, the program explores more traditional passive surveillance sources (e.g., MDR system; Brown and Woo, 2004) and new means of surveillance (e.g., through a nationwide surveillance network of emergency departments operated by the US Consumer Products Safety Commission; Wang *et al.*, 2010), explores methods of active surveillance (in state-wide and national registries) (Resnic *et al.*, 2010), explores use of claims data sources (e.g., Medicare claims to assess risk of negative pressure wound therapy in the elderly; Ritchey *et al.*, 2011), conducts systematic reviews and assesses observational literature (e.g., surgical mesh use and safety and effectiveness), and conducts applied research (e.g., endovascular grafts for abdominal aortic aneurysms and rupture rates) (Tavris *et al.*, 2010).

The ability of drug or device epidemiologists within the FDA to address issues, however, is at times limited for both practical and regulatory reasons. There may be practical resource limitations (e.g., limited staff or limited funding) or time constraints (i.e., issues requiring immediate resolution may not lend themselves to observational study). Limits imposed by the regulatory environment are most apparent when mandating postmar-

ket studies. The agency levies these studies on specific manufacturers of specific products. In doing so, there is no intent for comparative analyses, or pooled analyses, amongst manufacturers of similar products. Nor is there any intent on assessing cost effectiveness, or conducting other economic analyses, since this is not within the FDA's mandate.

Other practical limitations, with regard to medical devices, have to do with the type of information available from extant data sources. Many of the data sources used by pharmacoepidemiologists (e.g., hospital based, public health based as in Saskatchewan, or health maintenance organization based) may not have device-specific information, whether at the "device group" level such as an ultrasonic rigid laparoscope or carbon dioxide surgical laser, or certainly not at the model- or brand-specific level. Other data sources, such as medical care claims records, often collect procedure-specific, but not device-specific, information, leaving one to infer device use. Compounding this situation is the relative lack of data sources for assessing device exposure and difficulties in deriving the most appropriate denominator data (as noted previously with regard to AEs) (Bright, 2000).

These limitations notwithstanding, epidemiology continues to play a vital role in addressing agency device concerns. The role of epidemiology is exemplified by the following two cases. On the basis of concerns about use and performance of transmyocardial revascularization (TMR), the program undertook a collaborative effort with investigators who oversee the STS's National Adult Cardiac Surgery database (Peterson *et al.*, 2004). The study findings noted large-scale off-label use and higher operative risks in patients with a recent myocardial infarction and unstable angina. Potential reduction in mortality was suggested through optimization of timing of the procedure. Another soon-to-be completed FDA study with the STS is examining longer term effects of TMR, and relative safety of two current laser types. The epidemiology program was also involved in assessing the public health impact of a marketed continuous glucose monitoring system in the USA (Tavris and Shoaibi, 2004). A thorough review of the literature suggested that use of the system could result in a substantial reduction

in morbidity and mortality associated with diabetes.

## THE FUTURE

Given the heterogeneity and complexity of devices and the varied use environments, multiple approaches to detecting and assessing their potential safety and/or effectiveness are warranted. The FDA has recognized this need and has strived to enhance existing mechanisms and develop new approaches to build an integrated system for postmarket surveillance that will help assess and manage the risks and benefits of medical devices in as effective a way as possible given limited resources.

The FDA also fully appreciates that information that is learned about a product's performance in the "real world" is essential to continual product improvement, increasing patient benefit, and mitigating potential harm. Such information is part of the total product life cycle and affects, among others, device design and testing, clinical assessment for investigational indications, and postmarket oversight. All of the elements of an effective system for postmarket surveillance and benefit-risk assessment must be used in concert with other FDA activities to fully realize the benefits of the total product life cycle concept.

Although MDR will continue to be a key element of the system, many enhancements are envisioned. Electronic reporting offers significant benefits and approximately 50% of incoming individual reports are currently submitted electronically. To meet the goal of receiving all reports electronically, the agency is also moving ahead with the eMDR regulation, which will require that all manufacturers submit mandatory reports electronically beginning 1 year after implementation of the rule. The AE report database platform and user interface is being replaced with a system offering sophisticated search, trending, and analytic capabilities. A non-production test environment is being created to link internal pre- and postmarket datasources, including AE reports, to seamlessly search for relevant device safety, effectiveness, and performance data. Data mining, text mining, and related software and analytics are being explored as aids in: (1) enhanc-

ing the signal-to-noise ratio through "sifting" of noninformative reports; (2) augmenting AE report data with other relevant safety data; and (3) optimizing device signal detection through use of automated statistical algorithms. The latter has been demonstrated as possible through retrospective "proof-of-concept" studies (Herz *et al.*, 2011).

MedSun will be of ever-increasing importance as it consolidates its network of hospitals across the USA. Through its regional representative program, comprising frequent hospital visits and on-site interactions with healthcare professionals, Medsun facilitates on-site device safety education, as well as data gathering and investigations. "Virtual" capabilities, with institutions great distances from the FDA, are being explored. Survey capabilities are also being expanded to obtain timely input from the clinical community regarding issues of device safety and/or effectiveness, device use, device availability, and effectiveness of FDA communications and recalls.

To provide more robust surveillance, the FDA launched the Sentinel Initiative in 2007 (<http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm>). The principal aim of the FDA's Sentinel Initiative is to complement limited FDA post-market monitoring systems and capabilities with a national integrated electronic healthcare infrastructure for medical product active surveillance. The surveillance is to be done using national distributed data sources (with populations totaling in the tens of millions), transformed to a common data model(s), against which FDA queries (including active surveillance protocols) can be run and aggregate data received (Robb *et al.*, 2011). In preparation for Sentinel efforts, and to inform them, exploratory device work has been done using an automated computerized safety surveillance system for the early detection of potential safety signals of newly introduced cardiovascular devices within a contemporary mandated state registry (Resnic *et al.*, 2010). Further exploratory work will be done in a national cardiovascular registry as well as in an integrated health system.

In the future, the FDA will increasingly use other sources of data to address important device issues. As previously mentioned, national registries, maintained by professional societies, have become an

increasingly important means to address short-term safety issues. The FDA use of these data sources extends to international collaborations, as exemplified by the International Consortium of Orthopedic Registries (FDA, 2011). This FDA-initiated effort aims to develop collaboration, through use of common data models and analytics, amongst over two dozen orthopedic implant registries to understand real-world performance of these devices. Another important data source for use in understanding safety of medical devices is claims data, at the device-type (but not manufacturer-specific) level. Currently, the FDA is collaborating with Centers for Medicare & Medicaid Services in exploring use of Medicare and Medicaid data to assess safety of gastric bands, surgical mesh for pelvic organ prolapse, cardiac resynchronization therapy, and use of intra-ocular lenses post-cataract surgery in pediatric patients. Medicare claims data have also been linked with registry data to create longitudinal profiles to study devices such as drug-eluting coronary stents (Douglas *et al.*, 2009). As noted earlier, other important data sources will become available for device safety and effectiveness assessments once UDIs are incorporated, as will enhanced use of sources such as claims data for analyses to the manufacturer-specific level.

Other emerging themes are important in the development of device epidemiology. There is growing interest in synthesis of evidence from disparate data sources, such as clinical trials and registry data (Normand *et al.*, 2010), in the use of common data models in distributed networks, such as the Sentinel system, and in universal adoption of electronic health records. Frameworks for evidence evaluation for medical devices have been proposed (Sedrakyan *et al.*, 2010). Public-private partnerships have been gaining traction, and the FDA launched the Medical Devices Epidemiology Network (MDEpiNet) Initiative in 2010 (Marinac-Dabic *et al.*, 2011). Its aim is to develop a consortium of academic centers focused on bringing methodological expertise, data source, and other tools to bear on addressing pressing device issues, whether about real-world performance or methodological/analytical approaches.

Finally, surveillance efforts will continue to mature as the variety of methods, tools, and resources

noted above continue to develop and become available for increased and more sophisticated use. In addition, device innovation will spur other creative approaches to assessing real-world short- and long-term risks and benefits (Suter *et al.*, 2011). A comprehensive postmarket surveillance strategy, as called for in a recent Institute of Medicine report (Challoner and Vodra, 2011; Institute of Medicine, 2011), will assure robust oversight of the heterogeneous and complex world of medical devices. The FDA, in collaboration with other major stakeholders and partners, will continue to create that comprehensive strategy.

## ADDENDUM

A medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, that is (1) recognized in the official National Formulary, or the US Pharmacopoeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in humans or other animals, or (3) intended to affect the structure or any function of the body of humans or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of humans or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes (Section 201 of the Act, Title 21 US Code §321).

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Part V

CURRENT TOPICS



# The Efficacy and Safety of Selective Serotonin Reuptake Inhibitors for the Treatment of Depression in Children and Adolescents

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## INTRODUCTION

US concerns surfaced in the early 1990s that treatment with antidepressants (ATDs) in the selective serotonin reuptake inhibitor (SSRI) subclass might increase the risk of suicidal ideation or behavior in depressed adults (Teicher *et al.*, 1990) and in youth diagnosed with obsessive-compulsive disorder (OCD) (King *et al.*, 1991). The reports were based on a case series and a small clinical trial. This news led to a US Food and Drug Administration (FDA) hearing, but responses faded by the mid 1990s. In 2000, a systematic analysis from adult registration trial data concluded that suicides were *not* more

frequent for those treated with SSRIs than for those treated with placebo (Khan *et al.*, 2000). However, in June 2003, the suicide safety risk began to draw renewed media attention following the publication from the Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK of a preliminary report on paroxetine clinical trial data which revealed that children receiving this SSRI experienced harmful outcomes (episodes of self-harm and potentially suicidal behavior) that was 1.5 to 3.2 times greater than randomly assigned children receiving placebo. Following the warnings in the UK, in October 2003, the FDA issued a public health advisory informing physicians and the public

about the reports of increased "suicidality" (defined as suicidal ideation, suicide attempts, or completed suicides) in ATD trials for the treatment of youth with major depressive disorder (MDD).<sup>1</sup>

No labeling change was made in 2003, but a Psychopharmacologic Drugs Advisory Committee (PDAC) meeting was convened to discuss this issue. Based on the formal recommendation of the PDAC, which met in February 2004, a strongly worded suicidality warning was added to the FDA website in March 2004. The FDA also proposed labeling changes for ATDs in March 2004 to reflect the warning. The March 2004 warning was less equivocal than the October 2003 advisory. In addition, a comprehensive suicidality analysis was authorized. On review of the additional analysis in September 2004, a boxed warning on the increased risk of suicide-related events (SREs) for all ATDs was issued in October 2004, though no completed suicides had occurred in the trials. FDA hearings on this subject in February 2004 and September 2004 reviewed 24 US short-term, placebo-controlled pediatric trials of ATDs with respect to the risk of suicidality. These industry-conducted registration trials were submitted to the FDA, many in response to the FDA Pediatric Rule, which extended patent exclusivity for 6 months regardless of the trial outcome. The intense media coverage of the public hearings reflected the sharply differing public comments, either supporting or dismissing the clinical importance of the elevated risk of treatment-emergent suicidality based on depression trial data for youth exposed to SSRIs relative to placebo.

Subsequent to the 2004 meetings, the FDA expanded the exploration for suicidality in ATD trials to the adult population by analyzing 372 placebo-controlled ATD trials and almost 100 000 patients. These data were reviewed by the PDAC in December 2006, which led to an update to the 2004 boxed warning to include warnings about increased risks of suicidality in young adults aged 18 to 24

during initial treatment (generally the first 1–2 months) for all ATDs in May 2007.

Recommendations from the MHRA in the UK and the European Medicines Agency (EMA, 2005) contrast with US drug regulators (FDA, 2004) and have led to confusion and limited, often misleading interpretations of the pertinent scientific information. The UK announcements restricted use to fluoxetine, whereas in the USA no contraindication for SSRIs to treat depression in children and adolescents was recommended, only a suggestion discouraging use of paroxetine. Also in 2004, the EMA issued similar warnings for SSRIs, and like the UK also contraindicated prescription of SSRIs to treat depression in youths (EMA, 2005). In summary, throughout the period from June 2003 through October 2004, there was intense press coverage and debate in both the lay media and in the professional literature regarding the safety (and, to a minor extent, the efficacy) of SSRIs for the treatment of depression in children and adolescents in the USA. A review of the efficacy studies from clinical trials in youth is a critical starting point to contrast the European and US regulatory actions.

## EFFICACY FROM PUBLISHED CLINICAL TRIALS

Table 46.1 describes the major published SSRI efficacy studies conducted in US youth. The studies used a number of outcome measures, including: (1) symptom rating scale score change (e.g., CDRS-R) from baseline (intent to treat model, where everyone who begins the treatment is considered to be part of the trial, whether they finish it or not); (2) symptom rating scale score change at final endpoint (completers' model, where only those who finish the treatment are included in the analysis as defined in the protocol); (3) percentage improved; and (4) clinical global impression (CGI – where everyone who begins the treatment is considered to be part of the trial, whether they finish it or not) rating score change. Two of the fluoxetine studies did not meet the *a priori* primary endpoint of symptom score reduction from baseline (Emslie *et al.*, 1997, 2002), causing an FDA statistical expert to reject the efficacy claim (Safer, 2006). For the studies

<sup>1</sup>The term suicidality is unclear because a causal linking of ideation with suicidal behavior is not scientifically feasible because of the rarity of completed suicides. Consequently, some leaders in the USA and Europe prefer suicide-related events (SREs), emphasizing behavior rather than ideation, and is a term that will be used where appropriate in the text.

Table 46.1 Summary of major SSRI studies by primary author and drug, outcome in the total population (column 2), in children (column 3) and in adolescents (column 4).

	Total	Children, 6–11 or 8–12 years	Adolescents, 12–17/18 or 13–17 years
Wagner, MDD, 2003 Sertraline	% improved, 69 versus 59; 40% drop in CDRS-r, $p = 0.05$	Mean change from baseline CDRS-r –24.05 versus –22.20, ns. at 10 weeks, –31.44 versus –27.56, $p = 0.05$	Group diff mean CDRS-r –21.55 versus –18.20, $p = 0.01$ at 10 weeks, –28.95 versus –24.11, $p = 0.01$
Emslie, MDD, 1997 Fluoxetine	% improved, 29 versus 19, n.s.; remission, n.s. CGI improvement, 56% versus 33%, $p = 0.02$	8–12 y/o, 30% reduction from baseline, $p$ is n.s.	13–17, 30% reduction from baseline, $p = 0.075$
Emslie, 2002, MDD Fluoxetine	% improved, 65.1 versus 53.5, $p = 0.09$	8–12 CDRS-r 30% reduction, $p$ is n.s.	13–17 CDRS-r 30% reduction, n.s.
TADS, 2004, MDD, Fluoxetine			Fluox (unblended) + CBT > Fluox > CBT > Placebo

CDRS-r: clinical depression rating scale-revised; CGI: clinical global impression; CBT: cognitive behavior therapy; HAM-D: Hamilton depression scale; n.s.: not significant.

including both children and adolescents sertraline (Wagner) and fluoxetine (Emslie), significant improvement resided entirely in the adolescent group. Moreover, even in the age group most likely to benefit, symptom reduction was not different between active drug- and placebo-treated youth in the paroxetine study of adolescent depression (Keller *et al.*, 2001). The authors, therefore, based the conclusion of paroxetine efficacy on an endpoint different from the original proposed primary endpoint, calling the study results into question.

The National Institute of Mental Health (NIMH)-funded treatment of adolescent depression study (TADS) was added to the list of registration trials for the FDA safety analysis (see the “Safety from clinical trial Data” section). The TADS is listed here among the major efficacy studies, but it should be noted that it was primarily conducted to assess the efficacy of fluoxetine relative to a psychotherapy intervention of proven efficacy (cognitive behavior therapy (CBT)) and may better qualify as a management trial because of the limited use of blinded observations. The TADS authors concluded that for the treatment of adolescent depression fluoxetine in combination with CBT gave better results than fluoxetine alone, CBT

alone, or placebo. In summary, published US studies on SSRIs show modest but statistically significant effects over placebo in adolescents. Overall, the data do not support efficacy in children (Safer, 2006). Nevertheless, published clinical interpretations suggest moderate overall effectiveness (Vitiello and Swedo, 2004), are silent on this important distinction (Cheung *et al.*, 2005), or express preference for use based on (Brent, 2004; Cheung *et al.*, 2005; Mann *et al.*, 2006) the serious risks of the failure to treat depression irrespective of the absence of efficacy in children (Safer, 2006) compared with adolescents.

The net effect of the pediatric clinical trials on policy was the FDA regulatory action in 2003, which added MDD as a labeled indication for fluoxetine for youth aged 7–17 years, despite lack of significant improvement in 7–12-year-olds (Safer, 2006).

## META-ANALYSIS OF PUBLISHED AND UNPUBLISHED CLINICAL TRIALS

In addition to individual published trial analyses, there was a meta-analysis of all registration studies

from the UK (Whittington *et al.*, 2004). The authors divided the studies into peer-reviewed published and unpublished studies residing with the Committee on Safety of Medicines, now called Commission on Human Medicine. Efficacy measures included remission, response to treatment, and depression symptom score changes. Safety measures included serious adverse events, suicide-related behaviors, and discontinuation of treatment because of adverse events. The results were startling: published studies reported efficacy but the effect was lost when assessed along with results from unpublished studies. Overall, the authors found limited empirical support for the use of SSRIs to treat MDD in youth: fluoxetine use was supported, but one paroxetine and two sertraline trials had equivocal or had weak positive risk–benefit profiles. However, in these two cases, the addition of unpublished data shifted the results to an unfavorable risk–benefit profile. Data from clinical trials of citalopram and venlafaxine showed unfavorable risk–benefit profiles.

The meta-analysis is consistent with UK recommendations for a contraindication on the use of all SSRIs except fluoxetine to treat childhood depression. By contrast, the FDA has been silent on the efficacy issue, focusing its attention entirely on the question of SSRI safety with respect to treatment-emergent suicidal ideation and behaviors.

Bridge *et al.* (2007) assessed both efficacy and risk in pediatric ATD treatment clinical trials. Among the 27 trials studied, 15 examined MDD, 6 examined OCD, and 6 examined non-OCD anxiety. The findings on responder status suggested a response rank order of non-OCD anxiety > OCD > MDD. The authors reported age-stratified analyses of pooled outcome findings as indicating that only fluoxetine showed benefit for <12-year-olds with MDD, although the pooled results showed a trend ( $p < 0.08$ ).

From a research methodology perspective, unpublished trial data are a source of publication bias and, when excluded, render meta-analytic approaches virtually meaningless. Demands for an end to allowing unpublished study data to remain unexamined based on so-called proprietary rights have been advocated within US child psychiatry (Zito *et al.*, 2004). In addition, leading academic

medical journals have announced new rules restricting publication unless trials have been registered and all relevant data are available for review (DeAngelis *et al.*, 2005). The journal policy strengthens the goal of registration of all trials in a government-sponsored database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). In the decade since its inception, database compliance has been increasing, but its value continues to depend on the submission of accurate, informative data by the research community (Zarin *et al.*, 2011).

## EFFECTIVENESS FROM NATURALISTIC FOLLOW-UP STUDIES

Several follow-up studies to the TADS clinical trial have been published (Treatment for Adolescents With Depression Study (TADS) Team, 2009; Curry *et al.*, 2011). The major inferences from these follow-up studies at 1 year and 5 years are:

- 1 Depression is increasingly likely to recur as follow-up time increases.
- 2 Recurrence rates did not differ for TADS early initial responders compared with nonresponders. Decisions to restart ATDs and psychotherapy rest primarily on the severity of the symptoms and functional impairment (Curry *et al.*, 2011).

## SAFETY FROM CLINICAL TRIAL DATA

Prior to the FDA Advisory Committee meeting of February 2, 2004, an anonymous press report stated that the planned presentation of the analysis of the safety of ATDs with respect to SREs conducted by Andrew Mosholder was removed from the agenda. Subsequently, Columbia University epidemiologists conducted a reclassification of the adverse events reported in the trials (Posner *et al.*, 2011). After the revised data were available, the Mosholder analytic design for suicidality risk assessment (Office of Drug Safety (ODS)) and a second analysis conducted by Tarek Hammad for the Division of Neuropharmacological Drug Products (DNDP) were compared (Hammad, 2004; Mosholder, 2004; Safer, 2006). The analyses differ in the primary outcome measure: serious ADEs in the ODS study,

Table 46.2 Comparison of risk of serious ODS: Office of Drug Safety; Suicide-related events (SREs) (column 5) and outcome 3 (suicide attempts and ideation, column 4) from two distinct analytic approaches (ODS and DNDP analysis).

Category of trial	Total N drug	Total N placebo	ODS analysis Incidence rate ratios, SREs	DNDP analysis Risk ratios, Columbia U., outcome 3
Paroxetine	642	549	2.19 (0.92–5.24)	2.65 (1.00–7.02)
Sertraline	281	279	2.52 (0.49–13.01)	1.48 (0.42–5.24)
Venlafaxine	339	342	1.80 (0.52–6.20)	4.97 (1.09–22.72)
Fluoxetine	249	209	0.88 (0.32–2.44)	0.92 (0.39–2.19)
Citalopram	210	197	2.54 (0.91–7.05)	1.37 (0.53–3.50)
Mirtazapine	170	88	— <sup>a</sup>	1.58 (0.06–38.37)
Nefazodone	279	189	— <sup>a</sup>	— <sup>b</sup>
Fluvoxamine	57	63	— <sup>a</sup>	5.52 (0.27–112.55)
Bupropion	71	36	— <sup>b</sup>	— <sup>b</sup>
All MDD trials	1586	1299	1.95 (1.19–3.21)	1.71 (1.05–2.77)
SSRI <sup>c</sup> MDD trials	955	843	1.87 (1.10–3.18)	1.41 (0.84–2.37)
Non-MDD trials	712	653	1.31 (0.26–6.72)	2.17 (0.72–6.48)
All trials	2298	1952	1.89 (1.18–3.04)	1.78 (1.14–2.77)

DNDP: Division of Neuropharmacological Drug Products; ODS: Office of Drug Safety; SRE: Suicide-related events.

<sup>a</sup>Ratio undefined due to zero events in the placebo group.

<sup>b</sup>No events in either arm.

<sup>c</sup>Includes paroxetine, sertraline, fluoxetine, citalopram, and fluvoxamine.

with person-years as the unit of analysis, and suicidality as the outcome whereas individual person is the unit of analysis in DNDP. These differences resulted in the use of incident rate ratios for the former and relative risk estimates for the latter.

Table 46.2 depicts the results from 19 of the 23 trials evaluable for outcome 3 (suicide attempts and ideation) based on the Columbia revised data set (column 5) which compared the risk of serious SREs according to the standard regulatory definition; for example, life-threatening adverse drug experience, inpatient hospitalization or prolongation of hospitalization, or disability/incapacity (column 4). There is little overall difference between the two methods for outcome 3 and serious SREs. Both show an increased risk for all MDD studies, but the level of statistical confidence differs, altering the interpretation of the finding. The total risk measure for the youth MDD trials in which an SSRI was studied was 1.87 (1.10–3.18) in the ODS study and 1.41 (0.84–2.37) in the DNDP study. The analysis may be interpreted as showing a weak “signal” for risk of treatment-emergent suicidality, although the DNDP estimate includes 1 in the confidence interval – allowing the reviewer to dismiss the importance of the signal. A possible reason for

the variation between the two results concerns whether serious SREs and outcome 3 (suicidal attempts and ideation) are comparable risks. In the case of outcome 3, most events were ideation, an event that is likely to be three times more prevalent than attempts when lifetime self-reported data from adolescents are examined (Evans *et al.*, 2005) and could account for reducing the risk estimate. In fact, measuring the risk for ideation alone ( $n = 78$ ) compared with the risk for suicidal behavior ( $n = 33$ ) in the risk estimates of suicidality was shown to dilute the risk: 1.00 (0.52–1.94) versus 1.83 (0.89–3.77), respectively (Hammad, 2004: 38, Table 5.10.36). It is noteworthy that SSRI use in MDD represents only 38% of the study population in this analysis, although this is the central question from a clinical and consumer perspective. Equally important is the recognition that the estimate for SSRI use in any individual trial would not achieve statistical significance given the small sample sizes, brief duration, exclusion criteria on suicide risk, volunteer bias, and measurement inconsistencies (Avorn, 2005b).

In the DNDP analysis, several potential effect modifiers were examined: a history of suicidal behavior, age, and gender. But none was different

by treatment group. An interesting sub-analysis conducted by Dr Hammad assessed treatment-emergent hostility or agitation. These symptoms may be reflective of the clinical condition referred to as activation syndrome, which has been identified previously in SSRI studies and clinical practice (Wilens *et al.*, 2003). It has been referred to by various terms – for example, akathisia (Lipinski *et al.*, 1989) – and is suspected of putting patients at greater risk for suicidal behavior or ideation (Teicher *et al.*, 1990; King *et al.*, 1991). Across all MDD trials, the risk of hostility and activation was significantly elevated for SSRI-treated youths compared with placebo-treated youths (2.34 [1.24–4.41]). Overall, patients with symptoms of activation or hostility were up to 6.6 times more likely to have SREs than those without such activation; see Hammad (2004: slide 98). However, further analysis was not undertaken because of the lack of information on the temporal pattern for these symptoms with respect to reports of suicidality. Consequently, further study of the relationship of treatment-emergent agitation, activation, hostility, and suicidal behaviors is likely to be more fruitful than these initial broad analyses, which, in the case of the DNDP analysis, focused on a very broad operational definition of SREs, i.e., suicidality. In addition, age may be crucial to further understanding adverse events in relation to SSRI use. Using published trials in which child and adolescent data were recorded separately, adverse events (e.g., activation) were two to three times more prevalent in children than adolescents and accounted for more discontinuations than in adults (Safer and Zito, 2006).

Conclusions from the ODS and DNDP analyses differed: Mosholder suggested the data from the ODS study supported further analysis of events related to drug discontinuation and suggests inpatient hospitalization as an outcome. Hospitalizations might shed light on the general problem of behavioral toxicities (new psychiatric or behavioral symptoms following drug therapy for the control of psychiatric symptoms associated with medication for the treatment of psychiatric symptoms). The sequence of these events is critical to infer causality – drug exposure must precede new psychiatric symptoms. The history of past events is also

critical. Loss of symptoms upon discontinuation of the drug (dechallenge) would offer supportive evidence of an association. By contrast, the DNDP analysis reviewer concluded, “the strength of the suicidality signal, although it varies from drug to drug, is comparable to previous findings for most drugs,” a statement that seems to nullify the signal.

Hammad *et al.* (2006) published a revised analysis with data from the 24 available trials and measured risk ratios. All three measures were statistically significant, in contrast to the DNDP analysis that was available for the September 2004 FDA Panel meeting. The later analysis showed risk ratios of 4.62 (1.02, 20.92) in the TADS; 1.62 (1.02, 2.68) in the 16 SSRI depression trials; and 1.95 (1.28, 2.98) for 24 trials with all drugs and conditions included. The authors interpreted the findings as a modestly increased risk of suicidality. A risk difference of 0.02 (0.01, 0.03) suggests that in 100 treated patients an additional one to three patients would be expected to experience SSRI-emergent suicidality relative to the non-SSRI group.

The analyses conducted by the FDA after the reclassification of adverse events by Columbia University researchers also indicated that the risk of suicidality in pediatric subjects was highest in the first 4 weeks of initial ATD treatment. To this effect, the FDA boxed warning in October 2004 recommended that physicians provide increased observation by including weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment (Busch *et al.*, 2010). However, data from the NIMH-funded TADS indicated that the risk for suicidal events did not decrease after the first month of treatment, suggesting the need for careful clinical monitoring for several months after starting treatment (Vitiello *et al.*, 2009).

A number of limitations of these FDA-sponsored analyses should be considered. First, searching clinical trial data restricts the assessment to a relatively small and distinct drug-exposed population. In this case, there were approximately 2000 youth with MDD, mainly adolescents exposed to an SSRI. Since suicide events in a lifetime estimate for adolescents approximated 10%, it would appear that in a 4–6 week trial the likelihood of this occurring is slight, if not totally improbable, because the

study is not powered to find such rare events. Second, trial participants are subject to volunteer bias. Exclusion of suicidal patients was likely to increase selection bias, which makes an analysis of suicidality from clinical trial data particularly troubling. The positive gain from having youths randomized to drug and placebo conditions to avoid channeling or other treatment bias found in community-treated populations is offset by the restrictive inclusion criteria used in clinical trials (e.g., exclusion of suicidal behavior and volunteer bias). Hence, patients encountered in clinical trials often do not mirror populations of patients in the community (Marks *et al.*, 2009). Third, measurement bias may further limit the analysis because the overwhelming proportion of suicidal events in the DNDP (and 2006 as reanalyzed) and in the outcome 3 analysis relied on suicidal ideation reports – which resulted in a weak nonsignificant risk estimate. The prediction of completed suicide from suicide attempts is 400:1 for 15–19-year-old boys and 3000:1 for girls, while for suicidal ideation it is 9000:1 for boys and 19 000:1 for girls (Klein, 2006). Such ratios in children and adolescents are lower than for adults (Mann *et al.*, 2005) and render the FDA safety analyses from clinical trial data insufficient. Fourth, the short duration of the trials may miss the window when risk is greatest if it occurs after 8 weeks, the typical length of the trials in the study. Consequently, it is useful to review the safety findings from observational studies. These limitations notwithstanding, leading psychopharmacology researchers have concluded that the signal from the trials is not sufficient to support a risk of suicidality (Mann *et al.*, 2005). It is also of concern that the conclusions from these analyses did not urge funding for priority research initiatives to address the safety question in a more precise epidemiological fashion (Avorn, 2005b).

## **SAFETY FROM OBSERVATIONAL STUDIES**

To ascertain if SSRI treatment constitutes a risk for suicide in the general youth population (i.e., *community-treated individuals*), a number of ecological studies on SREs in relation to SSRI use have been performed. In these studies, temporal trends were

analyzed statistically for *completed suicides* in relation to trends in SSRI utilization within specific countries. The findings, strengths, and weaknesses of each of these studies are reviewed below.

Observational studies on the relationship between adult suicide and exposure to ATDs have been conducted on the Swedish population (Isacsson *et al.*, 1992, 1997). These studies conclude that adult suicides are associated with little or no ATD use at the time of death, thus, concluding that SSRIs protect against suicide. An alternative approach to the use of existing clinical data occurred in a British study that used a 2-year period of accident and emergency visit patient data to examine the relationship between deliberate self-harm and ATD class (Donovan *et al.*, 2000). The authors found significantly more deliberate self-harm events following the prescription of an SSRI than for tricyclic ATDs (TCAs) ( $p < 0.001$ ). They infer that changing to an ATD class that is safer in overdosage (SSRI rather than TCA) did not reduce the risk of morbidity from deliberate self-harm. The contrast between Swedish and British suicidality studies in treated adult populations points up the limits of generalizing from one country to another and from one approach to address drug safety to another. Neither study sheds light on the relative risk for suicidality in SSRI community-treated populations.

In the USA, where the recent concern has been on the risk for youth treated with SSRIs, reimbursement claims for prescription use in an insured population were collected for 1 month in 1989 and a corresponding 1 month period in 2001 (Olfson *et al.*, 2003). ATD rates per 1000 patients receiving any medication (in contrast to enrolled youths) were calculated stratified by sex and age group (10–14 years and 15–19 years) for counties with more than 100 prescriptions. To create data on suicides, the Centers for Disease Control and Prevention's Compressed Mortality Files were extracted to produce suicide rates for each county by age group and sex. County-level suicide rates were converted to three-digit zip code region rates. Adjusted linear regression models were used to assess the association between the change in ATD medication (independent variable) and change in suicide rate (dependent variable) accounting for regional racial composition, median income, and physicians per

capita for two time points (1 month in 1990 and in 2000). The analysis was also stratified by sex, age group, median regional income, and racial composition. A significant inverse relationship was observed between 1990 and 2000 for change in the regional rates of overall ATD medication treatment and change in the regional suicide rates after adjusting for change in race/ethnicity, median income, and the number of physicians per capita. The attempt to assess the data in terms of TCA use and change in suicide rate was limited by the very low exposure to TCAs at each time point (1.2% and 0.8% or three youths in 1989 and six youths per region in 2000).

Finally, treatment-emergent events following ATD use have been studied using pharmacoepidemiologic data. An analysis examining the association of ATDs with "treatment-emergent bipolar disorder" using a commercially insured population aged 5–29 years revealed that children aged 10–14 years had the highest risk of "conversion to mania" (Martin *et al.*, 2004). The term refers to the sequential occurrence of a clinical diagnosis of mania following the use of an ATD. The data rely on the validity of the physicians' diagnoses and are subject to an alternative interpretation; that is, the adverse symptoms may be indicative of treatment-emergent activation rather than true mania.

Several study limitations are prominent: (1) the total sample size of exposed youths in a 1 month window is too small to link with very rare events occurring at the population level; (2) the assumption that prescriptions dispensed were consumed; (3) the theoretical model suggesting that suicide and ATD use is strongly negatively correlated ignores many nonpharmacologic factors known to influence suicide rates; for example, firearms reduction, effects of nonpharmacologic therapies, and the broad national trend for suicide reduction in youth going back years before ATDs were being used. Also, it is difficult to interpret the data when the denominator is composed of youth treated with any medication, because the period from 1990 to 2000 could have produced artifactual changes in medication-users based on health insurance coverage plans. In addition, these patient-specific data are correlated with population-based suicide events, subjecting the analysis to the ecological fallacy. The

limitation of ecological data notwithstanding, this study is being cited prominently to support the use of SSRIs in the treatment of pediatric depression – a causal inference that is not justified by the data (Safer and Zito, 2007). A similar analysis focused on the association of prescriptions dispensed within a county and the suicide rate; it found no association for total ATDs but a significantly higher rate for TCAs and a lower rate for SSRIs (Gibbons *et al.*, 2005). These data invite the alternative explanation that TCAs are more lethal than SSRIs when self-harm occurs. Despite the number of ecological studies with strong conclusions, analysts have reminded research/clinical readers of the fallacies related to interpreting associations in these studies as causally related (Hammad and Mosholder, 2010).

Observational studies based on patient level rather than group level data are generally more persuasive. Three examples are described below.

Medical examination and treatment reports dealing with suicidality were obtained by Jick *et al.* (2004) from UK physicians reporting to the General Practice Research Database (GPRD). The GPRD physician office-based data were analyzed for the period from 1993 through 1999; they included treatment with TCAs as well as SSRIs in relation to suicide attempts, and completed suicides. A matched case-control study was conducted and the relative risk for newly diagnosed nonfatal suicidal behavior was not different for amitriptyline, fluoxetine, and paroxetine compared with the risk among dothepin users. New ATD use had to have occurred within 90 days prior to the index date for suicidal behavior of the cases. The authors found no substantial difference in the effect of the four drugs on people aged 10–19 years. The Jick report lends little evidence to the risk for US treated youth because SSRI use is threefold higher for youth in the USA than in the UK (Delate *et al.*, 2004; Murray *et al.*, 2004). Greater use of drug combinations, higher dosing, and greater duration of exposure are also likely to occur in US treatment patterns (Hunkeler *et al.*, 2005). A separate analysis using GPRD data from the UK had similar findings to the Jick finding of no association except for an age-specific difference (Martinez *et al.*, 2005). For current SSRI use in those 18 or younger, there was weak evidence for

nonfatal self-harm relative to TCA use ( $p < 0.05$ ). However, the possibility of channeling of SSRIs to patients at higher risk of suicidal behavior cannot be ruled out.

A second patient-level study (Valuck *et al.*, 2004) used US computerized commercial insurance claims data. The authors assessed suicide attempts from physician reports for the period from 1997 to 2003 for youths with a diagnosis of MDD and the authors compared suicide attempt reports on those treated with ATDs for 2 months or less with depressed patients treated with ATDs for 6 months or more. The study was based on 138 physician-reported cases of suicide attempts in an adolescent population diagnosed with MDD ( $n = 24110$ ), thus yielding a suicide attempt rate of 0.57%. The Valuck analysis lacks credibility because outpatient physician visits are not likely to be coded for suicide attempts (E-codes) and ICD-9 diagnostic codes do not identify suicidality.

A third study utilized health maintenance organization population data from the northwest region of the country (Simon *et al.*, 2006) and analyzed 82 285 ATD use episodes ( $n = 65103$  patients, adolescents and adults) with respect to the risk of suicide or serious suicide attempts (leading to hospitalization). The episodes included multiple events for an individual with more than one "new use" episode (defined as no use in the past 6 months). The authors concluded that the data do not indicate a significant increase in the risk of suicide or serious suicide attempt after starting treatment with newer ATDs. In a repeated-measures logistic regression model with adjustment for age, sex, and year of treatment, the risk of suicide death in the first month of treatment was not significantly higher than in subsequent months (odds ratio 1.2, 95% confidence interval (CI) 0.5–2.9). The number of suicide deaths in adolescents ( $n = 3$ ) was too small to support analysis of time trends. In agreement with the Jick *et al.* (2004) findings, there was a higher risk of suicide attempt in the first week of ATD treatment than in subsequent weeks. Although Simon *et al.* (2006) emphasized pre-ATD levels of symptom severity, their data are consistent with FDA's 2004 boxed warning that the risk of suicidality is highest during the first few weeks of initial ATD treatment. The authors suggest that a causal

model would require a randomized study with samples of single drug comparisons to placebo on the order of 300 000 to detect a twofold difference in risk of suicide death or serious suicide attempt during the first month of treatment. They recommend reliance on multiple data sources from both large observational studies and randomized trials.

Corroborating the findings of Stone *et al.* (2009), Barbui *et al.* (2009) conducted a systematic literature review of observational studies to evaluate the association between the risk of suicide and SSRI use. They included eight observational studies in their meta-analysis that reported completed or attempted suicides in depressed individuals who were exposed to SSRIs compared with those who were not exposed to ATDs. These eight studies constituted more than 200 000 patients with moderate or severe depression. The authors concluded that, "Based on data from observational studies, use of SSRIs may be associated with a reduced risk of suicide in adults with depression. Among adolescents, use of SSRIs may increase suicidality." In relation to suicidality, Stone *et al.* (2009) found the risk greatest before age 25.

## FUTURE STUDIES TO ADDRESS THE RESEARCH QUESTION

The main FDA clinical trial analysis (DNDP and the later revised analysis) looked at suicide ideation and attempts in relation to exposure to SSRIs, although using ideation and attempts as surrogates for completed suicide is of unknown validity. The limitations of available data on attempts include a low level of specificity and accuracy of recall on self-reported rates of suicide attempts, and variable and incomplete data on ATD doses, duration of drug treatment, concomitant medications, and drug switches. Furthermore, suicide attempts and self-mutilation are common in adolescence (Safer, 1997) and they often overlap; parent reports of suicide attempts in their offspring are underreported; and suicide ideation and suicide threats in adolescence are much more common than serious suicide attempts. Consequently, for better precision it is preferable to have more definitive evidence of documented medically serious

suicide attempts in relation to SSRI treatment. Such evidence could be obtained from the records of psychiatric-related hospitalizations and emergency department (ED) visits.

Survey data shed some light on the scope of the suicide-related medical service utilization. Self-reported suicide attempts in the past 12 months and those resulting in medical attention for adolescents (14–17-year-olds) in the 2009 CDC population-based high school surveys were 6.9% and 1.9%, respectively. Medical attention was not defined in the survey and presumably refers to outpatient care as well as hospitalization or ED visits (Eaton *et al.*, 2010). By self-report then, approximately 1 million US high school students made suicide attempts during the previous year.

To obtain more precise information on suicide attempts resulting in medical attention, ED data may be a useful approach. Specifically, administrative data on ED visits for older youth (e.g., 10–18 years) could be examined. Suicide-related reports in the ED can be sorted by age group, gender, method of attempt (e.g., cutting, overdose), and disposition. In one study based on a multistate epidemiologic examination of pooled E-coded discharge data and vital statistics (Spicer and Miller, 2000), the authors used E-codes 950–959.9 to calculate suicide attempts from hospitalizations or ED visits and found the rate to be 21/100 000 for those less than 15 years old and 259/100 000 among 15–19-year-olds. Overdoses and cutting accounted for 85–90% of attempts.

Other estimates of the frequency of ED use for intentional self-injury by youths suggest that it is, indeed, relatively low. In the state of Oregon from 1988 through 1993, suicide attempts by youths aged 10–17 years as recorded in emergency rooms represented 0.3% of all youths in that age range (MMWR, 2005). In another emergency-room report of 4072 adolescents (11–19 years old) presenting to an Arkansas Children's Hospital ED during a 1-year period in 1985, 27 (0.66%) deliberately injured themselves (Jay *et al.*, 2005). Thus, it is reasonable to assume that the intentional self-injury rate varies with the region and the completeness of identification and reporting. Another study indicates that of the youth who come to EDs related to suicidality, at least 40% came there

because of suicidal ideation, not attempts (Stewart *et al.*, 2001).

The data reviewed above suggest that administrative claims or computerized record data are likely to be a feasible approach to patient-level assessment of the association of psychiatric-related adverse events with medication exposure. Evaluating youth who have been given ATDs as outpatients and then noting their ED and hospital visit rate is a feasible means of directly linking the adverse events to the medication exposure. A more direct approach, the medical record audit, to assess emergency-room records might be feasible if the staff routinely recorded in their dataset prior and ongoing medication patterns of those admitted. Unfortunately, this is not generally recorded. Using a community-based dataset across a 4-year period would allow those with a prescribed ATD (among three subclasses) over a given time period to be identified. Total ATD-treated youth or those within selected diagnostic groups could then be evaluated along with other measures for their rate of psychiatric admission to an ED or a hospital as well as the recorded reason for such an admission (diagnostic codes and E-codes). The distinction between this study and the Simon *et al.* (2006) study is essentially that youth rather than adults would be studied; youth and not episodes would be the unit of analysis; only youth with a single ATD drug class would enter each group; and children and adolescents would be separated.

The ideal study to assess the relationship between SSRI use and SREs in youth requires a prospective randomized cohort study design in a large multisite usual practice community treatment setting. Now that there are serious concerns about the efficacy and safety of the SSRIs for youth treated for depression, the concern about depriving a youth of an effective marketed medication in a randomized protocol may be balanced by the uncertainty of outcome. The usual ethical concern would be overcome in this instance. In a randomized cohort study, three groups could be established: SSRI, other ATD, or a waiting list control. Following the cohort forward for 6 months would allow information to be collected on the effectiveness of treatment and reasons for discontinuation of the drug. Most importantly, psychiatric-related ED or

outpatient visits or hospitalizations related to hostility and activation could be distinguished from depression-related events to shed light on the major confound of many psychotropic drug studies, namely behavioral toxicity (Zito *et al.*, 2008).

## **IMPROVING THE SAFETY INFRASTRUCTURE**

In recent years there have been numerous calls for a major revision of the FDA's safety division originating from the professional (Wood *et al.*, 1998; Avorn, 2005a; Ray and Stein, 2006) and lay press. Many critics fail to see the rationale for continued primary reliance on the MedWatch system as a safety warning system. Its limitations include limited voluntary reporting, incomplete data, and lack of a reliable patient-based denominator from which to assess rates of adverse events. Moreover, the absence of regular national reporting of medication exposure data from administrative claims or electronic clinical records is puzzling in view of the opportunity such data would provide to generate exposure data for potential safety studies at minimal costs.

Adverse event reporting in psychotropic drug clinical trials for children has been severely criticized as inadequate (Greenhill *et al.*, 2001). Mainly, there is no consistency in terminology, method of elicitation of unwanted effects and reporting in published trials of adverse events.

## **US FOOD AND DRUG ADMINISTRATION 2004 SUICIDALITY BOXED WARNINGS AND CONSEQUENCES**

Since the heightened media coverage of treatment-emergent suicidality, which began in June 2003, the absolute number of dispensed ATD prescriptions for the treatment of youth has dropped (Rosack, 2005; Pamer *et al.*, 2010). The drop in dispensed prescriptions varied sizably with the age of the youth in the Medco Health Solutions data. Furthermore, prescription rate analyses of dispensed ATD prescriptions from 2003 to 2005 dropped 32% for youth under age 12 years, and 18% for youth

aged 12–18 years (Elias, 2005). Nemerooff *et al.* (2007) analyzed the effect of pediatric suicidality on physician practice patterns in the USA using retail pharmacy and IMS Physician Drug and Diagnosis Audit data. They found that psychiatrists prescribed a large percentage of ATDs in the post-warning period (44% in December 2003–February 2004 to 61% in December 2004–February 2005). They found an increase in the use of selective-norepinephrine reuptake inhibitors (venlafaxine and duloxetine) and in other ATDs (bupropion, trazodone, or mirtazapine), and a steep decrease in the use of SSRIs (Nemerooff *et al.*, 2007). Gibbons *et al.* (2007) examined annual prescription rates from 2003 to 2005 in the USA by zip code (IMS Health database) and Netherlands (PHARMO database). They found that the SSRI prescriptions for youths decreased by approximately 22% in both the USA and Netherlands between 2003 and 2005 (Gibbons *et al.*, 2007). Another study using an insurance claims database that covered approximately 50% of the Hawaiian Islands population concluded the SSRI prescription rates fell from 2002 to 2005 and the decrease was highest in the 0–12 years age group compared with the 13–18-year-olds (Hassanin *et al.*, 2010). The above-mentioned studies are based on total dispensed ATD prescription rate data rather than patient-level data analysis, and hence there is no information on the clinical diagnosis of the patient. In addition, the denominator in the above-mentioned studies was the total number of prescriptions rather than the number of patients. This distinction is critical to a refined understanding of the impact of warnings on the use of prescribed ATDs in youth.

Since 2004, when the FDA added a pediatric suicidality warning to ATD product labels, researchers have analyzed its impact on ATD treatment for youth (Kurian *et al.*, 2007; Libby *et al.*, 2007, 2009; Olfson *et al.*, 2008; Busch *et al.*, 2010; Pamer *et al.*, 2010; Chen and Toh, 2011). Pamer *et al.* (2010) used time-series data on the total number of patients dispensed ATDs monthly to assess the impact of the February 2004 FDA warning. They found that the ATD drug use levels were significantly lower in the post-FDA warning period compared with the forecasted use levels in youth (approximately 107 fewer patients per 100 000

subjects per month were treated with ATDs in the post-FDA warning period). Olfson *et al.* (2008) addressed the safety of the SSRI paroxetine by physician specialty (psychiatrists, primary care, and others) following the June 2003 FDA recommendation to avoid its use in children due to heightened risk. The authors assessed May 2002 through December 2005 commercial insurance (Medco) prescription claims in a time-series regression analysis and found psychiatrist-prescribed paroxetine use decreased by half in the 6-month period following the paroxetine warning. With the same data, they addressed the broader question relevant to this study by showing significant drops in three specialty physician groups, which occurred from June 2003 to October 15, 2004. After that, the difference in use pre to post was nonsignificant (October 2004 through December 2005). The authors acknowledged the absence of information on psychotherapy treatment data. The analysis of Libby *et al.* (2007) included psychotherapy, a useful alternative treatment for depressive disorders, particularly in children, where ATD efficacy data are lacking. That analysis used data from October 1998 to September 2005 in a commercially insured cohort of pediatric patients (5–17 years of age) diagnosed with any depression – ICD-9-CM: 296.2, 296.3, 300.4, or 311 (i.e., MDD, single episode; MDD, recurrent episode; neurotic depression; and depression not otherwise specified, respectively) ( $N = 65349$ ). A time-series regression model showed a change among depression-diagnosed youth in terms of ATD dispensings from 59.2% pre-warning to 55.0% post-warning, with no increase in psychotherapy following a new-onset depression diagnosis. Another study by Libby *et al.* (2007), using the same PharMetrics database, reported similar results, but showed a continuing decline in ATD treatment into 2007. Kurian *et al.* (2007) used Tennessee Medicaid youth data to measure the impact of the FDA warning in terms of new users of ATDs and estimated a 33% decline in new users aged 2–17 years beginning in January 2004. The researchers did not consider the clinical diagnosis of the new users of ATDs. Busch *et al.* (2010) used an administrative claims database (Thomson MarketScan 2002–2005) to examine changes in overall ATD use and also product-specific changes and whether

there was an increase in provider contact. They found an overall decrease in ATD use, with the highest decline in paroxetine users and an increase in fluoxetine users. It is important to note that in all the above-mentioned research on the impact of the FDA warning, all DSM-IV depressive diagnoses were included. However, the safety findings generated from meta-analysis of the pediatric clinical trials were based exclusively on youth diagnosed with an MDD (Bridge *et al.*, 2007). Another important limitation of the above-mentioned research studies is that each was based on time-series analysis of data in which individual patient-level characteristics are not available and grouped data are collapsed across each time point.

In addition, the methodology for assessing change is critical. For example, the warnings may have a different impact on new episodes versus prevalent MDD cases. From these reports, it is clear that whether SSRI use is adversely affected by the FDA warnings should be based on more detailed information than time-series data. Researchers should examine the impact of the warnings on psychotherapy use in youth diagnosed with MDD by analyzing patient-level data with a repeated-measures design.

To address the above-mentioned limitations of the existing literature, our research group (Valluri *et al.*, 2010) performed a more detailed evaluation, including comparison of children versus adolescents and patients with MDD (ICD-9-CM: 296.2x, 296.3x) versus less severe depression (ICD-9-CM: 300.4x, 311). We analyzed rates of ATD prescribing for young patients with newly diagnosed depression before and after March 2004. The study included more than 40 000 children and adolescents diagnosed with depression from 2003 to 2006, identified from a large commercially insured population. Youth diagnosed with depression after the FDA warning were 15% less likely to be prescribed ATD drugs. However, when youth with a diagnosis of depression were separated into those with MDD ( $N = 11532$ ) and those with less severe diagnoses of depression ( $N = 28777$ ) only the latter had a significant decrease in ATD treatment during the post-FDA warning period. In youth with less severe depression, the likelihood of ATD prescribing decreased by 21% after the warning.

In contrast, rates of ATD treatment were unchanged for children and adolescents with a diagnosis of MDD before and after the March 2004 boxed warning. As the overall ATD prescribing decreased, more children received psychotherapy after being diagnosed with depression in the post-warning period. The increase in the likelihood of psychotherapy was greater for children (31%; *p*-value < 0.0001), but still significant for adolescents (19%; *p*-value < 0.0001). The difference was most pronounced – from 37% before the FDA warning to 44% afterward – for youth receiving psychotherapy as their only treatment for depression: before and after the warning, about 80% of children and adolescents received some type of treatment (ATD, psychotherapy, or both) within 6 months following diagnosis with depression.

The results suggest that the decrease in ATD prescribing has been limited to patients with less severe depression (e.g., dysthymic disorder/neurotic depression, depressive disorder, not otherwise specified), who account for the great majority of depressed youth (DeBar *et al.*, 2001). Meanwhile, there has been no significant change in the likelihood of ATD treatment for children and teens with major depression. These findings were confirmed (Chen and Toh, 2011) in a national study conducted using the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey databases. Chen and Toh (2011) evaluated the national trends in prescribing pharmacologic treatments for youth (5–17 years) depression before and after the 2003 US FDA ATD advisory. The national estimates indicate that the youth depression visits and visits with an ATD prescribed dropped after the advisory, but youth with MDD were no less likely to be prescribed ATDs.

At the same time, the use of psychotherapy alone as initial treatment for depression increased – especially among children less than 12 years of age. In our interpretation, these findings suggest more clinically nuanced pediatric ATD prescribing patterns than was the case previously. We urge further studies to evaluate the impact of reduced ATD prescribing in young patients with less severe depression, especially in children.

In addition, research conducted using retrospective claims in the USA indicates that the frequency

of visits by patients with new episodes of depression treated with ATDs did not increase after the October 2003 FDA advisory was issued, even though the advisory recommended close monitoring of patients at the start of treatment when the risk of SREs is believed to be highest (Morrato *et al.*, 2008).

## CONCLUSIONS

This updated review aimed to address the pressing clinical question of whether SSRI use for the treatment of depression differs in youth than in adults. Both efficacy and safety data provide evidence that youth outcomes are different, particularly in children. Studies have been presented and their findings critiqued. Suggestions for further research are posed. Many publicized interpretations of the existing studies suggest the glass is “half full,” when the major long-term concern for use of SSRIs to treat depression in youth warrants a “half empty” interpretation. Regardless of the researchers’ and clinical readers’ perspectives and wisdom, FDA pediatric warnings urge caution and initial close monitoring of new young users of SSRIs. Hopefully, long-term monitoring of outcomes in a community cohort large enough and with sufficient validity to provide convincing evidence of the SSRI benefit–risk in young people with depression will be undertaken.

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# Nonsteroidal Anti-inflammatory Drugs – Cyclooxygenase-2 Inhibitors: Risks and Benefits

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## INTRODUCTION

The market withdrawal of the nonsteroidal anti-inflammatory drug (NSAID) rofecoxib in September 2004 was a major lesson in pharmacovigilance (Edwards, 2005). This chapter is a review of the risks and benefits of the cyclooxygenase (COX)-2 inhibitors and other NSAIDs, with an emphasis on the cardiovascular safety signal detection and subsequent safety assessment between 2000 and 2005, primarily from a US perspective and supplemented by selected publications through 2012.

NSAIDs as a class of drugs are used for symptomatic relief of pain and inflammation, with gastrointestinal toxicity as a major side effect (Wolfe *et al.*, 1999). Elucidation of the role of prostaglandins in inflammation and the discovery of two isoforms of cyclooxygenase (COX-1 and

COX-2) led to the hope of developing NSAIDs with less adverse effects. While inhibition of the inducible COX-2 has anti-inflammatory effects, inhibition of the constitutive COX-1 increases the risk of gastrointestinal toxicity (Warner *et al.*, 1999). Older NSAIDs, such as ibuprofen and naproxen, inhibit both COX-1 and COX-2 and are called nonselective NSAIDs. NSAIDs that selectively inhibit COX-2 without COX-1 inhibition, thus referred to as selective COX-2 inhibitors, would theoretically have the same anti-inflammatory effects as nonselective NSAIDs and be associated with reduced gastrointestinal toxicity, resulting in a favorable benefit–risk profile (FitzGerald, 2003). The first selective COX-2 inhibitor, celecoxib, was approved in December 1998 in the USA, and the second, rofecoxib, was approved in May 1999.

## POSTMARKETING CARDIOVASCULAR SAFETY SIGNAL

### TWO LARGE TRIALS: CLASS AND VIGOR

At the time of market approval of celecoxib and rofecoxib, upper gastrointestinal safety information of these two drugs was primarily based on placebo-controlled endoscopy studies. As the reduced frequency of mucosal injury in the upper gastrointestinal tract may not correlate well with incidence of serious upper gastrointestinal events that include ulcer, perforation, obstruction, or bleeding, manufacturers of celecoxib and rofecoxib sponsored large-scale trials of a COX-2 inhibitor against nonselective NSAIDs that were powered to evaluate the relative incidence of these serious gastrointestinal events. As a result of the large study sizes of the trials, safety information beyond the gastrointestinal system could also be assessed. The results are summarized in Table 47.1.

In the Celecoxib Arthritis Safety Study (CLASS), patients with osteoarthritis or rheumatoid arthritis were randomly assigned to receive celecoxib, ibuprofen, or diclofenac (Silverstein *et al.*, 2000). Approximately 20% of the study subjects took low-dose aspirin for cardiovascular disease prevention. The risks of upper gastrointestinal ulcer complications were similar among the study groups during the first 12 months of therapy (Hrachovec and Mora, 2001). Incidence of stroke, myocardial infarction, and angina in the celecoxib group was similar to that in the ibuprofen/diclofenac group during the first 6 months of therapy.

The first cardiovascular safety signal of a COX-2 inhibitor in North America came from the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) (Bombardier *et al.*, 2000). Patients with rheumatoid arthritis were randomly assigned to receive rofecoxib or naproxen with a median follow-up of 9 months. Unlike the enrollment criteria for CLASS, aspirin use was not allowed in VIGOR. Rofecoxib users had 60% lower risk of perforation, obstruction, and severe upper gastrointestinal bleeding than naproxen users. However, incidence of myocardial infarction was higher among the rofecoxib group (relative risk, 5.0; 95% confidence interval (CI), 1.68–20.13) (Curfman

*et al.*, 2005). The VIGOR investigators hypothesized that the finding could be due to cardiovascular risk of rofecoxib, cardio-protective effect of naproxen, or both.

### SPONTANEOUS REPORTS

The adverse drug reactions reporting system is usually the first line of defense in the detection of drug risks that are not apparent during premarketing studies, but the cardiovascular safety signal for rofecoxib was not detected by this system in the USA. After the VIGOR results were reported in professional society meetings in May 2000, the Netherlands Pharmacovigilance Center (Lareb) reported a cardiovascular safety signal for rofecoxib at the annual meeting of national centers that participated in the WHO Programme for International Drug Monitoring in October 2000 (Edwards, 2005), but that report was not widely known in the USA. In the USA, Mukherjee *et al.* (2001) searched for thrombotic or embolic events potentially associated with celecoxib or rofecoxib in the US Food and Drug Administration (FDA) adverse event reporting system in October 2000 and found that the number of cases that could be associated with celecoxib and rofecoxib were 102 and 99, respectively. Given the extensive use of celecoxib and rofecoxib in the USA by then, the small number of cardiovascular reports did not represent a strong safety signal.

### CARDIOVASCULAR SAFETY SIGNAL EVALUATION

#### BIOLOGICAL MECHANISM

The pharmacologic basis for cardiovascular risks of the COX-2 inhibitors is most likely the effects of these agents on prostacyclin (prostaglandin I<sub>2</sub>) and thromboxane A<sub>2</sub>. Selective inhibition of COX-2 would cause imbalance in the prostacyclin-to-thromboxane ratio and contribute to increased risk for thrombotic events (FitzGerald, 2004). COX-2 in endothelium is responsible for the production of prostacyclin, which inhibits platelet aggregation, causes vasodilatation, and prevents proliferation of vascular smooth-muscle cells. COX-1 in platelets,

Table 47.1 Large-scale clinical trials of cyclooxygenase-2 inhibitors.

Acronym (reference)	Study population/ disease	Drug regimens	Duration of treatment	Primary end point	Findings for cardiovascular (CV) outcomes
CLASS (Silverstein <i>et al.</i> , 2000; White <i>et al.</i> , 2002)	Osteoarthritis or rheumatoid arthritis	Celecoxib 400 mg twice daily, ibuprofen 800 mg three times daily, or diclofenac 75 mg twice daily; 22% used low-dose aspirin	Median exposure was more than 8 months	Upper gastrointestinal ulcer and complications	Relative risk (celecoxib versus ibuprofen and diclofenac combined) for serious CV events was 1.1 (95% CI, 0.7–1.16)
VICOR (Bombardier <i>et al.</i> , 2000; Curfman <i>et al.</i> , 2005)	Rheumatoid arthritis	Rofecoxib 50 mg once daily or naproxen 500 mg twice daily; no aspirin allowed	Median duration was 9 months, longest was 13 months	Upper gastrointestinal ulcer and complications	Relative risk (rofecoxib versus naproxen) for myocardial infarction was 5.0 (95% CI, 1.68–20.13)
TARGET (Farkouh <i>et al.</i> , 2004; Schnitzer <i>et al.</i> , 2004)	Osteoarthritis	Lumiracoxib 400 mg daily, naproxen 500 mg twice daily, or ibuprofen 800 mg three times daily; 24% used low-dose aspirin	Up to 1 year	Upper gastrointestinal ulcer and complications	Based on the Antiplatelet Trialists' Collaboration end point, relative risk was 1.77 (95% CI, 0.82–3.84) for lumiracoxib versus naproxen and was 0.66 (95% CI, 0.21– 2.09) for lumiracoxib versus ibuprofen
APPROVe (Bresalier <i>et al.</i> , 2005; Baron <i>et al.</i> , 2008)	History of colorectal adenoma removal	Rofecoxib 25 mg daily or placebo; 17% among the rofecoxib group and 16% among the placebo group used low-dose aspirin	Average of 2.4 years for the rofecoxib group and 2.6 years for the placebo group	Recurrence of colorectal adenoma	For thrombotic events, relative risk for rofecoxib versus placebo was 1.92 (95% CI, 1.19–3.11) during treatment period; for Antiplatelet Trialists' Collaboration end point and up to 1 year of follow-up after treatment period, relative risk was 1.79 (95% CI, 1.17–2.73)
APC (Solomon <i>et al.</i> , 2005; Bertagnoli <i>et al.</i> , 2006)	History of colorectal adenoma removal	Celecoxib 400 mg twice daily, celecoxib 200 mg twice daily, or placebo; 30% of patients used low-dose aspirin	Up to 3 years	Recurrence of colorectal adenoma	Based on a composite CV end point and comparing with placebo, relative risk was 3.4 (95% CI, 1.5–7.9) for celecoxib 400 mg twice daily and 2.6 (95% CI, 1.1–6.1) for celecoxib 200 mg twice daily

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Table 47.1 (Continued)

Acronym (reference)	Study population/ disease	Drug regimens	Duration of treatment	Primary end point	Findings for cardiovascular (CV) outcomes
Nussmeier <i>et al.</i> (2005) (no acronym)	Patients after coronary artery bypass graft surgery	Parenteral parecoxib followed by oral valdecoxib, parenteral placebo followed by oral valdecoxib, or double placebo Celecoxib 400 mg daily or placebo; 17% used low-dose aspirin	10 days after surgery	Post-operation pain control	Relative risk of myocardial infarction, cardiac arrest, stroke, and pulmonary embolism was 1.9 (95% CI, 1.1–3.2) for the two COX-2 inhibitors arms combined versus placebo
PreSAP (Arber <i>et al.</i> , 2006)	History of colorectal adenoma removal	Celecoxib 400 mg daily or placebo; 17% used low-dose aspirin	Up to 3 years	Recurrence of colorectal adenoma	Same CV end point as in the APC study, relative risk was 1.3 (95% CI, 0.65–2.62) for celecoxib compared with placebo
MEDAL (Cannon <i>et al.</i> , 2006), a pooled analysis of three trials	Osteoarthritis or rheumatoid arthritis	Etoricoxib 60 mg daily, etoricoxib 90 mg daily, or diclofenac 150 mg daily in two or three doses; 35% used low-dose aspirin	Mean duration of drug exposure was 18 months	Treatment discontinuation for gastrointestinal adverse outcomes in two trials, thrombotic CV events in the third trial	Hazard ratio for thrombotic events was 0.95 (95% CI, 0.81–1.11) for etoricoxib compared with diclofenac
ADAPT (ADAPT Research Group, 2006)	Subjects 70 years and older with family history of Alzheimer's disease	Celecoxib 200 mg twice daily, naproxen 220 mg twice daily, or placebo; 57% used low-dose aspirin	Median follow-up time of 22.1–23.5 months for the three study groups	Prevention of dementia	Hazard ratio for CV or cerebrovascular death, myocardial infarction, stroke, congestive heart failure, or transient ischemic attack was 1.1 (95% CI, 0.67– 1.79) for celecoxib compared with placebo and 1.63 (95% CI, 1.04–2.55) for naproxen compared with placebo
PRECISION (Becker <i>et al.</i> , 2009)	Osteoarthritis or rheumatoid arthritis	Celecoxib 100–200 mg twice daily, ibuprofen 600–800 mg three times daily, or naproxen 375–500 mg twice daily	At least 18 months of follow-up	Antiplatelet Trialists' Collaboration end point	Study is ongoing

which is not affected by the COX-2 inhibitors, is responsible for the synthesis of thromboxane A<sub>2</sub>, which has the opposite effects of prostacyclin, causing platelet aggregation, vasoconstriction, and vascular proliferation. Theoretically, selective inhibition of COX-2 would allow the physiologic effects of thromboxane to predominate and result in adverse cardiovascular outcomes.

The VIGOR investigators cited a study in healthy volunteers that quantified the extent of thromboxane A<sub>2</sub> production and platelet aggregation associated with use of different NSAIDs (van Hecken *et al.*, 2000). High-dose naproxen suppressed thromboxane A<sub>2</sub> production and reduced platelet aggregation, but how these pharmacologic actions would translate to prevention of myocardial infarction by naproxen was not verified in clinical studies.

#### PERI-APPROVAL CLINICAL TRIALS OF CELECOXIB AND ROFECOXIB

Mukherjee and colleagues studied the incidence of cardiovascular events observed in CLASS, VIGOR, and two unpublished trials of rofecoxib. The analysis covered a wider range of cardiovascular outcome than that published in the CLASS and VIGOR reports in 2000, as patients contributed more follow-up time and more cardiovascular events were adjudicated (Mukherjee *et al.*, 2001). In addition, manufacturers of celecoxib and rofecoxib conducted pooled analyses of cardiovascular safety data in the drug development programs and the reports were published from 2001 through 2003. While valuable as a safety assessment tool to rapidly respond to the safety signal identified in 2000, these reports need to be interpreted cautiously. Most of the premarketing trials were of limited duration for evaluation of analgesic efficacy, and some trials were designed for the evaluation of new indications such as prevention of Alzheimer's disease; therefore, the combined populations were heterogeneous with limited long-term follow-up information. The estimated relative risks associated with celecoxib or rofecoxib were difficult to interpret as the comparison groups included both placebo and nonselective NSAIDs. As noted for naproxen and further discussed below, cardiovascular risks associated with individual nonselective NSAIDs were not defined

at that time and the estimated relative risk would be dependent on the choice of comparator. Study subjects with established cardiovascular diseases were usually excluded, and the adverse cardiovascular outcomes that were evaluated ranged from myocardial infarction to the wider group of Antiplatelet Trialists' Collaboration (APTC) definition of cardiovascular outcomes that included cardiovascular, hemorrhagic and unknown death, myocardial infarction, and cerebrovascular accident (Antiplatelet Trialists' Collaboration, 1994).

For celecoxib, cardiovascular analysis of CLASS (Mukherjee *et al.*, 2001; White *et al.*, 2002) and the pooled analysis of clinical trials did not show an increased cardiovascular risk (White *et al.*, 2003). For rofecoxib, results from pooled analysis of the clinical trials were equivocal (Konstam *et al.*, 2001; Reisin *et al.*, 2002; Weir *et al.*, 2003). In VIGOR, the relative risk of serious cardiovascular events for rofecoxib was 4.89 (95% CI, 1.41–16.88), and a post-hoc stratification according to aspirin indication showed that among non-aspirin-indicated subjects the relative risk was 1.89 (95% CI, 1.03–3.45), suggesting effect modification associated with aspirin use (Mukherjee *et al.*, 2001).

#### CARDIOPROTECTIVE EFFECTS OF NAPROXEN IN EPIDEMIOLOGY STUDIES

The VIGOR results prompted more than 10 observational studies that evaluated the association between naproxen use and myocardial infarction and they were reviewed in a meta-analysis conducted by Jüni *et al.* (2004). A small reduced risk, on the order of 15%, of myocardial infarction associated with naproxen use was found. This magnitude of cardiovascular protection associated with naproxen could not solely explain the fivefold increase in risk of myocardial infarction in the rofecoxib–naproxen comparison observed in VIGOR, suggesting increased cardiovascular risk associated with rofecoxib.

#### OBSERVATIONAL STUDIES OF CELECOXIB AND ROFECOXIB

After VIGOR, observational studies were conducted to evaluate the cardiovascular risk of

celecoxib and rofecoxib in real-world medical care settings. Results from major studies published before the end of 2005 and a US study published in 2006 are summarized in Table 47.2. The studies were of different data sources and study designs, with different comparison groups and outcomes of interest. Unlike the clinical trials, both celecoxib and rofecoxib were evaluated in the same data environment in all studies. All but three reports were based on electronic healthcare databases in the USA (Ray *et al.*, 2002; Solomon *et al.*, 2004; Shaya *et al.*, 2005; Graham *et al.*, 2005; Velentgas *et al.*, 2006), Canada (Mamdani *et al.*, 2003; Levesque *et al.*, 2005), and Europe (Hippisley-Cox and Coupland, 2005; Johnsen *et al.*, 2005). Two reports were based on the UK prescription-event monitoring system (Layton *et al.*, 2003a,b). One was a case-control study with community controls (Kimmel *et al.*, 2005). The overall findings did not support an increased cardiovascular risk associated with celecoxib. For rofecoxib, most studies showed a relative risk in the range of 1.5 to 2, smaller than the fivefold increase in cardiovascular risk found in VIGOR. For studies that reported findings according to rofecoxib dose, all of them showed a higher risk associated with rofecoxib >25 mg daily than rofecoxib 25 mg or less daily. While none of the individual studies was definitive and some results could be explained by chance variation and uncontrolled confounders, they collectively strengthened the cardiovascular safety signal identified from VIGOR.

#### NON-THROMBOEMBOLIC ADVERSE CARDIOVASCULAR OUTCOMES

Incidence of increased blood pressure was higher among rofecoxib users than among celecoxib users in a head-to-head trial among patients 65 years or older with osteoarthritis and stable medication-controlled hypertension (Whelton *et al.*, 2002). Using electronic administrative data from Ontario, Canada, Mamdani *et al.* (2004) reported an increased risk of congestive heart failure among rofecoxib users but not among celecoxib users in an observational study.

#### SUMMARY OF CARDIOVASCULAR RISK INFORMATION OF CELECOXIB AND ROFECOXIB THROUGH JULY 2004

The VIGOR results clearly indicated that rofecoxib 50 mg daily was associated with higher risk of myocardial infarction. Epidemiology data available before mid 2004 corroborated this finding. Whether the use of rofecoxib 25 mg or less daily increased the risk of cardiovascular outcomes was less certain at that time. At the same time, there was no compelling evidence to suggest that celecoxib use was associated with increased cardiovascular risk.

#### LARGE DISEASE-PREVENTION TRIALS OF CYCLOOXYGENASE-2 INHIBITORS

See Table 47.1.

#### ROFECOXIB IN THE ADENOMATOUS POLYP PREVENTION ON VIOXX TRIAL

The study that led to the market withdrawal of rofecoxib was the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial (Bresalier *et al.*, 2005). The placebo-controlled trial was sponsored by the manufacturer of rofecoxib with the primary objective of evaluating the efficacy of long-term rofecoxib use in the prevention of adenomatous polyp recurrence among patients with a history of colorectal adenomas. Patients who had prior history of coronary heart disease and need for long-term NSAID therapy were not eligible. Trial enrollment started before the cardiovascular risk associated with rofecoxib was identified in VIGOR and enrollment completed in November 2001. A committee blinded to treatment assignment adjudicated all cardiovascular events and the composite end point was fatal and non-fatal myocardial infarction, unstable angina, sudden death from cardiac causes, fatal and non-fatal ischemic stroke, transient ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism. At an interim analysis that was conducted in September 2004, a relative risk of 1.92 (95% CI, 1.19–3.11) was

Table 47.2 Selected observational studies of COX-2 inhibitors, nonselective NSAIDs, and adverse cardiovascular outcomes.

Reference	Data source	Study design and data collection	Cardiovascular (CV) outcomes of interest	Selected comparison groups from published reports	Adjusted relative risk (95% CI)
Ray <i>et al.</i> (2002)	Administrative data from US Tennessee Medicaid and vital statistics	Retrospective cohort study with new users design based on electronic data	Hospital discharge diagnosis of myocardial infarction or death from coronary heart disease	Celecoxib versus no NSAID use Rofecoxib >25 mg daily versus no NSAID use Rofecoxib 25 mg or less daily versus no NSAID use	0.88 (0.67–1.16) 1.93 (1.09–3.43) 1.02 (0.76–1.37)
Mamdani <i>et al.</i> (2003)	Administrative data from Ontario, Canada	Retrospective cohort with new users design based on electronic data	Hospital discharge diagnosis of myocardial infarction	Celecoxib versus no NSAID use Rofecoxib versus no NSAID use	0.9 (0.7–1.2) 1.0 (0.8–1.4)
Layton <i>et al.</i> (2003a,b)	Prescription-event monitoring system in the UK	Cohort study based on mailed surveys to general practitioners	CV, cerebrovascular, and peripheral vascular events	Celecoxib versus meloxicam CV events Cerebrovascular events Rofecoxib versus meloxicam CV events	1.66 (1.10–2.51) 1.72 (0.87–3.40)
Solomon <i>et al.</i> (2004)	Administrative data from US Pennsylvania and New Jersey drug assistance program for the elderly	Nested case-control study based on electronic data and review of medical records of selected subjects	Hospitalized patients with myocardial infarction	Celecoxib versus no NSAID use Rofecoxib versus no NSAID use Rofecoxib (all doses) versus celecoxib	1.68 (1.15–2.46) 1.38 (0.71–2.67) 0.93 (0.84–1.02)
Shaya <i>et al.</i> (2005)	Administrative data from US Maryland Medicaid	Retrospective cohort study	Thrombotic events as defined by the Antiplatelet Trialists' Collaboration	Celecoxib versus non-naproxen NSAIDs Rofecoxib versus non-naproxen NSAIDs	1.24 (1.01–1.46) 0.99 (0.76–1.30) 1.19 (0.93–1.51)
Kimmel <i>et al.</i> (2005)	Patients admitted to 36 US hospitals	Case-control study with community controls, exposure and confounder information obtained through telephone interview	First nonfatal myocardial infarction	Celecoxib versus no NSAID use Rofecoxib versus no NSAID use	0.43 (0.23–0.79) 1.16 (0.70–1.93)

(Continued)

Table 47.2 (Continued)

Reference	Data source	Study design and data collection	Cardiovascular (CV) outcomes of interest	Selected comparison groups from published reports	Adjusted relative risk (95% CI)
Graham <i>et al.</i> (2005)	Administrative data from Kaiser Permanente, California, USA	Nested case-control study with electronic data and telephone survey of a random sample of subjects	Myocardial infarction or sudden death	Celecoxib versus no NSAID use during previous 60 days Rofecoxib (>25 mg daily) versus no NSAID use during previous 60 days Rofecoxib (25 mg daily or less) versus no NSAID use during previous 60 days Celecoxib versus no NSAID use within the previous year	0.84 (0.67–1.04) 3.00 (1.09–8.31) 1.23 (0.89–1.71) 0.99 (0.85–1.16)
Levesque <i>et al.</i> (2005)	Administrative data from Quebec, Canada	Nested case-control study with electronic data	First hospitalized myocardial infarction during the study period	Rofecoxib (>25 mg per day) versus no NSAID use within the previous year Rofecoxib (25 mg or less per day) versus no NSAID use within the previous year Celecoxib versus no use Rofecoxib versus no use	1.73 (1.09–2.76) 1.21 (1.02–1.43)
Hippisley-Cox and Coupland (2005) Johnsen <i>et al.</i> (2005)	Electronic medical records system in the UK	Retrospective cohort and nested case-control study	First acute myocardial infarction	Current celecoxib versus no use Current rofecoxib versus no use	1.21 (0.96–1.54) 1.32 (1.09–1.61)
Velentgas <i>et al.</i> (2006)	Danish National Patient Registry and the Danish Civil Registration System Electronic data from large US health plans and review of medical records	Population-based case-control study Retrospective cohort study	First-time hospitalization for acute myocardial infarction Acute coronary syndrome and sudden cardiac death	Current celecoxib use versus ibuprofen or diclofenac Current rofecoxib use versus ibuprofen or diclofenac	1.25 (0.97–1.62) 1.80 (1.47–2.21) 1.03 (0.83–1.27) 1.35 (1.09–1.68)

found. APPROVe was terminated on September 30, 2004, and rofecoxib was withdrawn from the worldwide market by the manufacturer on the same day. Extended follow-up of study subjects for up to 1 year after the 3-year treatment period showed a hazard ratio of 1.79 (95% CI, 1.17–2.73) for APTC end point (Baron *et al.*, 2008).

#### **CELECOXIB IN THE ADENOMA PREVENTION WITH CELECOXIB AND THE PREVENTION OF COLORECTAL SPORADIC ADENOMATOUS POLYPS TRIALS**

The APPROVe results prompted the US National Cancer Institute to carry out a cardiovascular analysis of celecoxib in the Adenoma Prevention with Celecoxib (APC) study (Solomon *et al.*, 2005). Co-sponsored by the National Cancer Institute and the manufacturer of celecoxib, APC was a placebo-controlled chemoprevention trial that evaluated the efficacy of a COX-2 inhibitor in the prevention of recurrence of colorectal polyps. History of cardiovascular disease was not an exclusion criterion. Subject enrollment was completed in March 2002 and the treatment phase was terminated on December 16, 2004, because of cardiovascular safety concerns. The safety committee evaluated a composite end point of myocardial infarction, stroke, congestive heart failure, and death due to cardiovascular disease during the 3-year follow-up period. In comparison with the placebo arm, increased cardiovascular risk was found among patients who received celecoxib 400 mg two times daily (relative risk 3.4; 95% CI, 1.5–7.9) and those who received celecoxib 200 mg two times daily (relative risk 2.6; 95% CI, 1.1–6.1) (Bertagnolli *et al.*, 2006).

The manufacturer of celecoxib sponsored another chemoprevention study of colorectal polyps called the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial. For the same composite cardiovascular end point used in APC, relative risk for celecoxib 400 mg once daily when compared with placebo was 1.3 (95% CI, 0.65–2.62) (Arber *et al.*, 2006). Furthermore, the National Cancer Institute commissioned a cardiovascular safety committee to combine data from APC and PreSAP and used a single set of criteria to blindly adjudicate cardiovascular outcomes

(Solomon *et al.*, 2006). The relative risk was 1.9 (95% CI, 1.1–3.1) for all celecoxib doses combined when compared with placebo.

#### **CELECOXIB AND NAPROXEN IN THE ALZHEIMER'S DISEASE ANTI-INFLAMMATORY PREVENTION TRIAL**

The US National Institute of Aging sponsored the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) that began recruitment in 2001. Subjects age 70 years or older with family history of Alzheimer's disease but no symptoms of dementia were randomly assigned to receive celecoxib, naproxen, or placebo. At an interim cardiovascular safety analysis conducted in December 2004, naproxen use was found to be associated with increased risk of cardiovascular or cerebrovascular death, myocardial infarction, stroke, congestive heart failure, or transient ischemic attack when compared with placebo (hazard ratio 1.63; 95% CI, 1.04–2.55). No increased cardiovascular risk in the celecoxib group in comparison with placebo was found (ADAPT Research Group, 2006).

#### **SAFETY EVALUATION OF OTHER CYCLOOXYGENASE-2 INHIBITORS**

See Table 47.1. In addition to celecoxib and rofecoxib, three other COX-2 inhibitors have been approved in major markets.

#### **VALDECOXIB AND PARECOXIB**

Valdecoxib was the third approved COX-2 inhibitor. Parecoxib, a prodrug of valdecoxib, is the only COX-2 inhibitor available for intravenous or intramuscular administration and is indicated for post-operative pain. A trial of the drugs among patients after coronary artery bypass graft surgery showed increased incidence of thromboembolic events in the active drug groups in comparison with the placebo group (Nussmeier *et al.*, 2005). In addition, the number of reported cases of Stevens–Johnson syndrome and toxic epidermal necrolysis suspected to be associated with valdecoxib in the FDA adverse event reporting system was higher than the expected

number based on the reporting rates of the same serious skin conditions for celecoxib and rofecoxib (La Grenade *et al.*, 2005). The cardiovascular risk and cutaneous toxicity of valdecoxib led to its market withdrawal in the USA in 2005 (FDA, 2005a). Parecoxib is not available in the USA and is available in Europe.

### LUMIRACOXIB

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) was conducted to evaluate the efficacy and safety of lumiracoxib (Farkouh *et al.*, 2004; Schnitzer *et al.*, 2004). Risk of upper gastrointestinal ulcer complications was lower in the lumiracoxib group than that in the naproxen/ibuprofen group (relative risk 0.34; 95% CI, 0.22–0.52). No increased cardiovascular risk as defined by APTC end point was found. Data from all lumiracoxib trials of duration between 1 week and 1 year were pooled for evaluation of cardiovascular outcomes and no increased risk was found (Matchaba *et al.*, 2005). Lumiracoxib is not available in the USA, and from 2007 through 2008 it was withdrawn from most of the countries that it was approved because of liver toxicity (EMA, 2007).

### ETORICOXIB

Currently, etoricoxib is the only oral COX-2 inhibitor other than celecoxib available worldwide, but it is not available in the USA. As a result of cardiovascular safety concern with COX-2 inhibitors, the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program was designed to pool data from three large trials of etoricoxib for osteoarthritis or rheumatoid arthritis, with diclofenac as the comparator (Cannon *et al.*, 2006). Risks of thrombotic cardiovascular events and complicated upper gastrointestinal events among etoricoxib users were similar to those among diclofenac users. While etoricoxib has been shown to have similar cardiovascular and upper gastrointestinal risk profiles as a widely used nonselective NSAID, the choice of diclofenac as the comparator has been questioned, as the comparator recom-

mended by the FDA has been naproxen (Psaty and Weiss, 2007).

## RESEARCH ACTIVITIES AFTER ROFECOXIB WITHDRAWAL IN 2004

### META-ANALYSIS AND DATA POOLING TO EVALUATE CYCLOOXYGENASE-2 INHIBITORS

Jüni *et al.* (2004) combined frequencies of fatal or nonfatal myocardial infarction from 18 clinical trials of rofecoxib for rheumatoid arthritis, osteoarthritis, or back pain. The combined odds ratio for the rofecoxib versus nonselective NSAID or placebo comparison was 2.24 (95% CI, 1.24–4.02). Kearney *et al.* (2006) reviewed 138 trials of COX-2 inhibitor with placebo or nonselective NSAIDs as comparator and evaluated a range of cardiovascular outcomes, including vascular events, myocardial infarction, stroke, and vascular death. Comparing all COX-2 inhibitors (celecoxib, etoricoxib, lumiracoxib, rofecoxib, and valdecoxib) with placebo, the relative risk of serious vascular events was 1.42 (95% CI, 1.13–1.78). COX-2 inhibitors as a group were associated with increased vascular risk when compared with naproxen (relative risk 1.57; 95% CI, 1.21–2.03) and was not associated with increased vascular risk when compared with non-naproxen nonselective NSAIDs (relative risk 0.88; 95% CI, 0.69–1.12).

McGettigan and Henry (2006) reviewed observational studies of COX-2 inhibitors and cardiovascular risks and the meta-analysis results were consistent with clinical trials findings. The review was updated in 2011 to include 51 studies, and the pooled relative risks (95% CIs) for celecoxib, rofecoxib, valdecoxib, and etoricoxib were 1.17 (1.08–1.27), 1.45 (1.33–1.59), 1.05 (0.81–1.36), and 2.05 (1.45–2.88), respectively (McGettigan and Henry, 2011). For celecoxib and rofecoxib, higher dose were associated with higher risk.

The US National Cancer Institute sponsored the Cross Trial Safety Analysis and pooled data from six placebo-controlled disease prevention trials of celecoxib with at least 3 years of follow-up (Solomon *et al.*, 2008). Evaluated outcomes

included cardiovascular death, myocardial infarction, stroke, heart failure, and thromboembolism. Hazard ratio for the composite cardiovascular end point associated with celecoxib 400 mg twice daily was 3.1 (95% CI, 1.5–6.1) and it was 1.6 (95% CI, 1.1–2.3) for all celecoxib dosage regimens combined, which included 400 mg twice daily, 200 mg twice daily, and 400 mg once daily. Similar dose-response results were found among subjects with cardiovascular risk factors or preexisting cardiovascular diseases, but no increased cardiovascular risk was observed for any celecoxib dose among subjects considered to have low baseline cardiovascular risk, suggesting substantial effect modification related to cardiovascular risk before celecoxib initiation.

Trelle *et al.* (2011) conducted a network meta-analysis of 31 large trials of COX-2 inhibitor or nonselective NSAID with active drug or placebo as comparator. Primary outcome of interest was myocardial infarction and all comparisons were made with placebo. For rofecoxib the rate ratio was 2.12 (95% CI, 1.26–3.56) and the 95% CIs of the rate ratios for all other drugs evaluated (celecoxib, etoricoxib, lumiracoxib, diclofenac, ibuprofen, and naproxen) all included one. Results for other outcomes, including APTC end point, stroke, cardiovascular death, and all-cause mortality, were not consistent with the myocardial infarction findings. Other than celecoxib and naproxen, each COX-2 inhibitor or nonselective NSAID studied was found to be associated with increased risk of at least one of the adverse outcomes.

For adverse non-thromboembolic cardiovascular outcomes, Aw *et al.* (2005) reviewed 19 trials involving COX-2 inhibitors and found that use of COX-2 inhibitors was associated with increased blood pressure when compared with placebo or nonselective NSAIDs. The effect on blood pressure was more pronounced among rofecoxib users than among celecoxib users. Zhang *et al.* (2006) reviewed 114 trials involving COX-2 inhibitors and found that rofecoxib use was associated with increased risk of arrhythmia, peripheral edema, hypertension, and renal dysfunction, but celecoxib use was not associated with increased risk of these outcomes.

## META-ANALYSIS TO EVALUATE NONSELECTIVE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The nonselective NSAIDs were approved at a time when cardiovascular safety of this class of drug was not systematically evaluated. When the cardiovascular risk of rofecoxib was identified in 2000, there was limited clinical trial or epidemiology data on the cardiovascular safety of nonselective NSAIDs, adding to the challenge of safety assessment of the COX-2 inhibitors. After review of relevant data at an advisory committee meeting in February 2005, the FDA requested the addition of a warning for potential cardiovascular risk to the package insert of all nonselective NSAIDs and celecoxib (FDA, 2005b).

Salpeter *et al.* (2006) identified 13 placebo-controlled trials of nonselective NSAIDs for arthritis or Alzheimer's disease that reported at least one cardiovascular event or death and found no increased cardiovascular risk associated with the nonselective NSAIDs as a group in a meta-analysis. In the meta-analysis of observational studies by McGettigan and Henry (2006), increased cardiovascular risk associated with diclofenac and indomethacin but not for ibuprofen and naproxen were reported. The updated meta-analysis showed increased cardiovascular risk associated with all commonly used nonselective NSAIDs (McGettigan and Henry, 2011). Pooled relative risks (95% CIs) for ibuprofen, naproxen, diclofenac, and indomethacin were 1.18 (1.11–1.25), 1.09 (1.02–1.16), 1.4 (1.27–1.55), and 1.3 (1.19–1.41), respectively.

## CELECOXIB AND PROSPECTIVE RANDOMIZED EVALUATION OF CELECOXIB INTEGRATED SAFETY VERSUS IBUPROFEN OR NAPROXEN TRIAL

See Table 47.1. In response to the cardiovascular safety concern with the COX-2 inhibitors, the manufacturer of celecoxib initiated the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) study (Becker *et al.* 2009). Patients with established cardiovascular disease or at high risk of

developing cardiovascular disease are randomized to receive celecoxib, naproxen, or ibuprofen and the primary end point is APTC composite end point. While the study may provide the most definitive information about relative cardiovascular safety profiles of the three study drugs in the treatment of osteoarthritis or rheumatoid arthritis, results will not be available until September 2015 (the December 2012 update is at <http://clinicaltrials.gov/show/NCT00346216>).

### BENEFIT–RISK ASSESSMENT OF THE CYCLOOXYGENASE-2 INHIBITORS AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The primary objective of NSAID treatment is to control pain and inflammation in patients with different forms of arthritis or pain conditions. No single NSAID has been demonstrated to be superior to others in terms of analgesic and anti-inflammatory effects, and patients' response to individual NSAIDs varies substantially.

An additional beneficial effect of the COX-2 inhibitors is prevention of colorectal polyp. Celecoxib use was found to reduce polyps in patients with familial adenomatous polyposis (Steinbach *et al.*, 2000) and it had approved indication for familial adenomatous polyposis before the indication was withdrawn in 2011 (EMA, 2011; Federal Register, 2012). Celecoxib and rofecoxib are efficacious in reducing recurrence of colorectal adenoma after adenoma removal in APC (Bertagnolli *et al.*, 2006), PreSAP (Arber *et al.*, 2006), and APPROVe (Baron *et al.*, 2006). Despite the promising role of COX-2 inhibitors in chemoprevention of colorectal cancer, celecoxib is less favorable than aspirin because of the cardiovascular (Psaty and Potter, 2006).

In the benefit–risk assessment of NSAIDs, adverse effects of NSAIDs in all organ systems need to be considered. In addition to gastrointestinal and cardiovascular risks, liver, renal, cutaneous, and hematologic toxicities associated with NSAIDs are important safety issues that have been described in the literature but not reviewed in this chapter. In

addition, drug risks of individual adverse outcomes within an organ system may be heterogeneous. For example, for ischemic heart disease outcomes, COX-2 inhibitors and nonselective NSAIDs are associated with increased risk for nonfatal myocardial infarction but appear to have no effect on fatal myocardial infarction (García Rodríguez *et al.*, 2011).

Not all COX-2 inhibitors and nonselective NSAIDs are the same in terms of risk profiles. For the nonselective NSAIDs, the European Medicines Agency concluded that diclofenac is associated with higher cardiovascular risk than other nonselective NSAIDs (EMA, 2012). For gastrointestinal toxicity, a recent review of observational studies showed substantial variation of risks associated with nonselective NSAIDs, celecoxib, and rofecoxib (Massó González *et al.*, 2010). For the COX-2 inhibitors, lower risk of upper gastrointestinal ulcers and complications when comparing with nonselective NSAIDs was only demonstrated for rofecoxib (Bombardier *et al.* 2000) and lumiracoxib (Schnitzer *et al.*, 2004), not for celecoxib (Hrachovec and Mora, 2001) or etoricoxib (Cannon *et al.*, 2006). How the COX-2 inhibitors compare with the combination of a nonselective NSAID and a proton pump inhibitor, an H<sub>2</sub> blocker, or misoprostol for gastrointestinal protection has not been adequately evaluated.

From a therapeutic risk management perspective, if high-risk patients can be identified before NSAID therapy, clinicians will be able to select the optimal regimen for individual patients. The benefit–risk calculus for a 70-year-old overweight man who has osteoarthritis, coronary heart disease, and prior history of gastric perforation is very different from that for a 35-year-old woman who has no history of heart disease or gastrointestinal complications and needs pain medication for rheumatoid arthritis. Results like that from the Cross Trial Safety Assessment Group, which reported findings stratified by baseline cardiovascular risks (Solomon *et al.*, 2008), are very useful in the choice of NSAID therapy. Lastly, with widespread use of low-dose aspirin in prevention of cardiovascular diseases, the aspirin effects on cardiovascular and gastrointestinal risks among those who need NSAID therapy should be considered.

## COMMENTS

The cardiovascular risk of rofecoxib illustrated the limited capacity of the spontaneous adverse drug reactions reporting system to detect drug safety signals with a moderate to high background incidence (FDA, 2008). If there had been no VIGOR and APPROVe, the cardiovascular risk of rofecoxib may not have been recognized until much later, if ever. For rare events that have previously been reported as drug-induced outcomes, such as Stevens–Johnson syndrome and serious liver injury, the medical care provider's level of suspicion may be high and the adverse event is more likely to be reported. For an adverse event like acute myocardial infarction in which the background rate is not rare and the risk factors are well characterized, the medical care provider may not readily attribute the myocardial infarction to the rofecoxib that the patient was taking. An additional data system like the FDA-sponsored Mini-Sentinel program is needed to augment the voluntary reporting system and provide population-based empirical information for drug safety assessment (Behrman *et al.*, 2011).

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# Introduction to Pharmionics: The Vagaries in Ambulatory Patients' Adherence to Prescribed Drug Dosing Regimens, and Some of Their Clinical and Economic Consequences

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## INTRODUCTION AND BACKGROUND

The general topic of this chapter is very old. Hippocrates is said to have complained that some of his patients did not take the medicines he prescribed, and then blamed him for a poor outcome. Given the state of therapeutics at that time, it is unlikely that many of the medicines that Hippocrates prescribed were very effective or free from toxicity. Thus, patients who declined to take his prescribed medicine(s) were perhaps more likely than not to be making the better choice.

The situation today is radically different. Beginning in the mid 1930s with the advent of the sulfa drugs, and catalyzed after 1945 by the advent of penicillin, the pharmaceutical industry has transformed itself from a minor to a major industry by discovering drugs and developing them into pharmaceutical products of increasing therapeutic and prophylactic power, whilst meeting increasingly rigorous standards for acceptable hazard. Since 1961, with the introduction of oral steroid contraceptives, a growing number of medicines have been developed for long-term prophylactic use by either

completely normal individuals (as is the case with oral contraceptives) or individuals who have certain precursor conditions (e.g., uncomplicated, mild hypertension; elevated lipid levels; decreased bone mineral density) that are deemed risk factors for the subsequent development of overt disease. A further transition in the use of pharmaceuticals has been the increasing use of drug response versus nonresponse as diagnostic information. A still further change, which will foreseeably continue, has been an increasing ability to see disease in its earliest stages, thus moving backward the somewhat fuzzy boundary between prophylaxis and treatment of disease. This last point is illustrated by the continually more aggressive efforts during the past two decades to modify, by increasingly intense pharmacological means, the concentrations in blood of various lipids, to lower the risk of coronary arterial disease.

In the arena of infectious disease, the past 60 years have seen an intense race between the emergence of microorganismal resistance to anti-infective agents in clinical use and the emergence of new anti-infective agents from the pharmaceutical industry's research and development efforts. There is a broad consensus that patients' erratic exposure to anti-infective agents, either through erratic execution of drug dosing regimens or early discontinuation of treatment, creates conditions that foster the emergence of drug-resistant microorganisms. Most infectious disease experts recognize that either form of undertreatment can drop the concentrations of anti-infective agents in blood or tissues to a point low enough to allow high rates of microorganismal replication, whilst still being high enough to exert so-called "selection pressure." Thus, mutant microorganisms, carrying mutations that confer drug resistance, are selected for, as they are believed to thrive better in an environment of partial exposure to antimicrobial drug action than wild-type microorganisms, which lack these mutations.

How soon after the onset of clinical use is a newly introduced anti-infective agent likely to begin to be confronted by drug-resistant microorganisms? There is great variability in the answer to this question. At one end of the spectrum is the continuing sensitivity of *Treponema pallidum*, the infective agent for syphilis. *T. pallidum* has never developed resistance to penicillin in almost 60 years of use to

cure syphilis – a disease that, in the preceding several centuries, was pandemic in the Western world, rivaling tuberculosis (TB) as the leading infectious disease and cause of mortality and major morbidity at all ages of human life. In contrast, other microorganisms, e.g. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus proteus*, have each more or less rapidly achieved resistance to successively introduced anti-infective agents. So have tubercle bacilli and the human immunodeficiency virus (HIV). Clearly, the topic of emergent drug resistance of anti-infective agents has many aspects that are specific to the drugs and the microorganisms involved. Such detail goes beyond the scope of this chapter, but suffice it to say that erratic exposure of infecting microorganisms to anti-infective agents, either due to erratic dosing or early cessation of dosing, is generally accepted as a crucial factor in the emergence of microorganismal resistance to antimicrobial drug resistance.

For many reasons that are beyond the scope of this chapter, prices of prescription drugs, which for many years lagged behind the consumer price index in the USA, have risen steeply in the past 15 years.

Thus, the advent of medicines with unprecedented therapeutic power and economic cost, some of which are indicated for multiyear or lifelong use, and some of which are beset by the problem of emergent drug resistance, has put increasing emphasis on the question of how well or poorly patients actually use prescribed medicines. That growing emphasis has led to the formation of a new subdiscipline of biopharmaceutical science called *pharmionics* (Urquhart, 2002; Blaschke *et al.*, 2012), which concerns itself with learning what patients actually do with prescribed drugs and analyzing the clinical and economic consequences of the various temporal patterns of drug exposure that arise from patients' variable adherence to prescribed drug dosing regimens. A natural by-product of this focus is an ongoing challenge to the optimality of recommended drug dosing regimens.

## PHARMIONICS IN OVERVIEW

This topic, if one takes a broad view, is one of many aspects of pharmacotherapeutics that was largely

neglected until relatively recently. A major reason for neglect of patient adherence was the poor state of available methods for compiling drug dosing histories in ambulatory patients. Sometimes called “external drug exposure,” reliable drug dosing histories are the cornerstone of understanding how prescribed drugs are actually being used by ambulatory patients. That understanding, in turn, is the foundation for understanding the clinical and economic consequences of observed patterns of drug usage/misusage. Thus, the qualities of methods for compiling drug dosing histories of ambulatory patients are a natural topic of this chapter. So too are the methods of analyzing the clinical and economic consequences of variable adherence to prescribed drug dosing regimens.

### DESCRIPTIVE ASPECTS

Three basic patterns characterize the main deviations from prescribed drug dosing regimens (Urquhart, 1997; Vrijens *et al.*, 2012). Some patients – usually in the range of 5–10%, but sometimes more or sometimes less – never start the prescribed course of drug dosing. This pattern is called “nonacceptance.” It is shown by the abrupt drop at time zero in the percentage of patients engaged with the drug dosing regimen, the heavy dark line labeled “persistence” in Figure 48.1. These are patients who never start the dosing regimen, though they have enrolled in the treatment program. They may take an initial dose or two, but most of them take none, and then disappear from the treatment program. There may be a time that they come back to treatment, but it does not fall within the duration of the study or treatment plan in question.

Once the patient engages with the drug dosing regimen there is an ongoing question of the quality of the patient’s execution of that regimen. The main errors that patients make in execution are to delay or omit doses. Sometimes they sequentially omit multiple scheduled doses, which are called “drug holidays” when they exceed 3 days’ duration. Occasionally, some patients take an extra dose, but missed doses generally outnumber extra doses by 4:1 or more. On any given day, within a group of patients still engaged with the dosing regimen, about 10% of prescribed doses are not taken, giving

rise to the gap, seen in the lower irregular line, labeled “adherence/compliance” – the irregularities being due to day-to-day variations in the proportion of prescribed doses that are missed. Within that gap, of course, lie some important details, the first of which is that most the gap arises from dose omissions made by about a third of ambulatory patients (Urquhart, 1997; Vrijens *et al.*, 2012), and of course includes drug holidays, most of which are taken by a small minority of patients, although within 6 months about half of patients monitored in the studies that comprise Figure 48.1 had had at least one holiday. The third major deviation from prescribed drug dosing regimens is early cessation of dosing, such that dosing stops and remains stopped without resumption within the time-frame of the study or clinical situation.

Figure 48.1 illustrates the foregoing points. Following the immediate drop due to noninitiators, we are left with patients who engage with the dosing regimen. S, about a third had discontinued what was meant to be multiyear, if not lifetime, treatment. Note the large gap between the “persistence” line and the “perfect adherence” line. This gap, which grows with time, indicates both the loss of patients from beneficial treatment, with its implications for public health, and the loss of sales revenues for the drug developer/manufacturer/marketer. When one sees year-by-year growth in revenues from a pharmaceutical indicated for long-term use, it signifies that the product’s marketing effort must not only recruit replacements for the nonpersisters, but also recruit additional patients. That process of intensive recruitment of new patients continues year after year. Some analysts refer to this costly and inherently wasteful process as “churn,” the high costs of which could be reduced if the gap between actual and perfect persistence could be narrowed.

One can expect to see variation within the above numbers, from one treatment situation to another, but the basic patterns of nonacceptance, incomplete execution, and early discontinuation are pervasive in long-term ambulatory pharmacotherapy. To illustrate one end of the range of variation, Catalan and LeLorier (2000) studied the persistence of Canadian patients with prescribed drugs of the statin category, following the patients for 5 years after they were prescribed a statin. Each patient’s drugs were fully

reimbursed, nullifying economic obstacles to continuity of treatment. Switches between one drug and another within the “statin” class were considered to represent continuity of statin treatment. The following are the percentages of patients still persisting from the first to the fifth anniversary of the original prescription: 33%, 24%, 17%, 14%, 13%. This pattern shows twice the loss of patients within the first year as shown in Figure 48.1. Perhaps the reasons for this exceptionally high rate of discontinuation in the Catalan and LeLorier study lie in the fact that the patients in this study were on full social assistance, which means that they were eligible for economic support by the state, in addition to getting prescription drugs at no cost. The various problems that led these patients to qualify for full social assistance may include factors that especially discourage long persistence with chronic-use medicines for asymptomatic conditions.

To illustrate the other end of the range of variation, the big confirmatory trials of several major drugs of the statin class show that over 90% of patients enrolled in the studies were continuing to attend scheduled clinic visits, and presumably were still taking the trial medication at some level of adherence/compliance (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al.*, 1995). That level of adherence/compliance could only be crudely indicated from these trials’ reliance on returned tablet/capsule counts as estimators of patients’ exposure to the test drugs, for reasons discussed later. It remains to be seen how many patients in big clinical trials continue to keep scheduled appointments but surreptitiously discontinue dosing, or take too few doses to have more than *de minimis* clinical effects. Suffice it to say, though, that these confirmatory trials certainly demonstrate that it is possible to maintain nominal persistence with trial medications at a very high level.

It seems reasonable to infer that the administrative apparatus of big clinical trials – the process of securing informed consent, multiple phone calls from trial staff to patients, other reminders, all adding up to more than usual professional attention paid to patients – serve to keep the vast majority of patients engaged with the treatment process over long periods of time, with an evident >90% persistence through year 5 – a stark contrast with the much lower persistence observed in studies carried out on

routine medical practice (Jones *et al.*, 1995; Benner *et al.*, 2002; Blaschke *et al.*, 2012).

## ARE EXECUTION AND PERSISTENCE IMPROVABLE?

The pharmionics field is just at the beginning of systematic work along these lines, with, as yet few published studies, and even fewer studies of satisfactory design and analysis. The best in this category is the 392-patient, 1-year study (Vrijens *et al.*, 2006), which has shown that community pharmacies, cluster-randomized between practice-as-usual and measurement-guided intervention, could use electronically compiled drug dosing histories to guide their interventional discussions with the patients, and achieve a statistically significant improvement in both persistence and compliance with the daily dosing regimen of atorvastatin, a leading drug in the statin class. This result clearly needs to be repeated, and to benefit from knowledge of, and avoidance of, problems that lurked beneath the surface of this study. For example, the interventional program was designed by committee, several members of which were adamant that the provision of a credit card-sized beeper would suffice to remind patients when to take the once-daily dose; in the event, however, only 22% of patients accepted the beeper card, and half of those rapidly discontinued its use – a phenomenon well-known in the consumer electronics arena as “beeper-fatigue.” Another limitation was that each pharmacist in the intervention group was allowed to improvise their interventional maneuvers.

Despite these problems, however, the study showed clear-cut benefits of measurement-guided medication management, as improvised on intuitive grounds by community pharmacists. The results of this study are probably best seen as a starting point for learning-curve-based improvements in results, combined with simplifications in method and corresponding economies.

## TAXONOMIC ISSUES AND THEIR RELATION TO SOUND ANALYSES OF DOSING HISTORY DATA

The foregoing discussion makes clear the three major categories of deviation from a prescribed drug dosing regimen in ambulatory care: acceptance, exe-

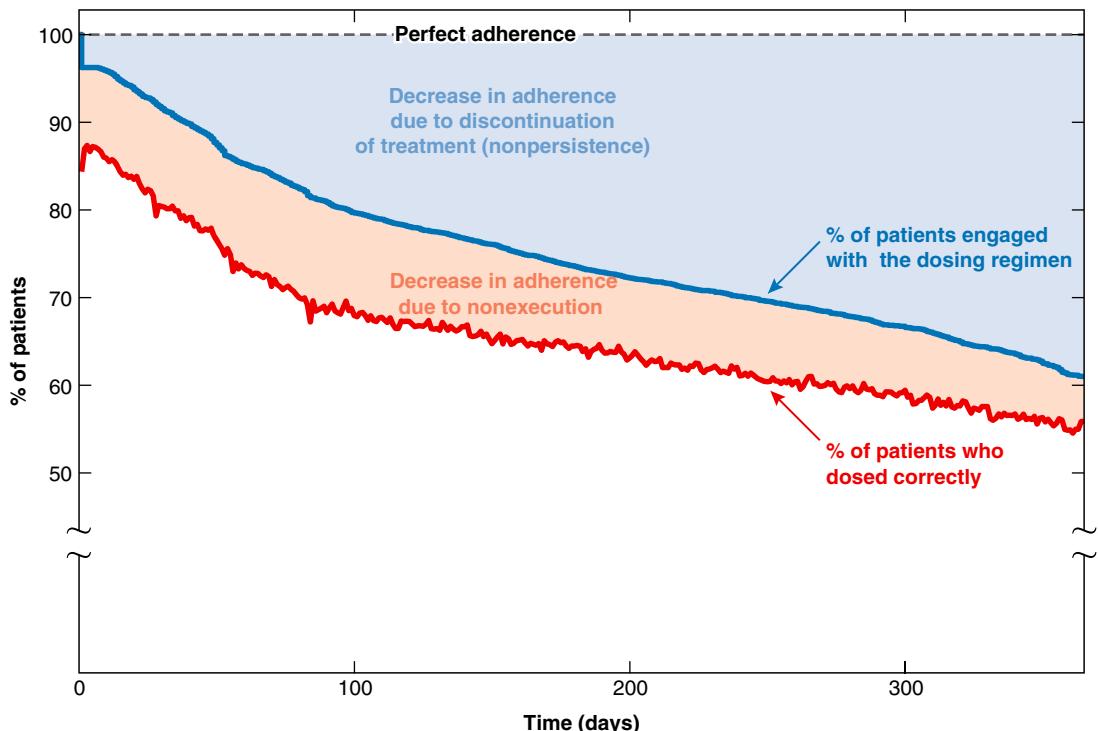


Figure 48.1 Kaplan-Meier plots of the time-course of the 3 adherence parameters of 16,907 patients, each prescribed an orally administered medication for one of a variety of chronic medical conditions in 95 studies, during the first year of treatment. The data are based on drug dosing histories, electronically compiled by MEMS® medication-event monitoring throughout the 330-day period of observation. The horizontal dashed line at the top of the figure shows how perfect adherence to the prescribed once-daily dosing regimens would be depicted. 'Perfect' adherence means: no patients quitting the treatment regimen, and no missed doses within the 330 days of observation. The smooth heavy dark line, which starts out at 100% of patients (left-hand axis) and declines steadily towards a value of 61%, at 330 days, shows an abrupt drop from 100% to approximately 96% at zero-time, reflecting that 4% of study patients never began treatment with the study agent. This phenomenon, which sometimes varies widely from one study to another, is called 'non-initiation'. As the data in Figure 48.1 show, approximately 96% of the study patients initiated the once-daily drug treatment, but the continuing, downward trajectory of the heavy dark line reflects a steadily growing number of patients who had ceased their persistence with the once-daily dosing regimen, such that, by day 330, only approximately 62% of the study-patients were still persisting with the prescribed, once-daily dosing regimen. The next lower line, which irregularly varies from day to day, indicates the proportion of still-persisting patients who took the prescribed once-daily dose on each successive day during the 330 days of observation. This lower, irregular line reflects the adherence parameter called 'implementation', which expresses the percentage of study patients who took the once-daily dose, day by day, up to day 330, when the studies closed. The gap between the smooth, upper persistence line and the irregular, lower implementation line, indicates the proportion of days in which still-persisting patients failed to take the prescribed daily dose – approximately 10% of prescribed daily doses went untaken by still-persistent patients who, but for occasional lapses in dosing, continued to persist with the once-daily dosing regimen. On the last day of the observation period, approximately 55% of the original cohort of patients in the 95 studies took that day's prescribed dose; approximately 61% of the original cohort were still persisting with the dosing regimen, even though they had omitted the prescribed dose for day 330, and perhaps several previous days as well. One must set a criterion for how many serially omitted doses can occur in still-persistent patients, until the point is reached at which one judges that the patient in question has ceased persistence with the once-daily dosing regimen, and has thus ended his/her participation in study's dosing regimen. Thus, 3 parameters characterize an ambulatory patient's adherence to a prescribed dosing regimen: initiation, i.e., how long after the start of the treatment-phase of the study did the patient commence taking the prescribed medicine? Implementation, i.e., what is the proportion of patients who took the prescribed dose day by day? Persistence, i.e., how long did the patient continue to take the prescribed medicine, subject to occasional lapses in dosing, until s/he ceased dosing altogether.

cution, and discontinuation. The time between the first-taken and the last-taken dose is called “persistence,” expressed in units of time. The quality of regimen execution is the outcome of a comparison between the patient’s dosing history and the prescribed drug dosing regimen – the outcome of the comparison of two time-series. As there are many facets to time-series data, there is no single parameter that captures all facets, so there are a number of ways to express the data (Vrijens *et al.*, 2012).

Many investigators have used only aggregate expressions, such as the percentage of prescribed doses taken, the percentage of days on which the correct number of doses was taken, or the percentage of interdose intervals that fall within certain limits of the interval implicit in the prescription (e.g., 24 h for once-daily dosing). Aggregate figures across long periods of time hide informative time variations in dose-taking behavior. For example, there is a marked “weekend effect” frequently evident, by which substantially and significantly more doses are missed on weekends than on weekdays (Blaschke *et al.*, 2012). Another time dependency is the tendency for the quality of regimen execution to decline gradually over long periods of time (Blaschke *et al.*, 2012).

The choice of limits on the dosing interval should ideally relate to the pharmacometric properties of the drug in question; for example, bendrofluthiazide, the diuretic widely used in the UK for hypertension treatment, has a 3 h plasma half-life (Jackson, 1995), but a 6.3-day duration of antihypertensive action after a last-taken dose; if one considers only the pharmacokinetic properties of that drug, the range would be set quite narrowly, perhaps  $\pm 1.5$  h, but given that the pharmacodynamic properties of the drug dominate, and confer a 6.3-day duration of action (Girvin and Johnston, 2004), one could reasonably accept a range of  $\pm 2$  days.

In the known pharmacometric properties of bendrofluthiazide, one gets a glimpse of how the search for a sound, quantitative answer to the question “How much adherence is enough?” represents a challenge to pharmacometric understanding of drugs and the dose- and time-dependencies of their actions. It also emphasizes the importance of examining not only pharmacokinetic information about the drug in question, but also pharmacody-

namic information, particularly the duration of drug action(s) after a last-taken dose. Either can be the determining factor in judging “how much adherence is enough,” which of course is a crucial but neglected aspect of determining an optimal drug dosing regimen. The “neglect” arises probably in large part from the prevailing delusion that achieving a once-daily dosing regimen for a product will automatically solve adherence problems. The case studies presented later serve to disabuse anyone of that foolish notion.

#### CONTRASTING DYNAMICS OF ACCEPTANCE, EXECUTION, DISCONTINUATION: WHY THERE CAN BE NO SINGLE PARAMETER THAT ENCOMPASSES ALL MAJOR DOSING ERRORS AND SUPPORTS SOUND QUANTITATIVE ANALYSIS

Acceptance and discontinuation are more or less binary occurrences, in that they are usually abrupt. Execution, in contrast, is a continuous process that can vary within days, between days, from week to week, or from month to month, and indeed does so, as noted above. It is not possible to combine binary and continuous processes in one parameter, except in a literary sense, but certainly not in the sense of having one parameter that supports sound, quantitative analysis.

“Adherence” is generally used as a blanket term for all aspects of how well or poorly a prescribed drug dosing regimen is followed by patients. As a literary expression it serves a certain purpose, but it does not support sound measurement, which must distinguish between nonacceptance, poor execution, and early discontinuation. As a concrete example, consider the following statement by the 6th Joint National Commission on High Blood Pressure (JNC, 1997): “Poor adherence to antihypertensive therapy remains a major therapeutic challenge, contributing to the lack of adequate control in more than two-thirds of patients with hypertension.” The problem with this statement is that it does not distinguish between nonacceptance, poor execution, or early discontinuation. In all likelihood each plays some role in the overall problem. Based on Figure 48.1, which includes a considerable amount of data from studies of hypertensive

patients, early discontinuation is almost certainly the biggest contributor to the distressing shortfall in the quality of antihypertensive drug treatment. As the Belgian atorvastatin study (Vrijens *et al.*, 2006) illustrates, a program of measurement-guided medication management can prolong patients' engagement with the drug dosing regimen, otherwise known as extended persistence, but if we are to do better than the results in that study, then it probably means attacking specifically each of the three major errors: nonacceptance, poor execution, early discontinuation.

#### THE IMPORTANCE OF DISTINGUISHING EARLY DISCONTINUATION AND POOR EXECUTION IN ANALYZING DRUG DOSING HISTORY DATA

A common manner of expressing adherence/compliance data goes as follows (Osterberg and Blaschke, 2005):

Rates of adherence for individual patients are usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period. . . . The average rates of adherence in clinical trials can be remarkably high, owing to the attention study patients receive and to selection of the patients, yet even clinical trials report average adherence rates of only 43 to 78 percent among patients receiving treatment for chronic conditions.

Expressing the percentage of prescribed doses taken during a fixed interval of time inevitably mixes together execution and early discontinuation. Thus, a patient will be categorized as having 50% adherence who doses strictly punctually but discontinues at month 6 in a 12-month study. Of course, if duration of the study had been set at 24 months, then the patient who discontinues at 6 months would be categorized as a 25% adherer. Also categorized as a 50% adherer will be a patient whose execution is such that s/he takes only half the prescribed doses, but continues to be engaged with the dosing regimen throughout the 12-month study. These two contrasting patterns of dosing, both of which are common occurrences, not exotic oddities, call for very different interventional approaches: targeted motivation in the first

patient to abort their intention to quit, versus a careful review with the patient of their day-to-day dosing patterns, with assistance in finding robust routines in their daily life to which their daily dosing can be linked, as suggested by Cramer and Rosenheck (1999). Then, ongoing follow-up is needed in the latter instance to see how well specific suggestions work and to provide changes and/or motivation, as needed, to maintain a high quality of execution. Ongoing observation of daily dosing patterns may, if the quality of execution starts to dwindle, signal a pending episode of discontinuation.

There are two important points in the foregoing. One is that the improvement of poor quality of execution is self-evidently a more difficult management problem than is the postponement of discontinuation to achieve longer persistence. The second point is that it is a fundamental mistake in the analysis of dosing history data to ignore the distinction between poor execution and short persistence. "Execution," or "implementation," self-evidently relates to what happens while the patient is engaged with the dosing regimen; when that engagement halts, execution (or implementation) is finished.

One might argue that, from a practical point of view, taking half the prescribed doses is the same, whether it occurs by ongoing faulty execution or by early discontinuation of correct execution. The counter-arguments are as follows. First, since there appears to be a major difference in the complexity and cost of intervening to improve execution (or implementation) versus intervening to prolong persistence, then we only engage with intervention when we know which we are trying to fix. Second, life goes on past the end of an arbitrarily defined study period, so that the patient who has quit taking the medicine will, unless re-recruited, generate no revenues for the manufacturer/developer/marketer, whereas the faulty implementers will, for as long as they persist, continue to generate revenues, albeit at a rate reduced by the extent of their ongoing underdosing. Third, the percentage of prescribed doses taken by the short persister varies with the duration of the study, as noted above; in contrast, the percentage of prescribed doses taken by a consistently poor implementer is unchanged

by altering the duration of the study, setting aside the tendency for the quality of execution to decline gradually with time since the start of treatment.

Figure 48.1 provides a clear format for expressing the basic findings from analysis of drug dosing histories in groups of patients. One can and should go further to characterize the occurrence of omitted doses and drug holidays on a patient-by-patient basis. The clinical correlates of substantial underdosing should be examined carefully, as they may, among other things, show whether the recommended drug dosing regimen provides either insufficient or a substantial excess of "forgiveness," which is defined as the post-dose duration of the drug's therapeutically effective action(s) minus the recommended drug dosing interval (Urquhart, 1997; Blaschke *et al.*, 2012).

Note that Figure 48.1 is a very simple, straightforward summary of pharmacokinetic data. Complexity in this field arises at the level of individual pharmaceuticals, because each has its own recommended dosing regimen and pharmacokinetic and pharmacodynamic properties. The clinical and economic consequences of early discontinuation, dose omissions, and drug holidays will depend directly on these product-specific properties. They are indeed more than drug specific, because differences in drug formulation not only can prolong drug entry into the bloodstream, but also alter its rate in sometimes clinically important ways – a key example being how the pharmacodynamics of nifedipine were beneficially altered by its reformulation in an oral, osmotic pump dosage form that releases the drug at a constant rate, versus the rapid highly time-varying release profile associated with the original dosage form (Breimer and Urquhart, 1993; Urquhart, 2000). Thus, the main complexities in this field arise from the fact that each of hundreds of pharmaceutical products can be expected to have different answers to the question of the clinical and economic consequences of commonly occurring dosing errors.

#### THE SPECIAL ROLE OF DRUG HOLIDAYS

The usually abrupt cessation and resumption of dosing that characterizes drug holidays provide an opportunity to search for important clinical cor-

relates that may contribute to the understanding of adverse reactions occasioned by either rebound effects, as dosing stops, or recurrent first-dose effects when post-holiday dosing resumes in patients who should be re-titrated after some period of interrupted dosing, as was done prior to the initial start of treatment. One of the missing elements of pharmacodynamic information about drugs with first-dose effects is the length of time, after dosing stops, needed to restore drug naïveté and the need for re-titration for least-hazardous resumption of dosing post-holiday. Such information would inform the answering of reasonable questions about the role of drug holidays and their potential hazards in trials of drugs like, for example, encainide and flecainide, which have hazardous or even lethal pro-arrhythmic effects that are triggered by unduly high rates of dose-escalation in the drug-naïve state. By the same token, the role of drug holidays remains unclear in the case of peripheral vasodilators that can have hazardous hypotensive episodes or reflex tachycardia when the rate of dose escalation is too high, or full-strength dosing resumes abruptly in the drug-naïve state (Urquhart, 2000).

While the various patterns and extents of underdosing seen in patients' dosing histories are, in a strict sense, observational data, their clinical correlates may send up useful "red flags," tentatively identifying, for example, dosing regimens that are set too high (Cross *et al.*, 2002; Heerdink *et al.*, 2002), hazardous rebound effects (Urquhart, 1997; Blaschke *et al.*, 2012), and recurrent first-dose effects (Urquhart, 1997; Blaschke *et al.*, 2012). Clinical correlates of a single holiday would naturally be difficult to interpret, but if holidays recur, as they do in some patients, one has the potential opportunity to see repetition of holidays and their associated events. Repetition and consistent time-sequence greatly strengthen the inference of causality. A common problem, of course, is that most clinical events cannot be measured continuously, and are only intermittently sampled, which, via white-coat adherence (Feinstein, 1990), is likely to prevent the occurrence of holidays in temporal proximity to the sampled clinical events. In contrast, holidays can be captured by means of automatic, continuous electronic compilation of drug dosing histories.

A noteworthy technical advance is the ability of the latest generation of implanted cardiac pacemakers and defibrillators automatically to compile complete records of electrophysiological activity throughout multiweek intervals between data downloads. That capability, combined with the prevalence of pro-arrhythmic effects among leading cardiac anti-arrhythmic drugs, provides a potentially rich area for enlightening research on the pharmacodynamics of the anti-arrhythmic drugs (Blaschke *et al.*, 2012).

## METHODOLOGICAL ISSUES IN COMPILING DRUG DOSING HISTORIES OF AMBULATORY PATIENTS

Until the latter 1980s, the available methods (clinical judgment, interviews, patient diaries, counts of returned, unused dosage forms, spot checks of drug concentration in plasma) were unreliable and biased by the ease with which patients can and do easily censor evidence for omitted doses. Thus, a brief review of methods for gathering drug dosing histories in ambulatory patients is a logical part of this chapter.

### CLINICAL JUDGMENT

A leading reason for the weakness of clinical judgment about patient adherence is that the doctor-patient relation is based on trust, which, when there is no reliable, contradictory source of information, leads most physicians to take at face value what patients tell them about their adherence to the prescribed drug dosing regimen. The result is strongly biased toward overestimation of the patient's adherence to the prescribed dosing regimen. What patients tell their physician or other healthcare personnel is strongly colored by two factors: (a) recall of day-by-day drug intake is often poor, unless the patient goes to extraordinary but infrequently made efforts to keep records of what was taken and when; (b) there is a pervasive reluctance among patients to inform the prescribing physician that they have never started taking the medicine, or have started it but executed the dosing regimen poorly, or have

completely discontinued taking the medicine much sooner than the physician had prescribed.

### INTERVIEWS AND PATIENT DIARIES

Reliability problems are obvious with interviews and diary entries, because patients can say or write whatever they choose, and whenever they chose to make diary entries. Work with a special diary that captures and stores the time of each diary entry has shown that only 11% of diary entries bore a credible temporal relation to the event being entered into the diary (Stone *et al.*, 2002).

### MEASURED DRUG CONCENTRATIONS IN PLASMA

An often misunderstood method is the direct measurement of drug concentration in plasma. This method, which has an aura of ultimate objectivity, runs headlong into the prevalent bias called "white-coat compliance" (Feinstein, 1990). This phenomenon occurs in patients whose adherence is poor most of the time, but shifts suddenly to correctness during the day or two prior to a scheduled visit to the physician or other caregivers. With 1–2 days of correct dosing having preceded the sampling of drug concentration, the measured value of drug concentration will, with the vast majority of conventionally formulated drugs, reflect drug intake for only 1–2 days. What happened before that brief period of time, or what happens afterwards, is unknown. The source of these numbers is pharmacokinetic theory, which teaches that measured drug concentration in plasma at a given time will reflect drug intake during a period of prior time equal to three to four times the drug's plasma half-life. It turns out that 87% of the several hundred most commonly used drugs have plasma half-lives of 12 h or less (Benet *et al.*, 1995). Thus, the measurement of drug concentration in plasma, as done in the usual way, with blood sampling done at the time of a scheduled visit, will, in most instances, reflect drug intake only during the period of white-coat compliance. If a measured drug concentration is zero, it signifies that no drug was taken during four prior half-lives, i.e. 2 days or less for the vast majority of drugs.

## PILL COUNTS

With dosage form counts (“pill counts”), many patients can and do discard untaken dosage forms before returning the drug package to the clinical staff – a problem clearly identified in two studies reported about 15 years ago (Pullar *et al.*, 1989; Rudd *et al.*, 1989). Since then, numerous studies have compared electronically compiled dosing histories with results of pill counts, with uniform demonstration of exaggerated results with pill counts (Urquhart, 1997; Blaschke *et al.*, 2012). Yet, to their shame, clinical researchers continue to perform counts of returned, untaken dosage forms, and solemnly report the results as if the method had not been thoroughly discredited, except in the infrequent instance when a patient returns all dispensed medicine untaken.

## HOW PILL COUNTS ARE (MIS)INTERPRETED

The usual result of pill-count data is that somewhere in the low 90% range of trial patients were satisfactorily compliant. “Satisfactorily” usually means that the patient has returned few enough dosage forms to support the conclusion that >80% of prescribed doses were taken. This almost universally applied, “>80% is OK” criterion has no roots in pharmacological science, and is supported only by uncritical repetition, having started in the 1970s as a self-evident guess (Sackett and Haynes, 1976). Yet, as already noted, such information is not only drug specific but product specific.

The inherently unscientific folly of universally applying the “80% is OK” criterion is revealed by the well-documented fact that the pharmaceutical products with which there is the greatest user-experience of all can fail to act even when all prescribed doses are taken, but are mistimed. The products in question are the low-dose, combined estrogen–progestin, oral contraceptives. As the UK labeling (Guillebaud, 1987) indicates, being more than 12 h late in taking the once-daily “pill” already increases the risk of breakthrough ovulation and conception during the part of the monthly cycle in which ovulation is most likely. Thus, a patient who routinely takes a daily “pill,” but wobbles in dose taking between doing so at the usual 7 a.m. or,

exceptionally, at bedtime, creates intervals between doses that exceed 36 h, which would appear to be the mean point at which the risk of breakthrough ovulation starts to rise. (Note that the 36 h mean implies that half the patients can be expected to have an even shorter margin for dose-timing error than 36 h.) Clearly, then, in the case of these most widely used products, the “80% is OK” criterion, which means missing one dose in five, and thus a series of 48 h or longer intervals between doses would allow many instances of breakthrough ovulation and correspondingly high likelihood of unwanted conception.

Thus, another factor having a major bearing on the question of “How much adherence is enough?” is the degree of “forgiveness” that each pharmaceutical product provides. At one extreme of forgiveness is bendrofluthiazide, a thiazide diuretic widely used in the treatment of hypertension in the UK, and which has a once-daily dosing regimen, though it is able to maintain antihypertensive action for over 6 days after a missed dose (Girvin and Johnston, 2004). At the other extreme of forgiveness are, as just discussed, the low-dose, combined estrogen–progestin oral contraceptives, with their minuscule average of 12 h of safety margin beyond the recommended 24 h interval between once-daily doses. In the latter instance, one can have product failure simply from errors in dose timing, even though 100% of prescribed doses had been taken. In the former instance, one should be able to omit several sequential daily doses and still have continuity of antihypertensive action.

## ELECTRONIC MEDICATION EVENT MONITORING

The technological advance that has lifted the topic of patient adherence out of its longstanding methodological morass has been the microelectronic revolution, which opened the door to the possibility of objectively compiling ambulatory patients’ drug dosing histories through the integration of time-stamping/data storing microcircuitry into standard pharmaceutical packages. The first commercially available electronically monitored drug package, the MEMS® Monitor, appeared in the scientific

products marketplace in 1988. This product inferentially compiled drug intake by detecting, timestamping, and storing times and dates of successive entries into the package in which prescribed drug is dispensed. Of course, the time of entry into a drug package is an indirect, or surrogate, measure of drug actually taken. This surrogate measure has been validated by demonstrating close correspondence between directly measured concentrations of drug in plasma at specific times, and, based on electronically compiled package-entry times, the pharmacokinetically projected concentration of drug in plasma at the same times (Vrijens *et al.*, 2005).

Electronic monitoring has been in use between 1989 and the present (2012), giving rise to over 600 peer-reviewed, published studies in which electronically monitored drug dosing times were used as a measure of drug intake. These studies provide a diverse array of demonstrations of the essential practicality of using the MEMS Monitors in clinical investigation, together with the often-surprising departures of reality from conventional assumptions about drug exposure in various treatment and research situations involving ambulatory patients.

It is also noteworthy that the vast majority of these studies were conceived, performed, analyzed, and reported by investigators whose only involvement with the manufacturer of MEMS Monitors was their purchase of the monitors and receipt of customer service advice re details of product use.

Many commentators or reviewers of the field of patient adherence have described the MEMS Monitors as “expensive,” leaving it to the reader to infer: (a) the costs of the various pre-electronic techniques of compiling drug dosing histories in ambulatory patients and (b) the values of having reliable data on ambulatory patients’ drug dosing histories (Blaschke *et al.*, 2012).

## CASE STUDIES

The history of adherence/compliance research is fitful, because of inconsistent efforts in clinical research to gather pharmionic data and understand their clinical, economic, and, in the case of infec-

tious diseases, public health consequences. There are, in the history of this field, three landmark studies that deserve review. They provide a basis for looking ahead at what can now be done with, for the first time, sound methods for compiling and sensibly analyzing ambulatory patients’ dosing histories.

The three areas are: (a) TB treatment and the role of directly observed therapy; (b) oral contraception and the problems of widely used but rather unforgiving oral contraceptive products; (c) the prevention of acute rheumatic fever, now an almost forgotten but once major public health problem. These three case studies teach what are probably the most important lessons to learn about the clinical consequences of variable underdosing by ambulatory patients.

### CASE 1. POOR ADHERENCE IN TUBERCULOSIS TREATMENT: CONSEQUENCES AND COUNTERACTIONS

Patient adherence began to gain awareness in the early 1960s when anti-TB drug treatments were clearly failing because patients did not take the medicines properly, or at all. Several early attempts were made at that time to construct drug containers that could provide audible reminders, and/or compile a record of patients’ dosing, but these were one-off endeavors that never went beyond their developers’ hands.

In the mid 1980s, the problems associated with treating ambulatory TB patients with anti-TB drugs had reached a point that the combination of failed treatment and emergence of multidrug resistant (MDR) tubercle bacilli was about to unleash an untreatable, exceptionally virulent form of the disease into the general population. The problem of emergent drug resistance is mainly attributable to on-again/off-again dosing that allows the concentrations of anti-TB drugs to pass through a range of concentration within which drug levels are low enough to allow TB bacilli to resume replication, but high enough to exert selection pressure, so that drug-resistant strains of tubercle bacilli thrive where drug-sensitive strains do not. It is a curious bit of biology that while MDR tubercle bacilli are more virulent than the “wild” bacilli, the situation with the HIV is the opposite, in that the MDR HIV

is less virulent than the wild strains. Note, however, that "less virulent" does not mean "no virulence" or that drug-resistant HIV cannot infect or cannot lead to the full-blown acquired immunodeficiency syndrome (AIDS).

The New York City Department of Public Health and Mental Hygiene (NYCDPHMH) was particularly beset by these problems in their efforts to control TB, due to the coincidence, starting in the early 1980s, in increasing numbers of patients with both TB and AIDS, which weakens the body's defenses against other infectious diseases, including TB. In desperation, and with a limited budget, the staff of the NYCDPHMH looked for ways to deal with the looming crisis, and opted in the early 1990s to institute what is called "directly observed therapy" (DOT), in which patients with a confirmed diagnosis of TB were required, if necessary by force of law, to attend the TB clinic the specified number of times per week, usually three or four, at which times the clinic staff observed their taking of the requisite doses of anti-TB medicines (Weis *et al.*, 1994).

This maneuver required that individual administered doses of anti-TB drugs be considerably increased, compared with the standard several-times-daily doses that had been in long use. Fortunately, the margins of safety for most of the anti-TB drugs were sufficiently wide to permit the requisite, several-fold escalation in the size of individual doses given on a four times weekly basis instead of on a twice/thrice daily basis. The larger administered dose allows for longer-maintained concentrations of drug in plasma, but drives the post-dose peaks in concentrations higher by several-fold. The ability of the anti-TB drugs to be tolerated in the three to four times weekly dosing mode appears to be virtually unique to the field of TB. In contrast, it would be impossible, for example, to make a comparable escalation in administered doses of the present group of antiretroviral drugs used to treat patients infected with HIV. Nor could one give the usual once-daily doses of anti-retroviral drugs on only four different occasions each week and expect them to reduce the HIV count in plasma (usually referred to as the "viral load").

It is noteworthy, however, that, as experience with DOT grew, the doses of some of the drugs were reduced, so that, in the end, patients got less

drug than they would have received with full adherence to the conventional several-times-daily dosing regimens. The reduced dose requirements reflect a prevailing tendency to overestimate dosing requirements during premarket development of drugs, so that some pharmaceuticals enter the market with a recommended dosing regimen that calls for twice or more the dose or dose-frequency than is actually necessary for full effectiveness (Cross *et al.*, 2002; Heerdink *et al.*, 2002).

DOT has turned out to be a remarkably successful addition to the treatment of TB (Weis *et al.*, 1994); NYC Health, 2012; WHO, 2013). It has worked so well that it has been widely adopted, including by the World Health Organization (Urquhart, 1993). Of course, it is something of a "brute force" approach to the problem of assuring continuity of drug exposure in ambulatory patients, as they have to show up in clinic three or four times a week, to be seen to be taking their prescribed anti-TB medicines. As a recent bulletin on the present status of TB treatment from the NYCDPHMH put it: "The physician who decides not to place a patient on DOT assumes responsibility for ensuring adherence and completion. It is unwise to assume that patients will take medications on their own." Those words apply equally well to every instance in which a patient has the responsibility for initiating and executing a prescribed drug dosing regimen throughout the prescribed period of time in any chronic disease situation.

Note that the effectiveness of a DOT program depends not only on the medicines used, but also on the quality of management of the program, so that patients can receive their assigned treatments with minimal delay in an efficiently run clinic. The few published studies that report unsatisfactory results with DOT would appear implicitly to be confessing to poor management of the program.

Several noteworthy features of the DOT process, since its implementation began in the early 1990s, have been (a) a shorter course of treatment with anti-TB drugs, known as DOTS (for DOT-short course); (b) reduction in the number of clinic visits from four to two per week, with corresponding reductions in the weekly amounts of drug taken, resulting in some reduction in drug-related adverse effects. These changes have made the DOT process easier to manage, more convenient for patients, and

less expensive than the original DOT dosing regimen; these are, effects subsumed under the “learning curve” rubric. Moreover, these changes are another example of how recommended regimens for drug dosing can change over time, based on growing experience and careful observation of what does and does not work when deviations occur from the currently recommended dosing regimen.

The suggested citation for data in this case study is Urquhart (1993).

### CASE 2. ADHERENCE TO VERY UNFORGIVING ORAL CONTRACEPTIVE DOSING REGIMENS: CONSEQUENCES AND COUNTERACTIONS

The original oral contraceptive “pill,” the combination of an estrogen and a progestational steroid, was introduced in 1961. Adoption of this revolutionary means of contraception was very rapid, resulting in a high proportion of women, mostly in their first decade of reproductive life, using the “pill,” as patients quickly began to call it. Oral contraceptives were the first pharmaceuticals to be used on a long-term basis in normal humans; prior to 1961, pharmaceuticals were limited in their uses to short-term treatment of patients with some kind of pathological process underway.

In the late 1960s, an unexpectedly high incidence of strokes, myocardial infarctions, and sudden death began to be apparent among users of the contraceptive “pill.” These “thromboembolic phenomena” are extremely rare occurrences in premenopausal women, which facilitated recognition of their increased incidence among oral contraceptive users. After due consideration, the decision was made to reduce the estrogen dose by half. The anticipated result was realized, namely that the incidence of thromboembolic phenomena dropped to levels that at the time were not distinguishably different from women who did not use the oral contraceptive “pill.”

An unanticipated result of the dosage reduction, however, was a notable increase in the number of unwanted conceptions among women who were using the new, low-dose “pill,” compared with the prior experience with the original, high-dose “pill.” It was correctly hypothesized at the time that the low-dose, combined estrogen–progestin oral con-

traceptive “pill” was much less forgiving of delayed or omitted doses than was the original high-dose product. That hypothesis was confirmed during the 1980s by five studies in which controlled substitution of placebo “pills” for active “pills” was carried out in groups of women who had previously had tubal ligations so that they could not conceive, although they continue to ovulate. The key question was (Guillebaud, 1987): How long was it, after a last-taken active “pill,” before ovulation occurred?

During the 1980s, ovulation could not be visualized directly, as is now possible, but could be inferred from the occurrence of rise in progesterone concentrations in plasma and/or a preceding, sudden sharp rise in the concentration in plasma of the pituitary hormone, luteinizing hormone (LH). This rise in LH levels is referred to as the “ovulating surge” of LH.

The data from the placebo-substitution-for-active “pills” showed that the risk of ovulation begins to rise after about the 36th hour following a last-taken low-dose, oral contraceptive “pill.” This finding means that a patient whose usual dosing time is, for example, 7 a.m., and who, on a particular day misses the usual 7 a.m. dose, will begin to incur elevated risk of ovulation by 7 p.m. of the same day. It is possible, therefore, that “breakthrough” ovulation might have occurred in a patient who missed her usual 7 a.m. dose, but at 11 p.m. recognized that she had missed that morning’s dose, and then took the missed pill. Obviously, ovulation puts the patient on the pathway to conception. In this scenario, one can see how a patient can have taken 100% of the prescribed doses but still conceive; this scenario also shows how a simple error in dose timing can nullify the contraceptive action of the contraceptive “pill.” The notion is clearly wrong that taking 80% or more of prescribed, once-daily “pills” would constitute effective contraception.

The suggested reference for this case study is Guillebaud (1987).

### CASE 3. PREVENTION OF RECURRENT ACUTE RHEUMATIC FEVER

Toward the end of the 1950s, acute rheumatic fever was a leading public health problem, not only because of its case fatality rate, but also because

of both short-term and long-term consequences of cardiac valve disease, leading gradually to either or both valvular stenosis or insufficiency. The operative theory, then as now, is that acute streptococcal infections can, in some patients, trigger the onset of acute rheumatic fever, as an autoimmune phenomenon, without evident bacterial involvement. This sequence suggested a pathway to eliminating acute rheumatic fever and its malign sequellae: prophylactic administration of penicillin to prevent the streptococcal infections, thus blocking the basic sequence of events leading to acute rheumatic fever.

To study the effectiveness of this approach, Harrison Wood, Alvan Feinstein, and their colleagues designed and executed a 5-year, 431-patient trial, summarized in Urquhart, 1993, in which patients, who had previously had one episode of acute rheumatic fever, were randomized to one of three treatment groups: professionally administered, monthly depot penicillin injections, daily oral penicillin, or daily oral sulfadiazine. A placebo group was judged to be unethical. The randomization assured that all three groups had equal representation of any special, disease-modifying or drug response-modifying factors.

The results showed that the depot injections of penicillin uniformly prevented both recurrent streptococcal infections and acute rheumatic fever. In contrast, in the two oral medication groups, the unsatisfactory compliers (who numbered about half of each of the two oral medication groups) had high rates of recurrent streptococcal infections, and, even among the satisfactory compliers, the streptococcal infection rate, though low, was appreciably higher than in the recipients of the monthly depot injections. The logical interpretation is that strict continuity of penicillin exposure is not only capable of preventing recurrent streptococcal infections, but necessary to provide absolute protection against these infections. Strict continuity of penicillin exposure was unequivocally provided by the professionally administered, monthly depot injections of penicillin, but was not necessarily always strictly maintained by patients whose interview results indicated them to have complied well (but probably sometimes not perfectly) with the daily oral dosing regimens. Another conclusion was that acute streptococcal infection

could occur during brief gaps in treatment with either of the two oral dosing regimens. Given that the authors used an interview technique to ascertain how well the trial participants executed their respective drug dosing regimens, it is not surprising that they could only discern three different levels of compliance amongst the trial patients: consistently correct dosing, questionably correct, and definitely incorrect. In their final analysis, they combined the questionable patients with the definitely incorrect patients.

About 15 years ago, the late Alvan Feinstein and one of us (JU) discussed some of the background to the design and execution of this study. Feinstein related that, in searching for a method for assessing drug intake by the trial patients, they rejected the counting of returned, unused dosage forms because of the evident ease with which patients could create a fake record of good compliance by simply discarding all or most of the untaken dosage forms. What they selected, in the absence of anything better, was a monthly interview with each patient, plus summary review at 6-monthly intervals, always probing for inconsistencies.

A noteworthy result in this trial was the finding that poor compliers with oral sulfadiazine, even though they had high rates of streptococcal infections, nevertheless had very low rates of recurrent acute rheumatic fever, in sharp contrast to the poor compliers with oral penicillin, who had high rates of both streptococcal infection and recurrent acute rheumatic fever. This surprisingly large difference between the two agents has never been explained, in part because acute rheumatic fever almost completely disappeared in developed countries as both a public health problem and a subject of research within a few years after this study was reported. This finding, however, is probably the first demonstration of a forgiving drug, in that one could delay or omit many doses in an oral sulfadiazine regimen without loss of its ability to prevent recurrence of acute rheumatic fever.

In the aftermath of this study, Feinstein and his colleagues went on to try to find an oral regimen of penicillin administration that, when evidently well complied with, could provide effectiveness comparable to that of the monthly injections of depot penicillin. That work, summarized and reviewed in

Urquhart, 1993, never succeeded in reaching that goal. In retrospect, it seems logical to assume that the occasionally missed daily dose of oral penicillin, which would escape detection by the interview method, could open enough of a drug-free window to permit streptococcal infection and its sometime sequel of recurrent acute rheumatic fever to occur. Electronically compiled drug dosing histories should be able to resolve such uncertainties.

The suggested reference for this case study is Urquhart, 1993.

## LESSONS LEARNED

A first lesson is that continuity of exposure to most pharmaceutical products results in a substantially greater effectiveness, relative to what can be achieved in the setting of “usual” or “typical” care. The conventional statistical analysis of drug trials – known as “intention to treat analysis” – provides an all-patient average of drug effectiveness, which is diluted by prevalent underexposure or, in some instances, no exposure at all. This dilutional effect is particularly stark in oral contraceptive trials, where the conception rate is 0.1% per year among women whose use of the oral contraceptive is, to use the CDC’s term, “perfect,” and 5% per year – 50-fold higher – among women whom the CDC terms “typical” compliers. The conception rate in women who are seeking to conceive is about 80% per year, with most conceptions occurring within the first 3 months after the decision to seek to conceive. Presumably what happens in some of the “typical” compliers is that they have brief periods during which, because of dosing lapses, they are running somewhere near the 80% per year rate. It takes only a few conceptions in a contraceptive trial to raise the evident conception rate from its full-compliance value of 0.1% to some intermediate value, greater than 0.1% and less than 80%. That intermediate value, which appears to be about 5%, probably describes no one, as it is too high for those who use the “pill” punctually and far too low to be descriptive of the patients whose usage of the “pill” is so marginal as to allow them to run at or near the physiological conception rate of 80% in noncontracepting, sexually active women.

A second lesson is that unforgiving pharmaceuticals can provide full effectiveness only for the 15–20% of patients who are strictly punctual in their remedication.

A third lesson is that implants or depot injections, if properly designed and developed, can provide continuity of drug exposure throughout the interval between placement and replacement of the implant, or during the interval between successive depot injections. How much residual drug should be left in the implant at the scheduled time of replacement depends on how much forgiveness one should design into the implant and its replacement regimen. Analogous considerations apply to depot injections.

A fourth lesson is that “professionally administered” medicines – for example, replacement of a long-term implant or administration of a depot injection – are basically a form of DOT.

A fifth lesson is that DOT is labor intensive, the costs of which should be included in any comparison of the costs of case management by other modes and the reckoning of overall cost, including the cost of treatment failures, plus the costs created by events among patients who drop out of treatment before the recommended time. Some aspects – for example, the prospect of preventing versus not preventing community-wide spread of MDR TB bacilli – cannot be effectively costed.

A sixth lesson is the need to have reliable, quantitative pharmionic data so that it is clear what role underusage of prescription drugs plays in failed therapy, thus also clearly distinguishing failures of pharmacological origin from failures of pharmionic origin.

A seventh lesson is that it appears to be possible for certain patterns of on-off-on dosing to create hazardous rebound effects or recurrent first-dose effects.

An eighth lesson is the crucial role that erratic dosing appears to play in the emergence of drug resistance in the treatment of infectious and parasitic diseases. On a worldwide basis, this lesson is probably the most important of all because of the leading role that infectious diseases play in morbidity and mortality, measured on a worldwide basis, instead of just in the developed countries, where infectious diseases, though hardly eliminated, have

nevertheless been greatly curtailed, and in some cases virtually or completely eliminated (e.g., syphilis, acute rheumatic fever as a sequel to streptococcal infections, trachoma, malaria). Prevalent underuse creates conditions that nullify the effectiveness of anti-infective or antiparasitic drugs and opens the door to emergent drug-resistant microorganisms, leaving as the only alternative to unchecked disease the often uncertain odds of drug discovery and successful development into effective pharmaceutical products that pose acceptable risk. Here, the key word is "acceptable," because what is acceptable is conditioned upon therapeutic need and what is already available. Were we to have, for example, only one drug of dwindling effectiveness for the treatment of malaria or TB or typhoid, the magnitude of acceptable risk for a new agent would necessarily rise, because the alternative in each case is unchecked lethal disease. It is hardly a welcome outcome, but rather the best of a bad bargain.

## WHERE WE STAND TODAY

There has been a missing link in the biopharmaceutical sciences: the study of what ambulatory patients actually do with prescribed medicines – *pharmionics*. Thus, one can redefine the biopharmaceutical sciences as being comprised by the following three subdisciplines: (a) pharmacokinetics (what the patient's body does to the drug); (b) pharmacodynamics (what the drug does to the patient's body); and (c) pharmionics (what the patients do with the prescribed medicine). In presently available knowledge, pharmacokinetic information vastly exceeds pharmacodynamic information. Pharmionic information is in its infancy, but already points to critical gaps in pharmacodynamic information that need to be filled for efficient selection of recommended dosing regimens, for understanding of how common variations in drug dosing patterns may create adverse drug reactions, and for intervening efficiently to minimize efficacy- and safety-compromising errors in ambulatory patients' use of prescription drugs (Blaschke *et al.*, 2012).

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# Design and Implementation of Surveys to Assess Patient and Healthcare Provider Understanding of Risks and Safe Use Conditions

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## INTRODUCTION

Understanding the benefits and risks of new pharmaceutical products or indications is critical for regulatory agencies, because they must determine whether the overall benefits of a new product or indication outweigh the overall risks before approving. In some cases, sponsors may be required to conduct activities beyond routine pharmacovigilance activities to ensure safe use. In the USA, these additional activities are described in a risk evaluation and mitigation strategy (REMS), and in the EU they are described as risk minimization measures (RMMs) (US DHHS, 2009, 2011a,b; EMA, 2012a). Both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) require assessments of the effectiveness of REMS and RMMs (referred to as postapproval

safety studies (PASSs) in the EU), although specific requirements for assessments vary by country. A variety of study designs may be used to meet regulatory requirements for postapproval assessments, including drug utilization studies that examine prescribing behavior and patient characteristics, as well as assessments of provider and patient knowledge and awareness of potential risks and precautions associated with a specific medication (or class). Drug utilization studies may be conducted using a database or through prospective data collection. Knowledge and awareness studies require direct feedback from the target population.

When designed and conducted using sound survey methods, assessment surveys are a useful tool in the management and evaluation of the effectiveness of risk minimization activities. In response to the call for more rigorous designs for assessment

surveys (US DHHS, 2012) and to assist epidemiologists and drug safety researchers who may not have experience with survey development, the focus of this chapter will be on the design of cross-sectional surveys for patients, prescribers, or other healthcare providers to assess awareness and knowledge of key safety messages, and where appropriate, risk minimization activities. We present design and methodologic considerations for cross-sectional surveys, as well as provide guidance on applying sound survey methods to the assessment of physicians and patients with a focus on understanding and minimizing bias.

The objective of assessment surveys is to measure how well the stakeholder group (most frequently healthcare providers and patients) understands and abides by the key safety messages associated with the product, most often communicated through the provision of educational materials. For patients, the primary means by which they receive this information is the patient medication guide or patient alert card. For physicians, the means include brochures provided by sales representatives, continuing medical education, dear doctor letters, and materials associated with programs that include other elements to assure safe use (ETASU). Regardless of the manner in which these messages are communicated, the methods applied to the development of the survey instruments and methodology remain consistent.

For patients, the surveys are designed to evaluate the following:

- receipt and review of the patient communication (patient medication guide, patient alert cards);
- knowledge and understanding of the key safety messages;
- behaviors/actions to be taken in the event of potential adverse drug reaction.

For healthcare providers, the surveys are designed to evaluate the following:

- receipt and review of the communication materials (e.g., dear doctor letter, physician information);
- knowledge and understanding of the key safety messages;

- knowledge and understanding of the prescribing guidelines, indications, and special patient monitoring requirements (e.g., laboratory tests);
- behaviors/actions to be taken in the event of potential adverse drug reaction.

Several factors related to the evaluation of these objectives must be considered in a well-designed study. In the following sections we will address a few of the most important considerations:

- overall design;
- questionnaire development;
- sampling and recruitment;
- considerations for interpretation and reporting.

## OVERALL DESIGN CONSIDERATIONS

Before initiating an evaluation survey, the first step is to ensure that a survey is the best approach for answering the question. A well-designed survey with a representative sample of respondents may be an acceptable tool if it is necessary to collect information directly from individuals (patients, prescribers, or other healthcare providers), the desired information can be answered by the available respondents (i.e., knowledge, attitudes, awareness, behaviors associated with a particular drug), and it is not possible to survey the entire population.

In designing the survey, it is important to consider approaches that will minimize the bias that is often associated with voluntary observational surveys, which can impact the validity and generalizability of the results. Selection bias (Are respondents different from nonrespondents?), misclassification bias (Was respondent exposed to the drug of interest?), and information bias (Can respondent recall accurately?) can all be introduced in a voluntary survey. As we discuss each section, we will further describe the potential for bias and discuss methods for minimizing and/or assessing bias.

A well-designed survey starts with a clear description in the study protocol of the objectives and approach for implementation and analysis. The International Society for Pharmacovigilance and Risk Management has published guidelines for

developing protocols for epidemiologic, noninterventional studies (ISPE, 2007), and the EMA has provided a template that is required for all PASS studies (EMA, 2012b). At a minimum, the protocol should include the following:

- background;
- study objectives;
- study population;
- data collection (describes questionnaire development and testing);
- definitions for key outcomes or variables of interest, including any thresholds;
- sample size (projected sample size and statistical precision);
- data management;
- data analysis;
- limitations;
- adverse event and serious adverse event reporting;
- plan for quality assurance and quality control procedures for all phases of the study;
- plan for protection of human subjects.

## QUESTIONNAIRE DEVELOPMENT

Arguably, the most important aspect of designing a quality survey is to develop a well-structured questionnaire that provides information across a sample of individuals in a manner that produces reliable and valid measures.

Risk management survey data collection instruments are developed for the purpose of evaluating knowledge, understanding, and sometimes behaviors. Therefore, the effectiveness of these instruments depends not only on following the standards of sound survey design and implementation, but also should meet standard principles of test development. Standards published by the American Educational Research Association *et al.* (1999) identify best practices for test design, development, and revision. These standards are currently being updated, and the new standards will include a set for “operations” that mirror the current standards for test design and development (APA, 2011). The standards identify several steps in the process of

test construction. Mislevy and Knowles (2002) summarized the required steps as follows:

- identify primary purposes and scope for an assessment;
- develop test framework and test specifications;
- develop, test, and select items and scoring rubrics for the assessment;
- assemble an operational test and evaluate it in preparation for deployment.

According to these standards, test specifications should include item and response formats in addition to item content. Further, the standards specify that item and response formats and item content should be selected based on test purposes.

For patient surveys, the primary purpose often includes assessing the frequency of the following items in the relevant patient populations: (1) receipt and review of the required patient materials; (2) general knowledge of correct medication use; (3) knowledge of serious risks associated with the product; (4) awareness of actions to take in the event of adverse reaction to the product; and (5) appropriate use of a product.

For healthcare provider surveys, the primary purpose most often includes assessment of the following: (1) healthcare provider’s practices for distributing required patient materials; (2) healthcare provider’s access to and knowledge of any relevant prescriber or pharmacist guide and checklist materials; (3) healthcare provider’s familiarity with appropriate prescribing conditions; (4) healthcare provider’s understanding of ETASU; (5) healthcare provider’s knowledge of important risks, known safety issues, and adverse event reporting requirements.

Given these objectives, these questionnaires rely on respondents’ abilities to accurately recall specific autobiographical events (e.g., whether a patient received a medication guide at the time of their last prescription). In this case, researchers are attempting to collect not only dichotomous information about whether the stakeholder group received the information, but are also bounding it in a period of time. This period of time is particularly important. Depending on the program, educational materials may be required to be provided with only the

first prescription of a product or with each prescription filled. Further, if the medication is taken acutely or for a short period of time, the question must account for a different period of time than if the medication is taken chronically. Regardless, one of the founding principles of questionnaire design is to provide the respondent with a specific period of reference for which the researchers wish to collect the information. Specifically, there are several principles that research shows are most likely to influence recall (Cannell *et al.*, 1977 (as cited by Fowler (1995); Eisenhower *et al.*, 1991 (as cited by Fowler (1995)):

- the more recent the event, the more likely it is to be recalled;
- the greater the impact or current salience of the event, the more likely it is to be recalled;
- the more consistent an event was with the way the respondent thinks about things, the more likely it is to be recalled.

Receipt of a medication guide or patient alert card is unlikely to be salient or impose a significant impact on a respondent's daily life; thus, it may be more difficult to retrieve a memory of the event. Therefore, a shorter recall period will support the collection of more accurate data. For example, limiting the inclusion of respondents to those who have filled a prescription in an appropriately short period of time and focusing on whether they received a medication guide or alert card with their most recent prescription is likely to lead to more accurate memory recall and reporting than asking respondents who have not filled a prescription in more than a year. It is important to note that the salience of the event is likely to be influenced both by the severity of the disease/potential adverse

event, as well as the communication by the health-care provider. While this hypothesis has not been widely studied, a recent REMS evaluation study suggested that patients who were counseled by a healthcare provider were more likely to report receiving and reading the medication guide.

A number of strategies may be employed to stimulate recall of a particular event. First, the use of retrieval cues, such as a brief introduction to orient the respondent to the question, may improve reporting accuracy. For example, including a paragraph such as "This set of questions focuses on your experience with [product] and some written materials you may have received with your medicine. We are asking these questions to understand what information people are getting about their medications." This last sentence helps to avoid the possibility of overreporting based on the tendency to present oneself in a favorable light, by assuring respondents of the question's intent (Groves *et al.*, 2009). Another retrieval cue to further stimulate recall is to provide a small picture of the medication guide (or whatever material you are assessing) with the information being assessed by the study obscured.

In some cases, subjective information, which measures subjects' *attitudes* or judgment about a given topic, is desired. Subjective information is unique in the case of surveys measuring patient or physician knowledge and understanding of safety risks, because there are no right answers. The basic task for questions in this category is to place answers on a single, well-defined continuum, the most common of which includes such formats as agree/disagree and other Likert scale options (Figure 49.1).

For the purposes of assessment surveys, questions measuring a subjective state do not directly

<b>The medication guide for [product] is easy to read.</b>
<input type="checkbox"/> Strongly agree <input type="checkbox"/> Somewhat agree <input type="checkbox"/> Somewhat disagree <input type="checkbox"/> Strongly disagree

Figure 49.1 Example question.

meet the regulatory objectives of measuring stakeholder knowledge and behavior. However, such questions may provide an important indicator of causality of any deficiencies in knowledge levels.

Information must also be collected to measure subject's *knowledge* of the key safety messages outlined in the medication guide or other materials (depending on components of the REMS/RMP and the stakeholder group). Fowler (1995) reports that, in survey research, knowledge is generally measured in five ways:

- asking people to self-report what they know;
- true-false questions;
- multiple-choice questions;
- open-ended short-answer questions;
- vignettes.

As would be expected, research shows that knowledge of the key safety messages is dramatically higher among those who report receiving and reading the materials (Hollis *et al.*, 2011). That said, many factors may influence subject response to these questions. These questions are particularly tricky to construct, because if they are too easy the subjects may be able to guess the correct answer. If the questions are too difficult, then subjects may second guess their response, even if they know the correct answer. Medical terminology may also impact a subject's ability to answer correctly; terminology is much more of an issue with patients than with healthcare providers. In reading an item asking about the potential side effects of taking a product, if the subject cannot decipher the medical term or knows the product only by a common name, there is high potential for misreporting. Furthermore, if there is a long list of potential side effects or other knowledge questions, a subject may resort to "satisficing," a model proposed by Krosnik and Alwin (1987) to describe the tendency to understand a question just well enough to provide a reasonable answer without fully reading the question. In such cases, subjects may select the "I don't know" option for every question or choose the same answer for every question. In surveys evaluating patient and physician knowledge of safety messages, researchers ideally want to avoid asking open-ended or constructed-response questions. The

majority (if not all) of the questionnaire items should be closed ended, because the resulting data are easier to analyze and interpret (particularly with a large sample size), making closed-ended questions generally more efficient, cost effective, and conducive to statistical analyses. Likewise, constructed-response questions are significantly more burdensome to respondents to complete. However, if all the possible response options for a particular survey question cannot be listed, a closed-ended question with "other, specify" as a possible response option could be considered. Development of survey items should consider the possibility that open-ended questions could potentially increase the reporting of spontaneous reports of adverse events or adverse drug reactions. Although one does not want to discourage physicians or patients from reporting such events, evaluation surveys are not the ideal place to capture this kind of information.

True-false and multiple-choice questions thus remain as a common format for measuring respondent knowledge. These questions rely on subject recognition of the correct response rather than recall, as would be required in an open-ended format. Likewise, these questions depend heavily on constructing plausible wrong answers, which can be a challenging task in questionnaire development, particularly in the evaluation of stakeholder knowledge of the potential side effects of the drug. Recognition is easier than recall from a cognitive perspective (Fowler, 1995). However, from this perspective, the rate of correct responses is likely to be an overestimate of actual knowledge, because a random guess will produce the correct answer at least some of the time. An overestimate of actual knowledge is much more likely with true-false formats; but even with multiple-choice formats, researchers must take care to develop plausible choices that are discrete and unambiguous.

Because there are often multiple potential side effects associated with a given product, it may prove difficult to craft responses that are identifiable by the patient while remaining distinct enough from an actual side effect and not appearing too obviously incorrect. If, for example, a potential side effect is QT prolongation, one might want to avoid any incorrect responses associated with heart

<b>Select All that Apply</b>		<b>Forced Choice Format</b>																			
<p><i>Certain conditions may increase a patient's risk of developing pancreatitis (inflammation of the pancreas). Because of this risk, which of the following conditions should a patient tell their doctor about before taking [product]? Select all that apply.</i></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> A history of alcoholism</li> <li><input type="checkbox"/> Stones in the gallbladder (gallstones)</li> <li><input type="checkbox"/> High blood triglyceride levels</li> <li><input type="checkbox"/> Pancreatitis (inflammation of the pancreas)</li> <li><input type="checkbox"/> I don't know</li> </ul>		<p><i>Certain conditions may increase a patient's risk of developing pancreatitis (inflammation of the pancreas). Because of this risk, which of the following conditions should a patient tell their doctor about before taking [product]?</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 5px;">A history of alcoholism</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> I don't know</td> </tr> <tr> <td style="padding: 5px;">Stones in the gallbladder (gallstones)</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> I don't know</td> </tr> <tr> <td style="padding: 5px;">High blood triglyceride levels</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> I don't know</td> </tr> <tr> <td style="padding: 5px;">Pancreatitis (inflammation of the pancreas)</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> Yes</td> <td style="padding: 5px;"><input type="checkbox"/> I don't know</td> </tr> </table>				A history of alcoholism	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know	Stones in the gallbladder (gallstones)	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know	High blood triglyceride levels	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know	Pancreatitis (inflammation of the pancreas)	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know
A history of alcoholism	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know																		
Stones in the gallbladder (gallstones)	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know																		
High blood triglyceride levels	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know																		
Pancreatitis (inflammation of the pancreas)	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> I don't know																		

Figure 49.2 Example of forced-choice format versus select all that apply.

conditions, because patients may confuse the terms. Furthermore, using this same example, the term “QT prolongation” may not be familiar to many patients, so some description of the terminology is advisable; for example, QT prolongation (an irregularity in the heart’s rhythm).

Because the primary objective of these surveys is to measure knowledge of key safety messages, a common practice in survey development is to include an option for “I don’t know.” While including this option helps to minimize the chance that respondents randomly guess the correct answers, research indicates there is also a higher possibility that respondents will overuse this option when it is explicitly provided, even when they may truly know the answer (Schuman and Presser, 1996).

Another good practice in the development of multiple-choice questions in evaluation studies is to randomize or rotate the response order. Doing so is more practical when using an electronic format (e.g., Web or telephone administration) than when using a paper survey. There is strong evidence to suggest that response order significantly affects respondents’ answers (e.g., Malhotra, 2009).

The theory of primacy and recency effects suggests that respondents are more likely to choose the option presented first (primacy), particularly in cases where the question is presented visually (as in a Web-based survey), or to select more frequently the option presented last (recency), especially in

cases where the question is presented orally (e.g., telephone administration). This theory is a clear example of how the questionnaire design is influenced by the mode of administration. To minimize order effects, researchers may opt to randomize the order of response options or, when using scales, to rotate the order.

Forced-choice formats are also preferred over “select all that apply.” There is some evidence to suggest that order effects may be more predominant in select-all-that-apply questions, because respondents more frequently select the first options presented, whereas in forced-choice formats the respondents are required to answer each question individually. Our experience suggests that respondents also are more likely to choose “I don’t know” when asked to select all that apply than when they are provided an “I don’t know” option for each item. The example shown in Figure 49.2 illustrates this question design.

Vignettes may also be an effective means of evaluating knowledge, particularly for healthcare providers. Detailed questions are constructed to provide hypothetical scenarios that mirror situations the healthcare provider may encounter in actual practice, to evaluate their application of knowledge. These vignettes may be perceived as more authentic and assess more in-depth knowledge; however, they can be difficult to construct and administer, and there is a risk that the respondent

will focus on extraneous information. Table 49.1 summarizes advantages and disadvantages for different types of response formats.

It is important to consider the order in which questions are presented in the overall layout of the

questionnaire. Standard practice for assessment surveys is to move from general to more specific questions, asking the most important questions first and ending with demographics. Furthermore, given the nature of the knowledge questions, there

Table 49.1 Key advantages and disadvantages for alternative item and response formats.

General response format	Item type(s)	Advantages	Disadvantages
Selected response	True-false and multiple choice	<ul style="list-style-type: none"> <li>• Low burden to respondents</li> <li>• Easy to administer many items in relatively short time, allowing fuller sampling of content domain</li> <li>• Low dependency on high reading levels and well-developed writing skills</li> <li>• Relatively easy to develop scoring rubrics for response formats that include one correct response</li> <li>• Relatively easy to ensure consistent scoring</li> <li>• Relatively fast scoring; can be scored by machine</li> <li>• Minimal per-item costs for scoring</li> <li>• Generally easy to administer in a variety of modes, including telephone, mail, and Web survey modalities</li> <li>• Straightforward approaches for assessing differential item function</li> <li>• Relatively straightforward analysis and reporting</li> </ul>	<ul style="list-style-type: none"> <li>• Item development requires well-articulated measurement goals and skilled item writers</li> <li>• Viable false responses are a key factor affecting item difficulty</li> <li>• Clear question specifications required for appropriate foil development and selection</li> <li>• Weighted scoring rubrics can be difficult to develop when response formats include options that are partially correct</li> <li>• Difficult to assess higher order thinking skills, which may be important for surveying prescribers and/or pharmacists</li> <li>• Response selection prone to effects of guessing</li> </ul>
Constructed response	Short answer	<ul style="list-style-type: none"> <li>• With careful development, may be able to assess deeper respondent understanding</li> </ul>	<ul style="list-style-type: none"> <li>• Takes somewhat longer to answer, increasing burden and/or reducing number of items and breadth of construct sampled per unit of time</li> <li>• Respondents more likely to react to extraneous aspects of item or response task</li> <li>• Consistent scoring requires carefully developed and well-circumscribed scoring rubric (e.g., set of acceptable responses)</li> <li>• Resulting data are likely to be somewhat more difficult to analyze and report</li> </ul>

(Continued)

Table 49.1 (Continued)

General response format	Item type(s)	Advantages	Disadvantages
Constructed response	Extended response	<ul style="list-style-type: none"> <li>Particularly effective for assessing relatively deep understanding</li> </ul>	<ul style="list-style-type: none"> <li>Takes longer to administer and/or answer</li> <li>Relatively costly and slow scoring</li> <li>Effective scoring rubric requires effectively anticipating respondent answers</li> <li>Unanticipated scoring factors often require adjustments, retraining, and rescoreing</li> <li>Analytic scoring requires identifying key dimensions for scoring and developing scoring rubrics for each</li> <li>Holistic scoring requires identifying a single effective scoring rubric that is effective across possible item dimensions</li> <li>Reliable and valid scoring requires detailed scoring rubric, careful training, monitoring, and retraining as needed</li> <li>Respondents may react to extraneous aspects of item or response task</li> <li>Generalizability susceptible to person-by-task interaction</li> <li>Relatively difficult to assess differential item functioning</li> <li>Depending on scoring approaches, data may be particularly difficult or time-consuming to analyze and report</li> </ul>
Vignettes		<ul style="list-style-type: none"> <li>Versatile: can be used with variety of response formats, depending on measure models and measurement goals</li> <li>Face validity: typically perceived as more authentic</li> </ul>	<ul style="list-style-type: none"> <li>Relatively difficult to administer as part of a telephone survey</li> <li>Dependent on reading level when administered in written format</li> <li>Development requires detailed item specifications that (1) maps vignette details to components of correct response and (2) ensures item developers avoid including misleading or superfluous information</li> <li>Respondents may react to extraneous aspects of item or response task</li> <li>Requires sufficient pretesting to avoid differential item function across cultural and sociodemographic groups</li> </ul>

Modified from Andrews *et al.* (2012).

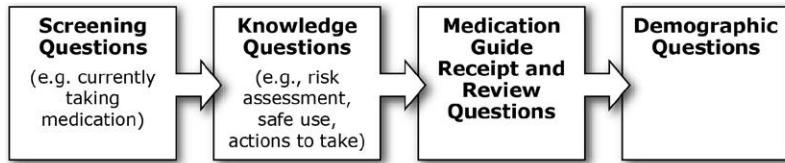


Figure 49.3 Question ordering.

is some risk that respondents may learn as they progress through the questionnaire; therefore, it is not advisable (at least with electronic modes of administration) to allow respondents to return to previous questions. Of course, this rule is not enforceable with paper surveys, even though researchers may provide this guidance to respondents. We suggest the question order shown in Figure 49.3.

#### MODE OF ADMINISTRATION

Finally, the mode (or modes) of administration must be determined during the questionnaire development process, because it will have a significant impact on how the questionnaire is designed. For example, a Web-based format may help minimize response error (i.e., edit checks are programmed) and allow for the use of images or more lengthy questions or response categories, but this format may also limit accessibility (and therefore representation) to those with Internet access. By comparison, a paper-and-pencil questionnaire must be designed for ease of use with clear instructions for completion. If self-administration is not appropriate, telephone or in-person interviews may be used. However, these modes may also inadvertently influence participants' responses. If one is developing a telephone-administered questionnaire, consideration must be given to providing short questions and concise response categories, because respondents are unable able to read (and reread) the question presented to them. Often, a mixed-mode approach is desirable to provide respondents with the most flexibility. However, care must be taken to ensure comparisons are made between modes to identify any issues or differences in response. In summary, mode of administration is a critical design com-

ponent that must be carefully considered. Groves *et al.* (2009) provide a good discussion of the effects of different methods on survey error and describe the implications of mode selection to include sampling frame, coverage, nonresponse, measurement quality, and cost. Additionally, Flanigan *et al.* (2008) summarize the literature on conducting survey research with physicians and other health-care providers and provide useful information about the effects of mode of administration on provider response to surveys.

#### COGNITIVE TESTING

Despite the care and proficiency devoted to questionnaire design, it is critical to pilot test the questions, response choices, and instructional text with the target population, to identify and eliminate potential sources of measurement error (Willis, 2005). The cognitive interview process is a rigorous qualitative research methodology developed in the 1980s to optimize survey instructions, question wording, response options, and questionnaire format through an evaluation of the cognitive process that respondents use to answer questions, including item comprehension, information retrieval, and response selection (Willis *et al.*, 1991; Schuman and Presser, 1996). Thus, conducting a cognitive pretest prior to survey implementation will optimize data quality and contribute to the success of any REMS/RMM assessment program.

Interviewers will ask participants to complete the questionnaire while thinking aloud or describing their thought processes as they answer each survey item. The interviews should be conducted using an interview guide. The interview guide should include probes designed to help interviewers understand how each participant interprets and chooses

their answers for each item in the survey. This procedure facilitates the identification of many types of potential problems, including confusing terminology, ill-defined concepts, and inadequate response options, and helps ensure that respondents understand the questions and answer them accurately. The pretest interviews also provide an opportunity to test procedures and introductory materials in an effort to increase participation and thoughtful consideration of the survey by respondents during study data collection.

Researchers who undertake field surveys without a cognitive pretest in the target population risk including poorly written questions. A poorly written or confusing question can lead respondents to select the wrong answer when they may really know the correct one, making data interpretation quite challenging. Interpretation should not only be consistent across respondents, but also should be consistent with the researcher's intentions for measurement (USDHHS, 2009).

Cognitive pretesting is typically conducted in two iterative rounds of six to eight respondents who generally represent the population of interest. Following the first round, changes may be made to the instrument based on feedback from the initial set of respondents. The second round is used to test those changes. If no additional issues are identified, the researcher may be satisfied that the intended audience for the instrument interprets the questions consistently.

#### **RECAP OF GOOD QUESTIONNAIRE DEVELOPMENT PRACTICES**

- Rely on closed-ended, selected response formats as often as feasible given measurement goals.
- Avoid select-all-that-apply question structures.
- Keep language simple and provide descriptions for medical terminology that may be unfamiliar to the respondent population.
- Use simple sentence structure.
- Present questions using concrete, unambiguous language.
- Limit recall period.
- Minimize the burden to the respondent by keeping the instrument short and using constructed-response formats judiciously.

- Pay attention to the question order to ensure that the general or the most important questions are asked first.
- Use cognitive testing methods throughout questionnaire development, to ensure that wordings are interpreted as intended and also understood consistently across respondents

#### **SAMPLING AND RECRUITMENT**

While it is important to ensure that the questionnaire measures the relevant constructs required to meet the study objectives (in this case, knowledge of key safety information) in a reliable and consistent way, it is equally important to ensure that the questionnaire is administered to a sample that allows inferences to be made about the target population. This is no small order, and it is reasonable to assume that unless all members of the target population are surveyed, researchers can expect to fall short of the goal due to selection bias. Even in some programs where the entire prescribed population is accounted for (e.g., restricted distribution programs with mandatory registries), it is generally not efficient to attempt to survey the entire population, nor is it likely to achieve 100% response. Therefore, this section's objective is to discuss key considerations for the identification and sampling of a population in an effort to reduce the impact of coverage and sampling bias on study results.

As with any voluntary survey, nonresponse bias is a concern. With the advent of the Internet, potential respondents (both patients and physicians) are overloaded with requests to complete surveys for various reasons. It is becoming increasingly hard to minimize nonresponse bias, especially among physicians who are often sent multiple requests to complete REMS/RMM assessment surveys, often for medications in the same drug class. One approach to minimize nonresponse bias is to offer a reasonable incentive for respondents that compensates them for their time spent but is not considered coercive. Other approaches include reminder letters, emails, or calls to nonrespondents; however, owing to the time constraints for REMS/RMM assessments, it is not always feasible to employ these methods.

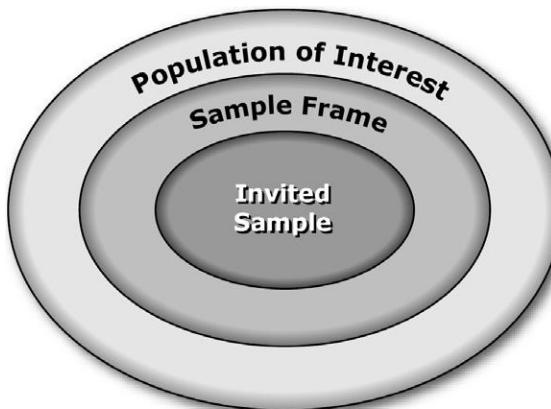


Figure 49.4 Sample selection.

Figure 49.4 illustrates the process by which respondents are identified and selected for participation in a survey.

### POPULATION OF INTEREST

The target population or population of interest is the group (of individuals) about whom the survey investigator wants to make inferences by using the sample statistics (Groves *et al.*, 2009). In the case of assessment surveys, the target populations are most often prescribing physicians and patients receiving the medication of interest. For example, a target population may be defined as adults who are prescribed (product) for the treatment of type 1 diabetes. While it appears to be a simple exercise to identify the population, it is important to ensure that the definition is as broad as reasonable to ensure the inclusion of as many individuals exposed to treatment as possible. For example, if a significant proportion of the treated population is under the age of 18 years, then, despite the additional provisions required for research with minors, researchers should remove or lower the age provision.

### SAMPLING FRAME

Once the target population has been identified, researchers must define the sampling frame that will be used for the study. The sampling frame is

the resource(s) used to identify individuals in the target population and is the mechanism by which they are identified and recruited. It is important to first consider the characteristics of the target population, because these may impact a researcher's ability to define and measure knowledge in the group.

In the case of patient populations, consider the following questions:

- Are the patients limited by their condition or other characteristics (e.g., would they be prevented from participating in the study)?
- Is the condition rare or the market share of the medication small?
- What are the time restrictions (e.g., are they taking the medication for a chronic condition, acutely, or as needed)?
- Where do patients receive their medication and medication guide/alert card (e.g., retail pharmacy or infusion center)?

In the case of physician populations, consider the following questions:

- What specialties prescribe the medication?
- Is there a restricted distribution program or physician communication plan that may impact the number of physicians prescribing or how they prescribe?
- Are there treatment guidelines that may impact how and when physicians prescribe?

In the case of an ETASU with a mandatory registry, the sampling frame is very straightforward and ensures coverage of the target population, as is the case with the TOUCH prescriber program for Tysabri (FDA, 2012). However, this is rarely the case, and so researchers must determine an appropriate frame from which to select the sample. Careful selection of the sampling frame is essential in minimizing the potential for bias; however, there are numerous options from which to choose.

The sampling frame for patients may be identified through many avenues but must be selected with the representation of the source in mind. For example, patients may be identified through prescribing physicians, pharmacy databases, product

support initiatives, consumer panels, and ETASU registries, to name a few. The degree to which the sample frame is representative varies by the source. Each sampling frame provides varying levels of representation of the target population in a given program. For example, the frame may be defined as retail pharmacy records in a given network. In this case, while the full patient population may not be included, if there is appropriate distribution of pharmacies across regions and patient groups (e.g., private insurance versus Medicare), then this frame may be as representative as is feasible for the target population. Some researchers have opted to (or been required to) include several frames to ensure coverage of the target population (e.g., using a consumer Web panel and physician records). However, as a word of caution, just because multiple frames are used, this does not necessarily translate to better representation of the target population. There may be one frame that is more representative than all the others combined.

One might think that prescribing physicians would be more easily identified. There are numerous comprehensive lists of physicians publicly available, as well as any number of physician panels maintained by market research companies. Likewise, sponsors have ready access to prescriber lists from their sales force. Such lists, however, may be unduly slanted to high prescribers, or they may underrepresent physicians outside a particular prescribing program. Physicians are often wary of participating in survey research, particularly when it is perceived as market research. These fears may be exacerbated by regulations such as the Physician Compensation Sunshine Act, which requires disclosure of physician compensation for research activities to tax authorities. These considerations likely have an impact on physician response rates and, as a result, may influence how well a particular sampling frame represents the prescribing population.

It is often extremely difficult to determine preemptively the ideal frame or the degree of undercoverage associated with the choice of a given frame. Researchers need to factor in not only the representation of a selected sampling frame, but also other considerations that may affect the reliability of study results. Researchers should consider the following questions when selecting the frame:

*Does the selected frame have the potential to overrepresent or underrepresent a significant portion of the target population?* For example, if a sponsor-provided product support group is used to select patients taking a product, it is likely that the patients using the resource are receiving additional education or are more engaged in their treatment and, therefore, may not represent the overall target population with respect to awareness of key safety information.

*Does the selected frame have the potential to influence the study results?* For example, if physicians are used to identify and recruit patients for the survey, there is a good chance that they may change their educational practices, and patients in that frame would receive more education than they would have otherwise.

*Does the selected frame ensure coverage of eligible participants?* For example, a consumer panel may rely on self-reported diagnosis and treatment rather than confirming eligibility through a pharmacy or physician.

## SAMPLE SELECTION

The next step is to ensure a systematic selection of individuals for inclusion in the survey. Ideally, a random selection will be employed to ensure that each unit in the sampling frame has an equal probability of being selected and to minimize the potential for sampling bias. However, this can be enormously expensive, unless using a large database or panel for recruitment (e.g., consumer panel). In practice, cluster sampling is often employed. For example, if patients are identified and recruited through physician offices, a diverse selection of sites (or clusters) will be selected to provide geographic coverage and to ensure representation of various clinic characteristics. Within these clusters, patients may be selected randomly or systematically (to avoid cherry picking).

There is often the need to ensure that subgroups in the population are included in the sample. Quotas may be established if subgroups are identified that must be accounted for in the final sample. This is particularly important in prescriber samples as there can be significant variability across prescribing specialties and patient volume. Quotas may be

Table 49.2 Expected 95% confidence limits.

Sample size	Level of awareness/ understanding (%)	Lower 95% confidence limit (%)	Upper 95% confidence limit (%)
200	80	74.0	85.1
200	85	79.5	89.5
300	80	75.2	84.2
300	85	80.6	88.7
400	80	75.9	83.7
400	85	81.2	88.3

established to reflect the distribution of specialities based on prescribing patterns. Some researchers suggest that sampling be distributed by prescribing deciles, which attempts to include in the sample a larger proportion of higher prescribers than lower prescribers, to reflect the comparatively larger impact of patient exposure among the high prescribers. There are numerous strategies described in the literature that may be used to pursue a sample selection that best reflects prescribing practices and patient characteristics. Researchers need to account for the characteristics of the target population and the selected sample frame when determining the most appropriate strategy to employ.

## CONSIDERATIONS FOR ANALYSIS AND INTERPRETATION

### SAMPLE SIZE

Determining the appropriate sample size in evaluation surveys may be difficult, because there usually is not a clear hypothesis to be tested. Typically, sample size estimates are based on the level of precision desired to demonstrate awareness of a key message. For example, if the primary outcome measure is knowledge rate, defined as percentage of respondents answering a single question correctly, then the expected true knowledge is 85% and the minimum acceptable width of the 95% confidence interval is 10 percentage points, then one would need a sample size of 200. However, if subgroup analyses are anticipated, or if expected knowledge levels are likely to be lower (e.g., 50–60%), larger sample sizes may be necessary. Alternatively, if

the population is difficult to access, there may be logistical justifications for proposing a lower sample size.

Table 49.2 shows the expected 95% confidence limits assuming various combinations of sample size and level of awareness.

### NONRESPONDER ANALYSIS

As described by Andrews *et al.* (2012), nonresponse bias is a particular concern in risk minimization assessment surveys, because it is possible that study respondents and nonrespondents may differ in important ways, including medication compliance and awareness of risks. Although availability of data on this topic is often restricted, it is important to design assessment surveys of patients and health-care providers in a way that minimizes selection bias in the sample used and allows some comparison of the characteristics of respondents to nonrespondents and to the target population of the REMS.

To determine whether the applied recruitment strategies are successful at enrolling populations of respondents who reflect the target population, studies should compare characteristics of responders and nonresponders to determine if there are any differences that would influence the validity and generalizability of the study results. The level of detail available for comparing responders and nonresponders will depend on the availability of and access to individual-level data and the specific data fields available in the source database. For example, in studies where patients are identified through a pharmacy network, it is possible to compare a limited number of characteristics for respondents

and nonrespondents, including state of residence, age or age category, sex, and type of health insurance. Data on socioeconomic status and level of education would be helpful but are often difficult to access. Other data sources (e.g., programs for medications that require all patients to be registered) may provide data on a large number of variables.

Other useful analyses to evaluate responder bias include the following:

- comparison of the age and sex distribution of respondents with the expected age and sex distribution of the target population;
- review of the percentage of participants who complete the required assessment by mode of data collection, if multiple modes of data collection are employed.

## WEIGHTING

Different weighting strategies may also be employed to account for the potential biases associated with sample selection and response. For example, it may be desired to oversample minorities for certain patient surveys. In this case, it may be desirable to weight the responses to account for this oversampling (“weighting for probabilities of selection”). In addition, if there is observed nonresponse in certain subgroups in the sample, it may be desirable to apply a nonresponse adjustment to the final analysis. Other types of weighting that may be considered for these surveys are poststratification weights, which use information from the full study population to potentially improve the accuracy and precision of the results (Heeringa *et al.*, 2010). Owing to the variety of weighting techniques, it is important to engage a statistician or other trained researcher with background in this technique to ensure that the benefits of weighting outweigh the potential risks, including additional bias or increased variation and more complicated analytical techniques.

## THRESHOLDS AND SCORING QUESTIONNAIRES

Particularly with respect to US REMS programs, there has been much discussion around the topic of

gauging the success of a risk minimization educational goal, with particular focus on the issue of setting thresholds for rates of knowledge, either as a standard across risk minimization programs or specific to each assessment program.

Many evaluation programs have established pre-specified thresholds; however, there are inherent problems with establishing thresholds *a priori* and with applying the same threshold across all programs. First, thresholds may be arbitrarily set, not based on evidence of the minimum knowledge necessary to minimize a product's risk. Further, knowledge may be high among a particular subgroup for whom the medication risk is most relevant, while overall knowledge rates may fail to meet the threshold. For example, in a recent REMS assessment survey, researchers found that the sample population overall had relatively low awareness about a particular risk, but when they explored knowledge among a subgroup for whom the risk was most relevant, knowledge levels were higher. The overall program may have failed to achieve a threshold had one been set *a priori*, when in fact those who were most at risk were knowledgeable about that risk.

Likewise, results from assessment surveys vary significantly across programs and can be influenced by many factors, including severity of disease, severity of potential risks, physical or cognitive impairments of study participants, relevance of medication risk to particular subgroups, time the medication of interest has been on the market, length of time a participant has been on treatment (e.g., new users), counseling by a healthcare provider, and involvement in an REMS program that includes ETASU. In many cases, there are multiple risks associated with a particular drug. Therefore, consideration should be given to whether the threshold should be set on knowledge of only the primary risk or include other important risks as well and whether secondary outcomes should have the same threshold as the primary outcome. Furthermore, consideration should be given to whether knowledge of risk(s) is sufficient or whether thresholds also should be set for awareness of signs and symptoms of potential adverse reactions.

Challenges to the determination of success may be encountered if a clear standard is not established. However, it may be preferable to estimate

and provide justification for selected thresholds in study protocols or to simply analyze and report results at an item level and across relevant strata in some context around the potential root cause of lower awareness. For instance, if older men show lower awareness of risks to pregnant women, it may be simply because the risk is not relevant to them.

Finally, knowledge rate is a measure of only one aspect of a risk minimization strategy. It is possible that a program is adequately minimizing risk through intervention by a physician or other health-care provider, despite poor awareness among patients. The results of awareness surveys should be evaluated in the context of the success of the overall risk minimization program.

## DISCUSSION

It is worth noting that, even under the best of circumstances, the objective of these surveys is only to measure knowledge and behaviors (and, in some cases, attitudes) relating to the information intended to communicate key safety messages. Therefore, even if the surveys are well designed and reflect the target population's knowledge and behaviors, this still does not provide a means to evaluate the associated impact on patient safety outcomes. The quality of data from a survey depends on the size and representativeness of the sample from which data are collected, the techniques used for collecting data, the quality of interviewing and/or questionnaires, and the extent to which the questions are good measures (Fowler, 1995). The methods outlined in this chapter support the development of sound survey programs to evaluate patient and prescriber knowledge of key safety messages. Good references in this chapter (e.g., Fowler, 1995; Groves *et al.*, 2009; US DHHS, 2012) provide additional in-depth guidance of survey research methodologies.

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Part VI

**TRAINING AND EDUCATION AND DIRECTIONS**



# Eu2P: The First European Online Public–Private Joint Training Program in Pharmacovigilance and Pharmacoepidemiology<sup>1</sup>

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## INTRODUCTION

The faster discovery and development of better and safer medicines for patients is a European priority (Kneller, 2010; Goldman, 2012a). Over the last 10 years, pharmacovigilance practices and post-licensing evaluation of medicines has evolved towards a more proactive approach leading to the emergence of new job profiles, such as project managers, pharmacoepidemiological coordinators,

risk–benefit analysts, and people able to interfere with statisticians and clinicians. Alongside the need for skilled persons trained in risk–benefit assessment, risk management plan elaboration, risk minimization, and risk communication have been highlighted by industry, regulatory and academic bodies. In Europe, high-quality postgraduate courses in pharmaceutical medicine in the UK, Spain, Sweden, Netherlands, France, and Italy's universities and higher education institutions delivering the various disciplines of medicines research and development do exist. However, the current organization of European postgraduate training

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<sup>1</sup>Written on behalf of the Eu2P consortium.

facilitates the building of silos, where each scientific area lives its own life without much interaction with other areas. This is contributing to the fragmentation of European education and research. As a result, Europe has many high-quality universities and higher education institutions, but individually these are too small and in many cases are locally, not European, focused.

In 2008, the European Commission associated with the European Federation of Pharmaceutical Industries and Associations (EFPIA) have created the Innovative Medicines Initiative Joint Undertaking (IMI JU) and launched a first call in which an Education & Training project in pharmacovigilance and pharmacoepidemiology was proposed (Goldman, 2011, 2012b; see also [www.imi-europa.eu](http://www.imi-europa.eu)). One rule of this call was to build a public–private consortium gathering European reputed universities, regulatory institutions, patients associations, and pharmaceutical companies. For the first time, big companies were officially invited to collaborate with universities and regulators, to share their knowledge and expertise. An initial European public consortium led by the University of Bordeaux answered this call by submitting the project Eu2P in July 2008. Ranked first by the international experts panel appointed by IMI JU among the whole call applicants, the Eu2P public consortium was enlarged by 15 pharmaceutical companies from EFPIA at the end of 2008 in order to submit an extended public–private proposal at the beginning of 2009. The public–private Eu2P Consortium was then again ranked first by the same international experts panel and funded by IMI JU in September 2009 for a period of 5 years to develop and implement the successful proposal. This Eu2P proposal objective was to build the first European public–private education and training initiative to improve the understanding of benefit and risk of medicines at the international level. This proposal has been developed by the Eu2P Consortium, constituted of seven reputed European universities, the European and French Medicines Agencies, and 15 pharmaceutical companies (see Table 50.1). The University of Bordeaux is the academic coordinating institution for the Eu2P program, and Roche is the industry coordinator.

Table 50.1 Description of the Eu2P Consortium partners.

Eu2P partners type	Eu2P partner's name
Eu2P academic partners	Université de Bordeaux France Erasmus Universitair Medisch Centrum, Netherlands Fundació Institut Català de Farmacologia, Universitat Autònoma de Barcelona, Spain University of Hertfordshire, UK Università di Verona, Italy Utrecht Universiteit, Netherlands Karolinska Institutet, Sweden European Medicines Agency, UK
Eu2P regulatory partners	Agence française de sécurité sanitaire des produits de santé, France
Eu2P private partners	Amgen NV AstraZeneca AB Bayer Schering Pharma AG Boehringer Ingelheim International GmbH Eli Lilly and Company Limited GlaxoSmithKline Research and Development Ltd F. Hoffmann-La Roche AG H. Lundbeck A/S Janssen Pharmaceutica NV Laboratorios Almirall SA Novartis Pharma AG Novo Nordisk A/S Orion Corporation Sanofi-aventis Recherche et Développement UCB Pharma SA

## THE Eu2P CONSORTIUM EXPERTISE

This Eu2P Consortium brings together academic and industry knowledge experts, experienced in developing and delivering training programs and courses in the fields of pharmacovigilance and pharmacoepidemiology. Eu2P provides the unique opportunity to consolidate this expertise into a pan-European accredited program of education in pharmacovigilance and pharmacoepidemiology,

designed to satisfy the needs of industry, academia, and regulators and enhanced by the development of innovative new courses.

In France, the Department of Pharmacology of the University of Bordeaux includes a clinical pharmacology unit, a regional pharmacovigilance center, and a pharmacoepidemiology unit, and conducts large field studies of medicines utilization, safety, and performance, the results of which contribute to recommendations for optimizing benefits and minimizing risks of medicines. In Spain, the Fundació Institut Català de Farmacologia (FICF – Catalan Institute of Pharmacology) of the Autonomous University of Barcelona has major research activities in pharmacoepidemiology and pharmacovigilance and specifically case-control studies, case-population studies, voluntary reporting systems, medicines utilization studies, meta-analysis, and benefit-risk evaluation and is one of the World Health Organization's (WHO's) collaborating centers for research and training in pharmacoepidemiology. In UK, the University of Hertfordshire currently offers a part-time postgraduate program in pharmacovigilance with awards of master's and postgraduate diplomas developed with the support of the Pharmaceutical Information and Pharmacovigilance Association, the professional organization for individuals in the pharmaceutical industry involved in the provision and management of information; this program is recognized as being of particular importance to the training of professionals from both industry and regulatory agencies. In the Netherlands, the Netherlands Institute for Health Sciences (NIHES) of the Erasmus University Medical Centre is an international center for postgraduate research and training in the disciplines of epidemiology, clinical epidemiology, health services research, public health, and medical informatics, which prepares people for international careers as investigators, executives, or advisors in clinical medicine, medicines research, public health, or health policy development. The Utrecht Institute for Pharmaceutical Sciences of Utrecht University is one of the leading international academic groups on the interface between pharmacoepidemiology, pharmacovigilance, and medicines innovation, and an acknowledged WHO collaborating center of phar-

macoepidemiology and pharmaceutical policy. This group has close links to regulatory agencies such as the Dutch Drug Evaluation Board and the European Medicines Agency (EMA). In Italy, the University of Verona has extensive experience in discussing issues related to risk-benefit communication and strategies. In Sweden, the Karolinska Institute is a WHO collaborating center in medicines utilization studies and clinical pharmacological services with expertise in aggregate and population-based data; it includes one of the regional pharmacovigilance centers in Sweden providing real-life skills in benefit-risk assessments, with both a regulatory and public health focus applying medicines utilization data to adverse drug reactions reporting.

All the above European universities provide courses and postgraduate diplomas in the disciplines of epidemiology, clinical epidemiology, health services research, public health, medical informatics, medicines utilization studies, clinical pharmacological services, and risk-benefit communication and strategies. All these universities prepare people for a European and international career in the field of medicines research and development process in an individual and a disseminated manner, but also in their local language.

Most of the consortium members have expressed their interest in the EMA's European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) project, and have been involved in discussions regarding its development ([www.emea.europa.eu/](http://www.emea.europa.eu/)). The courses that are taught in these centers are identified on the International Society for Pharmacoepidemiology teaching resource list ([www.pharmacoepi.org/resources/educational\\_programs.cfm](http://www.pharmacoepi.org/resources/educational_programs.cfm)). These existing programs have proven capacity in training specialists in pharmacovigilance and who are then attractive recruits for academia, industry, and regulatory authorities.

The two regulatory authorities, the EMA and the French Agency for the Safety of Health Products (ANSM), coordinate pharmacovigilance activities respectively in Europe, in collaboration with national authorities, and within its territory, in France. The EMA brings its expertise within the regulatory aspect of pharmacovigilance, risk management, and

pharmacoepidemiology, and the ANSM's experience is in medicines risk communication.

The private pharmaceutical members of the consortium represent companies and individuals with a strong interest in high-quality pharmacovigilance and pharmacoepidemiology training and are all part of EFPIA. Individuals from these companies have established track records as lecturers and course organizers for recognized external programs and courses, and are recognized as experts in this field. Therefore, they have the potential to provide expertise in the different management and training tasks of the Eu2P program, such as the development and establishment of training programs, quality project management, as well as communication planning and program promotion.

## THE EU2P TARGETS AND TRAINING CURRICULUM

The public and private members of this consortium have put their strengths together to elaborate a training curriculum that meets the job market needs for healthcare professionals, students, and nonspecialists, but also the preoccupations of the stakeholders in charge of the post-licensing evaluation of the medicines. This curriculum is consistent with the professional core competencies reported by the International Society of Pharmacoepidemiology (Jones *et al.*, 2012).

The Eu2P Consortium initially focused on building online curricula and delivering related joint academic diplomas in the framework of the Bologna process, also complying with the standards of the European Association for Quality Assurance in Higher Education. The Eu2P curriculum offers comprehensive training with a range of qualification levels (certificate, master's, and PhD) in pharmacovigilance and pharmacoepidemiology recognized by academia, the pharmaceutical industry, and regulatory bodies across Europe. The Eu2P curriculum fits the need of certificate, master's, and PhD courses. It offers training in seven domains: basics for pharmacovigilance and pharmacoepidemiology; benefit assessment of medicines; medicines pharmacovigilance and regulatory aspects; medicines risk identification and quantification; medicines benefit–risk assessment; medicines and

public health; and medicines risk communication. These domains include 25 various course modules from introductory to advanced levels.

Each course module is accredited on the base of the European Credit Transfer and Accumulation System (ECTS). This system is a European academic standard for comparing the study attainment and performance of trainees of higher education across the European Union. For successfully completed training, ECTS credits are validated with the view to obtaining a qualification. In the Eu2P Consortium, one ECTS credit represents 25 h trainee's workload. A standard training module corresponds to three ECTS credits; that is, it runs over 9 weeks and corresponds to a trainee workload of 1 day a week followed by an examination.

Eu2P training has been developed to be adapted to the current ways of working of professionals (see Figure 50.1). Trainees are able to build their curriculum by choosing one or several modules leading to a certificate or master's degree. The Eu2P curriculum can be followed in a flexible way. First, the training can be modulated by choosing a part-time or full-time master's and by performing the master's research project at work. Second, the online training permits one to make the most of time-availability and to interact with the training team and trainees' network. It also allows trainees to attend the course from wherever they are and to learn and stay in their job.

The Eu2P program has been designed for health and life science specialists, such as pharmacists, physicians, and scientists, as well as for experienced pharmacovigilance professionals. It is also developed for non-healthcare specialists, such as media members, lawyers, and patients who want to understand medicine-related risk communication.

To know more about the Eu2P organization, training contents, diplomas, and modalities of applications, you are invited to visit the Eu2P website ([www.eu2p.org](http://www.eu2p.org)).

## ONLINE TRAINING DELIVERY IN EU2P: A JOB-TRAINING APPROACH

Eu2P courses are delivered in English using the Eu2P virtual learning environment, a unique and innovative modular approach integrating e-teaching

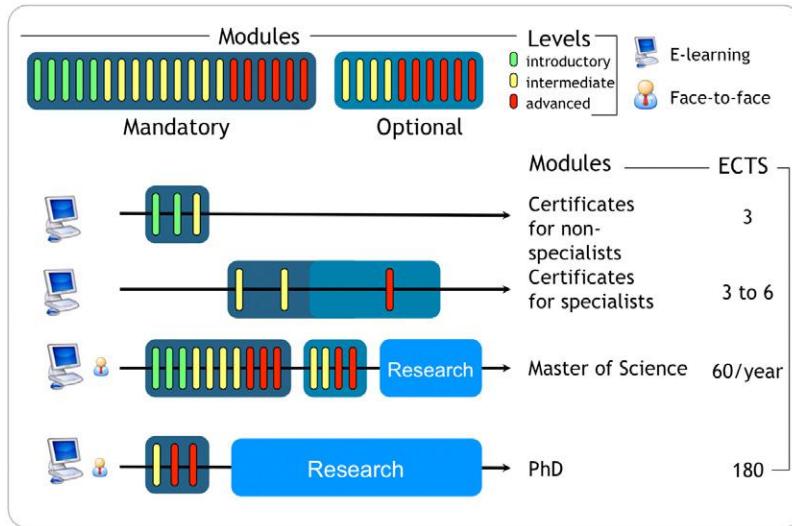


Figure 50.1 Representation of the organization of the Eu2P training program.

and e-learning formats through an e-learning platform and web-based examinations developed specifically for the Eu2P project. This platform enables trainees to access e-learning resources (learning paths, recorded lectures, readings, tests) and personal progression, to interact with their teachers (forum, internal board, videoconferences/chat), to work with other students on specific projects, to be informed about course events, and to give feedback about courses and general training programs (survey tool). By means of this platform, trainers are able to inform students about course events, internal agendas, email alerts, to interact with students, make them work collaboratively (forums, chats, internal boards, task/group assignments), to consult student learning path access, progress, and time spent, to consult student test scores, to access and correct student assigned work files, and to organize live meeting events (lectures, seminars, workshops).

## OUTCOMES OF THE EU2P TRAINING PROGRAM

Further, among the particular strengths of the program are (i) the insistence on a standard approach, using industry-quality standard operat-

ing procedures, (ii) work practices throughout the European Union, (iii) information only in English, and (iv) the diverse, internationally experienced faculty drawn from within and outside academia. Consequently, Eu2P now knows its first successes in 2012. ENCePP lists Eu2P training for high quality and independent pharmacoepidemiology and pharmacovigilance programme on its website ([www.encepp.eu/Training.shtml](http://www.encepp.eu/Training.shtml)). Eu2P has won a Special Mention Trophy rewarding the most innovative information and communication technology for education projects awarded by the Professional Education Congress “Educatec Educatice,” supported by the French Minister of National Education and the Minister of Higher Education and Research ([www.univ-bordeauxsegalen.fr/fr/etudes/l-actualite-des-etudes/formations/trophee-pour-l-eu2p.html](http://www.univ-bordeauxsegalen.fr/fr/etudes/l-actualite-des-etudes/formations/trophee-pour-l-eu2p.html)). Overall, trainees’ enrolment has more than doubled, while enrolment in the master’s program has almost tripled in 2 years. Following an official audit from the Innovative Medicines Initiative in May 2012, the consortium has been told that the Eu2P project is run very well by the academic and industrial partners, including registration, fees, program planning, tutoring, internship, and diploma recognition. The public-private consortium also manages the general processes of quality control and quality assurance within the program,

and the commitment to industry and academia-standard principles and practices was highly appreciated.

## CONCLUSIONS AND PERSPECTIVES

The outcome of the Eu2P initiative is that health professionals trained by Eu2P have a common European and international theoretical and practical understanding in medicines' benefits/risks, professionals not directly related to health get a chance to improve their knowledge about medicines' benefits/risks, and patients get a chance to be trained in medicines risk communication (Palin *et al.*, 2012). As Eu2P is largely supported by big pharmaceutical companies, the consortium has adopted a strategy towards official European recognition of the new Eu2P training offer. This strategy has been crucial to guarantee the high academic value of the Eu2P program to the ministries of higher education and future trainees. In addition, this accreditation process has guaranteed Eu2P reliability regarding the innovative way of fully online course delivery and assessment. However, Eu2P private partners and collaborators have highlighted

the need of additional training formats and new topical and emerging themes tailored to continuous professional development and on-the-job training.

Therefore, health professionals together should be more efficient and coordinated in Europe, while non-health professionals and patients should be better informed, more familiar with medicines, and better health-protected.

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# Teaching and Learning Pharmacovigilance

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## INTRODUCTION

There are two closely connected dimensions of educational need associated with the field of pharmacovigilance. The principal dimension is that of the clinical practitioner who needs knowledge, understanding, and wisdom about effects of pharmaceuticals in their day-to-day healthcare practice. The secondary dimension is that of professionals in the field who must amass and evaluate emerging evidence from broad populations exposed to pharmacotherapies.

A vital nexus between these two dimensions is found in the spontaneous adverse drug reaction (ADR) report that, for many years to come, is likely to remain a key element in the intelligence-gathering systems of professional pharmacovigilists.

The educational needs of practitioners in each of these fields have considerable interdependency. On the one hand, beyond personal empirical observation, the healthcare practitioner needs to keep

abreast of new knowledge about benefits and possible harms associated with the pharmacotherapies they customarily use. On the other hand, the professional pharmacovigilist needs to develop and maintain discriminating skills for the same evolving clinical knowledge, as well as mastery of the increasingly complex systems of signal generation, systematic investigation of signal meaning, and effective communication back to the public and healthcare practitioners.

This chapter therefore addresses the educational needs, opportunities, and challenges for both groups: characterized respectively here as learners and teachers of pharmacovigilance.

Two political undercurrents have powerfully influenced the field of pharmacovigilance over the past decade; these currents have created a notable undertow that has magnified interest in, and extended the scope, of teaching in this field. These two forces have resulted in a more lively interest in the communication of pharmacovigilance findings

to all those engaged in overseeing pharmacotherapy in practice.

The first of these currents derives from increased publicity about mistakes and mishaps in conventional healthcare service. The second has emerged from the contemporary expectation that available therapies should be uniformly "safe" in customary usage. Both of these movements will be examined in this chapter. Implications will be discussed for both the individual practitioner's need to learn pharmacovigilance in their customary care of patients and also for training health professionals in pharmacovigilance management techniques.

## CURRENT INFLUENCES ON PHARMACOVIGILANCE EDUCATION

The World Health Organization's (WHO's) definition of pharmacovigilance (WHO, 2002) is scoped very broadly: "The science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems." This definition evolved considerably during the period 1961–2000 and includes, through the term *prevention*, a clear call for knowledge gained through pharmacovigilance activities to be influencing and improving outcomes from use of medicines. This call is reflected in contemporary expert commentary on the importance of surveillance and drug safety (Bahri *et al.*, 2011): "Public communication on safety concerns over medicines and advice on how to prevent medicine-induced patient harm is a decisive challenge for the overall success of those responsible for pharmacovigilance." For the individual healthcare professional to reliably learn and incorporate pharmacovigilance in their routine patient care is now a key challenge.

## THE "MISTAKES AND MISHAPS IN HEALTHCARE" MOVEMENT

Commencing some 20 years ago, well-publicized studies of mistakes and mishaps in care of hospitalized patients in both the USA (Brennan *et al.*, 1991) and Australia (Wilson *et al.*, 1995) led to substan-

tially heightened levels of public interest in achieving less harm from customarily delivered healthcare. In the USA, the landmark Institute of Medicine report *To err is human* (Kohn *et al.*, 2000) acted as a platform from which has been launched a range of initiatives that have drawn attention to, and now actually improved, patient safety (Sinkowitz-Cochran *et al.*, 2012).

Parallel action was taken in the UK and other countries to address rising public concern about the high levels of patient injury and morbidity occurring because of patient contact with established healthcare systems. In the UK, a pivotal report from the National Health Service (NHS) chief medical officer (Donaldson, 2000) led to the establishment of a National Patient Safety Agency that was tasked with reporting, analyzing, and disseminating the lessons of adverse events and "near misses" involving British NHS patients. Its current vision remains: "... to lead and contribute to improved, safe patient care by informing, supporting and influencing healthcare organisations and individuals working in the health sector."

Evidence of significant numbers of incidents associated with medication use, and by implication unsafe healthcare practice, is found in reports associated with this movement. Recently, in the UK, 12% of reported patient safety incidents in acute hospitals and 21% of such incidents in general practice were noted to be associated with medications (National Reporting and Learning System, 2011). The relationship between medication errors and adverse drug events is complex. Researchers have used a variety of definitions when assessing incidence of either of these types of events in published studies (Lisby *et al.*, 2010). It has been estimated that about a third to a half of adverse drug events are typically associated with medication errors; however, of course, not all adverse drug events necessarily spring from medication errors (Morimoto *et al.*, 2004). Using a methodology established in the USA in 1995 for simultaneous evaluation of inpatient medication errors and adverse drug events (Bates *et al.*, 1995) a recent study of 3459 Japanese inpatient episodes (Morimoto *et al.*, 2011) has provided useful insights into the relationship between these two types of incident (see Figure 51.1).

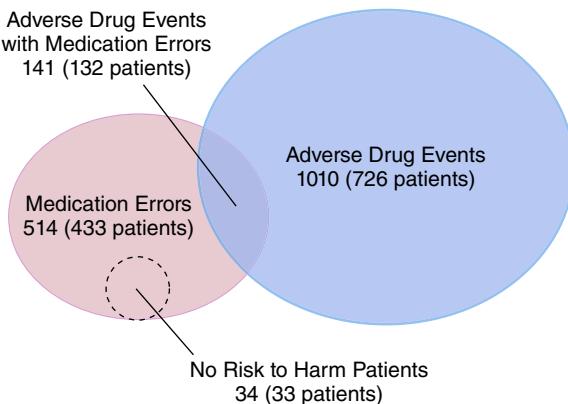


Figure 51.1 Medication errors and adverse drug events observed in 3459 consecutive admissions to wards of three Japanese hospitals over a 6 month period in 2004 (Morimoto *et al.*, 2011). With kind permission from Springer Science+Business Media: *Journal General Internal Medicine: Incidence of Adverse Drug Events and Medication Errors in Japan: the JADE Study*, 26, 2011, 152. Morimoto, T., Sakuma, M., Matsui, K., Kuramoto, N., Toshiro, J., Murakami, J., Fukui, T., Saito, M., Hiraide, A., & Bates, D., Figure 1.

The close intersection of medication error and adverse drug events now demands careful attention in curricula associated with pharmacovigilance. Whilst the generally accepted definition of medication error asserts that, by their nature, such errors must be preventable (National Coordinating Council for Medication Error Reporting and Prevention, 2012), other workers in the field have suggested that medication errors might also be “ameliorable”: a kind of gradation of preventability (Morimoto *et al.*, 2004). Morimoto and colleagues proposed a comprehensive system for detecting and classifying medication-related incidents and suggested that, in relation to each such incident, gaugings can be taken of the level of severity, resultant disability, preventability, or ameliorability as well as the stage and setting of care when such incidents occur.

There are clearly important implications for use of the term “error” when applied to medication use. When does a side effect of a drug become an adverse event, an ADR, or a medication-related error? Clearly, different players in the healthcare system will have different perceptions on this point.

For the patient (or the pharmacovigilant noticing events recorded in a healthcare database), what appears to be an error may prove to have been the result of an individual prescriber’s conscious judgment that perceived clinical benefits outweighed possible harms of the medication. The only “error” that may have occurred in such circumstances might have been the failure of the prescriber to openly share with the patient the considered basis for the chosen pharmacotherapy.

For the pharmacovigilant, whether an “error” actually occurred too often remains uncertain, depending on the distance in time and space from the event and its specific circumstances.

## “SAFETY” AS A CONSTRUCT IN HEALTHCARE

The dilemma with “errors” in healthcare parallels problems associated with the use of the term “safety” as it relates either to healthcare or to pharmacotherapy. Safety as a term in current usage generally implies an absolute state: healthcare being perceived to be either safe (free from danger or risk) or unsafe. In this customary usage of the term by the general public, the matter of how relatively unsafe a particular practice is is usually not in question. Thus, arguably, an unfortunate misnomer has been applied, and public concerns about “safety” in healthcare as such can never be sufficiently addressed. Certainly, the adoption of these terms “error” and “safety” with respect to issues in healthcare will continue to cause difficulty for those trying to make health services less likely to harm and less error prone.

Very frequently, a sort of reciprocal of these terms “error” and “safety” is embodied in a much more complex and difficult-to-define concept of “quality” in healthcare. The quality-in-healthcare movement has now gained very considerable currency with countries such as the USA having poured substantial resources into quality improvement organizations as part of their publicly funded Medicare system. However, the benefits and efficiency of these “quality” systems in the USA at present remain somewhat controversial (Marciniak *et al.*, 1998; Snyder and Anderson, 2005; Stevenson and Mor, 2009).

The semantic considerations around terms such as “error,” “safety,” and “quality” are particularly relevant for those teaching and learning pharmacovigilance in the local clinical setting. Healthcare professionals in practice are generally acutely aware of their ability to both make and also to contribute to mistakes within the healthcare system. However, they are also equally aware of their responsibilities to achieve healthcare quality and, in particular, to strive for the best balance between benefit and harm in all that they do to assist restoration of health for their patients.

#### PUBLIC ASPIRATIONS FOR “DRUG SAFETY”

The second major current that has energized the field of pharmacovigilance derives from efforts of both drug regulators and the pharmaceutical industry to meet increasingly insistent public demand for new pharmaceuticals to be proven “safe.”

In the past decade, the highly publicized withdrawal from sale of many extensively used drugs has elicited wide but shallow public debate about harms and benefits associated with use of pharmaceuticals. Regrettably, this discussion has been confounded by increasingly prevalent perceptions of a global pharmaceutical industry that is unsupportably rapacious (Peterson, 2008). In addition, in some countries, such as the USA, there has been a growing belief that existing regulatory systems designed to evaluate relative benefits and harms of individual products, both before and after licensure for sale, have been compromised, with poorly structured government oversight being partly to blame (Carpenter *et al.*, 2012).

Most of the public discussion has been predicated on the assumption that effective new drugs need to be “safe” to a level that is almost entirely unachievable. Certainly there is a marked contrast in relative levels of “safety” between newer drugs that have recently been withdrawn and older drugs that have been generally available for many years. Drugs such as warfarin, digoxin, or aspirin are widely used and yet are known to produce very significant morbidity and mortality.

However, whether the public’s perception of levels of exemplary pharmaceutical “safety” are ever achievable, it is clear that far too little has been

done in the past to systematically evaluate positive and negative drug effects beyond the point of initial marketing licensure. The implications of past failure to make such postmarketing assessments has been analyzed, and the need for decisive action has been clearly laid out by Dr Jerry Avorn in his pivotal book *Powerful Medicines: The Benefits, Risks and Costs of Prescription Drugs* (Avorn, 2004: 383):

The first day a new drug is on the market should mark the start of a systematic ongoing evaluation of how wisely doctors are prescribing it, how thoroughly patients are taking it, what adverse events it causes in routine care, and (eventually) whether its promised benefits are actually being realized with routine use. (Avorn, 2004).

Additionally, beyond licensure for marketing, there is also a need for comparative studies assessing both pharmaceutical harms and benefits at different dosing levels between drugs of the same class, as well as drugs used for the same purposes, across broad end-user populations.

This has been perhaps a key conclusion after controversies surrounding negative cardiovascular effects associated with the nonsteroidal anti-inflammatory drugs and more recently the glitazone class of drugs. It has been the failure to recognize differential levels of benefit and harms amongst members of these classes of drugs and their therapeutic alternatives that have resulted in precipitate drug withdrawals (Edwards, 2005; Asher, 2011) Why retain relatively more hazardous forms of these drugs on the market when beneficial effects can be achieved from other members of the class (or, alternatively, different classes of drugs) having lower levels of negative cardiovascular effects? Regrettably the information that might allow some degree of certainty about these relative benefits and risks in actual practice is often not available.

Failure to consistently require postmarketing studies of this kind is a major deficiency in public regulation of drug “safety” at present. Global movements in the health technology assessment field are now starting to at least partially address these deficiencies. Pharmaceutical “technology

assessment" has in the past been performed largely from an economic, rather than a relative benefit-harm perspective. Such movements became initially established in Australia in 1993 when the national public subsidy scheme for pharmaceuticals first required evidence of cost effectiveness (embracing both benefits and harms) before new medicines could be listed by the scheme (Hailey, 2009). Canada and the UK followed this approach during the 1990s, and many other countries have now adopted similar schemes (Breckenridge *et al.*, 2010). The US Federal Government through the American Recovery and Reinvestment Act of 2009 and the Affordable Care Act of 2010 defined and allocated substantial funding to comparative effectiveness research. Comparative effectiveness research has been defined in the Affordable Care Act as "research evaluating and comparing health outcomes and the clinical effectiveness, risks, and benefits of two or more medical treatments, services and items." It is to be hoped that the Patient-Centered Outcomes Research Institute established under this legislation will undertake comparative effectiveness research within, and across, drug classes in the whole US population, thereby addressing in a more timely way relative benefits and harms of medicines such as nonsteroidal anti-inflammatory drugs and glitazones (Garber, 2011). These developments are highlighting and deepening the field of medicine "safety" and leading to learning needs far from traditional pharmacovigilance activities of past decades.

Recent important work has been done by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This body consists of pharmaceutical industry and drug regulators from the EU, Japan, and the USA. Most recently, the ICH has been consolidating its work from the mid 1990s on "safety" reporting for marketed drugs and has now developed guidance for periodic benefit-risk evaluation reporting (ICH Expert Working Group, 2012). This guidance has received qualified acceptance from ICH partners, but is ultimately likely to result in a more consistent global approach to the postmarketing effectiveness and "safety" surveillance of medicines in common use. The ICH also developed significant guidelines for pharmacovigilance planning that have now been

adopted in each of the major developed world jurisdictions of the pharmaceutical market (ICH Expert Working Group, 2004). These guidelines suggest that marketing licensure should be conditional upon pharmacovigilance planning throughout each product lifecycle.

Actions in these pharmacovigilance plans are intended to extend throughout the period of patent protection for pharmaceutical manufacturers. Mandatory surveillance of individual products in whole-population use, using comparative observational studies, targeted clinical investigations, and descriptive drug utilization studies are all suggested as possible components of such pharmacovigilance plans. These aspirations have now taken clearer form within the 2012 E2C(R2) guidelines for periodic benefit-risk evaluation reporting (ICH Expert Working Group, 2012).

These developments, coupled with global activity in the emerging comparative effectiveness research movement, will provide for collection of much-needed intra-class drug hazard/effectiveness data that will color a more complete picture of key issues in pharmacovigilance of the future.

While the study and classification of ADRs remains a core activity for pharmacovigilance, study of and communication about risks as well as benefits of pharmaceuticals in whole user populations is now confronting pharmacovigilance educators as the new frontier where energetic action is now needed (Avorn and Fischer, 2010).

## LEARNING PHARMACOVIGILANCE

A principal educational challenge for contemporary pharmacovigilance is that of translating results of findings in a timely manner into the customary practice of clinically based health professionals. Additional to this challenge (but beyond the scope of this chapter) is the challenge of effective communication with the public.

Conventional methods of communication of pharmacovigilance knowledge have generally been restricted to letter writing, label wording, and package insert warnings. Unfortunately, there is now considerable evidence that these processes have very limited success in achieving the goal of an

informed prescriber ready to apply pharmacovigilance intelligence in their everyday practice (Belton *et al.*, 1995; Smalley *et al.*, 2000). Similarly, with the general public, largely ineffective communication has been observed using these conventional tools (Berry *et al.*, 2002). In many respects, these difficulties in communication are paralleled by the well-recognized difficulty of translating evidence-based medicine into widespread clinical practice.

It is clear that an important factor missing in the conventional communication of pharmacovigilance messages relates to the essentially negative nature of the messages. For clinician learners of pharmacovigilance it is generally necessary to place such negative messages in the context of offsetting pharmacotherapeutic benefits. Thus, pharmacovigilists wishing to communicate their messages to a clinical context need to study and apply known effective techniques for achieving clinical practice change.

A summary of 26 systematic reviews of the effects of continuing medical education on improving physician clinical care and patient health (Bloom, 2005) concluded that:

Interactive techniques (audit-feedback, academic detailing/outreach, and reminders) are the most effective at simultaneously changing physician care and patient outcomes. Clinical practice guidelines and opinion leaders are less effective. Didactic presentations and distributing printed information only have little or no beneficial effect in changing physician practice.

Interactive techniques and judicious use of reminders need to constitute a foundation for communication of the fruit of ongoing pharmacovigilance alongside the more traditional methodologies. There are an increasing number of opportunities for achieving more rapid and effective dissemination of practice-changing pharmacovigilance messages.

#### **INTERACTIVE TECHNIQUES FOR LEARNING PHARMACOVIGILANCE**

##### **The Adverse Drug Reaction Reporting Process**

For a clinician noticing an adverse drug effect during their management of pharmacotherapy, the

act of filling in an ADR report represents an important opportunity for learning. Too frequently, this opportunity for learning is lost.

Regrettably, in most settings, insufficient resources are available to allow routine interaction between the reporting clinician and staff of the national/regional authority who record and codify such reports. Certainly for those reported events where there is a suspicion that a significant new signal may be involved, such feedback and interaction has become more prevalent in recent years. However, for events that appear superficially to be more mundane, effective educational interaction with monitoring authorities rarely occurs.

There may be many ways to remedy this lost opportunity, and certainly in some local institutional settings the discussion of, and interaction about, ADR reports becomes a matter of routine. Such arrangements need to be purposefully fostered. Multidisciplinary hospital drug and therapeutics advisory committees can be a useful forum for such learning, and in settings where high-level clinical pharmacy practice is in place the clinical pharmacy practitioner can be an empowering influence to catalyze discussion about, and learning from, any jointly observed incident.

Encouragement of more formal interactive local learning circles represents a further important opportunity to be fostered; such circles have taken many forms in Europe, with 10 countries being judged to have "substantial activities" in this format (Beyer *et al.*, 2003). In particular, such multidisciplinary groups have been in place amongst community-based practitioners in the Netherlands for more than 30 years and have proven themselves to be mostly effective in gaining changes in history taking, communication with patients, follow-up decisions, and drug prescribing (van Eijk *et al.*, 2001; van Driel *et al.*, 2007).

#### **Continuing Professional Education**

Higher levels of ongoing educational attainment are now being required for the maintenance of professional practice accreditation by many professional authorities associated with medical and allied health disciplines. These developments provide an opportunity for more disciplined

approaches to pharmacovigilance learning and education at the clinical practitioner level (Shojania *et al.*, 2012). In particular, interactive audit and feedback requirements within continuing medical education programs are becoming more prevalent, and this form of continuing medical education offers many opportunities for personal exploration of unexpected drug-related events in relation to established pharmacovigilance knowledge.

### Service-Oriented Academic Detailing-Led Programs

After many years as a concept being subjected solely to research, a considerable number of countries have developed interactive, one-on-one public interest-oriented academic detailing programs for primary care practitioners. Such programs have largely been oriented to providing commercially unbiased information concerning therapeutic and diagnostic issues. Social marketing, or the “selling” of patient outcome-improving ideas/evidence according to the perceived needs of individual practitioners, is central to this academic detailing concept.

Ongoing initiatives of this kind aimed at public health improvement have been established in a variety of countries, including the UK, USA, Belgium, Canada, and Australia. Generally speaking, these programs have fostered supportive relationships with primary care practitioners, which have then spearheaded application of additional educational and behavior-changing initiatives.

In Australia, “NPS: Medicinewise” (previously the National Prescribing Service) has been extending academic detailing-led programs throughout the Australian continent. These programs have aimed for the improvement of general practitioner (GP) discrimination in their use of pharmacotherapies as well as overall better patient health outcomes (NPS, 2012b). The GP–academic–detailer relationships have then been used to increase credibility and uptake of a range of other NPS-initiated practice improvement programs.

The central approach taken in these service-oriented programs has often been to deliver key clinical behavior-change messages targeting achievement of a better balance of benefit and risk

associated with pharmacotherapies (May and Rowett, 2000). In this context, these public-interest programs provide an effective vehicle for the delivery of pharmacovigilance learning into primary care practice: steps need to be taken to integrate findings from pharmacovigilance studies into the activities of such groups.

One of the features of one-to-one social marketing-driven encounters is the opportunity to place evolving evidence about risks and benefits of pharmaceuticals into a clinical context frequently marked by uncertainty. Evolving and changing scientific knowledge then joins seamlessly with the professional’s daily experience of uncertainty in their clinical practice (McWhinney and Freeman, 2009). Another of the central tenets of the academic detailing model is the acknowledgment of both sides of controversial issues (Soumerai and Avorn, 1990).

This interactive presentation of pharmacovigilance messages stands in contrast to conventional use of the printed word for such communications: static delivery of this information in letters or label warnings frequently needs qualification for it to be entirely true and fair.

Academic detailing–spearheaded initiatives are ideal carriers for pharmacovigilance messages, placing complex information into a context that will generally modulate individual clinical practice (O’Brien *et al.*, 2007).

### Reminders

The use of reminders was also characterized by Bloom (2005) as an additional effective interactive technique for achieving professional clinical practice behavior change. The steady increase in the adoption of electronic systems of record keeping in healthcare practice (including primary care) has created the opportunity for broader use of electronic reminders in computer-based prescription management software. These systems have been found to be modestly effective for issues such as provision of warnings about drug interactions, when to prescribe specific medications, when to provide vaccinations, or when to order tests (Shojania *et al.*, 2009).

The potential for the integration of electronic cautionary notes into the physician’s desktop

computing facility offers the opportunity for translating pharmacovigilance-derived knowledge into practice. The critical nature of the functional design and operational ease of use of such software-based reminder systems remains a key challenge for their developers (Patterson *et al.*, 2005). Reminder systems are most practical for pharmacovigilance messages where only few uncertainties exist about the nature of the response called for by practitioners; unfortunately, such circumstances are relatively unusual. The inflexibility of much currently available software limits its usefulness for educationally effective delivery of electronic reminder warnings.

## TEACHING PHARMACOVIGILANCE AT UNDERGRADUATE LEVELS

For all healthcare disciplines involved with prescribing, administering and monitoring effects of pharmacotherapies, there is a well-recognized body of knowledge seen as being necessary for professional practice. This body of knowledge has its basis in studies of human behavior, including communication, ethics and philosophy, physiology, patho-physiology, clinical and laboratory sciences, including pharmacology. Preparation for practice in medicine, nursing, pharmacy, dentistry, and other such professions requires admixtures of each of these disciplines to a greater or lesser degree depending on the profession itself and the scope and nature of subspecialization.

Building onto these basic health sciences, pharmacotherapeutics education needs to be solidly grounded on principles of benefits, risks, and harms from drug therapies. This paradigm of benefit, risks, and harms needs to be the foundation for understanding of both absolute and relative effects of medicines used in therapeutics.

The judicious and effective management of the benefits and risks of pharmacotherapy then needs to be taught as a key skill to be mastered by all health professionals. Whilst health professions in different settings will have different roles to play in this management process, the concept of benefit-harm management is fundamental to sound prepa-

ration for practice in any of the disciplines that are involved in pharmacotherapy processes.

The current structure, methods, and operational imperatives of the global pharmaceutical industry also need to be taught to undergraduates in an open and intellectually honest fashion. The real benefits to humanity from this enterprise need to be projected clearly in the context of the inevitable risks to health, and the potential harms which also accompany the benefits from pharmacotherapy.

Coupled with the paradigm of benefits and harms of drug therapies, the undergraduate health professional needs to be instructed at the outset in the realities of both error and uncertainty in healthcare. Techniques for dealing purposefully with error and personally managing the breadth of uncertainty involved in ongoing healthcare practice need to be absorbed at the earliest opportunity. Equally, the complex nature of the public's expectations for "safety" of pharmaceuticals needs to be the backdrop against which evolving knowledge of benefits and harms of medicines is viewed.

In this context, students in the professions participating in pharmacotherapy need to leave the undergraduate setting with expectations of a future lifelong learning experience. Suggestions for effective adult learning in the field of pharmacovigilance have been outlined above.

Building on this approach to pharmacotherapy at the undergraduate level, pharmacovigilance and a continually refreshed knowledge of risks, harms, and potential benefits from pharmacotherapy should become central to the experience of all healthcare clinicians.

The benefits of ongoing pharmacovigilance research will only be able to be fully realized when healthcare practitioners have consistent expectations for this ongoing learning experience.

## AT POSTGRADUATE LEVELS

Pharmacovigilance professionals are generally drawn from a wide range of disciplines, not all of which necessarily have a basis in the health professions. In particular, statisticians and computing professionals are key personnel needed for effective operation of large-scale spontaneous reporting systems, as well as for the increasingly

important activity of mining large data sets of longitudinal healthcare records for pharmacovigilance intelligence.

A range of educational authorities in different countries have developed and continue to deliver valuable educational programs for professionals working within the discipline of pharmacovigilance itself.

The International Society of Pharmacovigilance (ISoP: <http://www.isoponline.org/>) is a nonprofit organization whose aims are to foster pharmacovigilance both scientifically and educationally, and enhance all aspects of safe and proper use of medicines. Educational courses in pharmacovigilance principles are periodically available through ISoP, which acts as a key global meeting place for those engaged in collecting, assessing, and disseminating information about risks of medicines in broad use throughout the world.

Another organization having a rather broader remit for the evaluation of both benefits and risks of pharmacotherapies is the International Society for Pharmacoepidemiology (ISPE: <http://www.pharmacoepi.org>). ISPE is an international organization dedicated to advancing the health of the public by providing a forum for the open exchange of scientific information. It also develops policy, educational programs, and advocacy for the field of pharmacoepidemiology, including in areas such as pharmacovigilance, drug utilization research, comparative effectiveness research, and therapeutic risk management. It maintains authoritative guidelines for good pharmacoepidemiology practices (ISPE, 2008). Greater confidence can be placed in inferences drawn from observational studies of drug benefits and harms when such studies conform to these guidelines. The guidelines are now formally recognized in many countries by reference in government regulatory requirements. ISPE also provides periodic training courses and educational programs in sound pharmacoepidemiological methods, therapeutic risk management, drug utilization research, comparative effectiveness research, and related fields.

There are many other authorities that provide disciplined training for professionals working specifically in the fields of pharmacovigilance and therapeutic risk management; for example, the

Drug Information Association (DIA: <http://www.diahome.org>); the UK Drug Safety Research Unit (<http://www.dsru.org>) and the London School of Hygiene and Tropical Medicine (<http://www.lshtm.ac.uk/courses>). The European Agency for the Evaluation of Medicinal Products (<http://eudravigilance.ema.europa.eu/human/training.asp>) in collaboration with the DIA provides training for pharmacovigilance professionals. These DIA programs are particularly relevant for pharmacovigilance professionals working within the pharmaceutical industry.

Pre-eminent and leading for many years in this field of education for professional pharmacovigilists has been the World Health Organization Collaborating Centre for International Drug Monitoring. This remarkable center now located in Uppsala, Sweden, has since the 1960s been active in setting global operational standards for public-health-oriented pharmacovigilance activities (The Uppsala Monitoring Centre, 2011). Staff from this center have developed benchmark training programs, which since 1993 have inspired and fed the development of many national spontaneous ADR reporting systems around the world.

## CONCLUSIONS

The education and training needs of both professional pharmacovigilists and also clinical practitioners (as those who need to learn watchfulness about the therapies they administer) have been significantly influenced by recent social developments. The contemporary public health focus on better management of risk in use of pharmaceuticals has contributed to a renaissance of thinking about pharmacovigilance. This new thinking is embodied in the transition from thinking primarily about drug “safety” to more consistent thinking about balancing and managing both risks, harms, and benefits of pharmaceuticals in individual patient care.

These developments have been propelled by the elaboration of significant harms that can be caused by health services in general and pharmaceuticals in particular.

The Erice Declaration of 1997 (Anon, 1998) and subsequent related statements (Anon, 2010) by the most respected figures associated with the field of pharmacovigilance have clearly enunciated international aspirations for more effective communication of drug safety information. However, as has been shown through expressions of deep public concern about high-profile drug withdrawals from the global market, the effectiveness of these communications now needs careful scrutiny.

Within the health professions, these developments demand action to improve clinical education and training on how to better manage risks, harms, and benefits associated with drug therapies. Action is needed in this regard at the level of both the learners and the teachers of pharmacovigilance. To purposefully communicate the meaning of risks of therapy that have been elaborated through good pharmacovigilance practice, it is necessary to place these messages within a framework acknowledging the balance that clinicians and their patients must achieve between both risks and benefits.

The movement to measure and improve quality in healthcare (particularly as it refers to pharmacotherapeutics) is especially relevant in this regard. A clear understanding of the nature and direction of the quality-in-healthcare field is vitally important. Pharmacovigilance professionals need to be able to share with proponents of this significant global movement the benefit of their experiences of success and failure in timely identification, evaluation, and communication of risks associated with drug use in therapeutics.

Pharmacovigilance has been relatively successful at the macro level of government regulation in achieving the removal of pharmaceuticals deemed "unsafe"; however, it has been rather less successful in dealing with pharmaceuticals that have less florid negative effects, particularly those balanced by significant aggregate clinical benefit. Certainly in the matter of pharmacovigilance communication with clinical practitioners about drugs with more marginal levels of risk, attempts to communicate such risks in the absence of parallel communication about acknowledged benefits have met with only limited success. This is a lesson that those advocating improved quality of healthcare need to absorb.

The spontaneous ADR report is going to continue to be a key link between teachers and learners of pharmacovigilance: it provides vital raw material for clarification of the extent and nature of risks of specific drug therapies. The aspiration for improved individual clinical watchfulness for adverse effects from pharmaceuticals draws attention to the point that closer educational attention also needs to be paid to the act of prescribing itself.

In recent years a considerable body of research and commentary has identified inadequacies in education for prescribers in the USA (Garbutt *et al.*, 2005), Europe (Richir *et al.*, 2008; O'Shaughnessy *et al.*, 2010), the Middle East (Al Khaja *et al.*, 2005), and Australia (Hilmer *et al.*, 2009). Prescribing, of course, is an action that prefigures the discipline of pharmacovigilance itself. It is now clear that there has been a failure to recognize prescribing as a practical skill that requires both clinical pharmacology education and contextualization in the deep complexity of each patient's circumstances and preferences.

Two published curricula are available for training prescribers (de Vries *et al.*, 2012; NPS, 2012a), and these programs have now both been subjected to evaluation for effectiveness and student satisfaction (de Vries *et al.*, 1995; NPS, 2010).

It is clear that the paradigm of benefit and risk of harm from pharmaceuticals, and the prudent management of these dimensions of drug effect, now need to become a basis for therapeutics training for all health professionals. Equally important is the subsequent shared and informed decision-making between prescriber and patient that provides proof of sound management of the balance of benefits and harms from drug therapies.

Establishing and maintaining pharmacovigilance education on these lines will enhance the discipline's impact on the health of the public.

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## Practical Experience in Teaching Pharmacovigilance

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A Short Course in Pharmacoepidemiology and Pharmacovigilance at the London School of Hygiene & Tropical Medicine (LSHTM) was started in 1997 and has run each year since then. This short chapter is written from a European perspective and clearly does not attempt to cover the situation outside Europe.

There are only a limited number of university-based examined courses in Europe in which pharmacovigilance is a major component. Another example that has been around for several years is a flexible Masters course in pharmacovigilance taught at the UK University of Hertfordshire. This has components that can lead to a diploma or certificate. This course largely uses external teachers, and is now part of the Eu2P Programme (see below).

The LSHTM is Britain's national school of public health and a world-leading postgraduate institution in Europe for public health and tropical medicine. Part of the University of London, the

London School is an internationally recognized center of excellence in public health, international health, and tropical medicine with a remarkable depth and breadth of expertise. It has approaching 4000 students and over 1300 staff working in over 100 countries.

The LSHTM course is part-time and comprises 300 h (approximately 1.5 days per week) which are spent as follows: 90 h formal teaching and contact time, 110 h self-directed study, and 100 h project work. Currently, formal teaching takes place during three sessions of 4 days in a week (total 12 days) spread over 5 months, but there are plans to extend this and to provide Distance Learning modules to be included in both the short course and the wider MSc programme. Examinations and a project are used to assess students, and there is a high, but not 100%, pass rate with successful students being awarded a Certificate.

While LSHTM has a sizable active group of researchers studying adverse effects of medicines

(over 100 publications in the last 5 years), the course uses external teachers also. Outside experts, particularly from regulatory agencies and those with industry experience in pharmacovigilance, help teach, and some hold honorary positions in LSHTM. A variety of teaching methods are used, with both lectures and workshops, where students are able to apply what they have learned as well as share knowledge and experience from their own practice.

The experience, both of teachers and participants, seems to have been generally very positive. Students have come from a wide variety of backgrounds, and while most are from Europe, students also regularly come from North America, Africa, Asia, and the Middle East, with numbers per year generally being about 20–25.

Not surprisingly, the last few years have seen an increase in the number of courses teaching these subjects, with those offering a recognized qualification being well attended. Some courses in pharmaceutical medicine or pharmacy may have a notable component in pharmacoepidemiology or pharmacovigilance (e.g., Bath University). In addition, many institutions have PhD programs; at LSHTM there are about eight staff with major interests in the field and there are typically six to eight PhD students at any one time.

A short “commentary” on the LSHTM course was published by Dunn and Thorogood (2002), though it has developed further since that publication. The number of face-to-face days spent has increased and may increase further. In addition, a new 4-day course (unexamined currently) has begun. This was initially called “Advanced Pharmacoepidemiology,” but is now called “Practical Pharmacoepidemiology” and involves students using the large General Practice Database to analyze data having set out design parameters.

The Eu2P is the most extensive program in Europe. It is a training partnership composed of seven universities in France, Netherlands, Italy, and Spain, as well as in the UK (noted above). Other organizations involved are the European Medicines Agency, the French Medicines Agency and 15 pharmaceutical companies from the European Federation of Pharmaceutical Industries Association. The Université Bordeaux Segalen is the co-ordinating institution for the whole Eu2P program that includes a Masters degree, Certificates and a PhD in Pharmacovigilance and Pharmacoepidemiology. It has been funded by European grants to develop an online program and it has now been running for 3 years very successfully.

The Drug Safety Research Unit, associated with the University of Portsmouth, UK, has increased its range of training courses and now also offers Postgraduate Certificates, Diplomas and Masters degrees using both face-to-face and distance learning.

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## FURTHER DETAILS

Details for the LSHTM course can be seen at <http://www.lshtm.ac.uk/study/cpd/scpp.html>.  
 For the University of Hertfordshire, see [http://perseus.herts.ac.uk/uhinfo/prospectus/faculty\\_ns/dep\\_bio\\_mg\\_bioscience/c\\_pharmacovigilance.cfm](http://perseus.herts.ac.uk/uhinfo/prospectus/faculty_ns/dep_bio_mg_bioscience/c_pharmacovigilance.cfm).  
 For the Eu2P program, see <http://www.eu2p.org/>.  
 The University of Bath: <http://www.bath.ac.uk/pharmacy/masters/>.  
 The DSRU: <http://www.dsru.org>.

# An Historical Perspective of the Future of Pharmacovigilance<sup>1,2</sup>

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## THE EARLY DAYS AND THE DEVELOPMENT OF PHARMACOVIGILANCE METHODS

Previous scandals concerning drug safety resulted in the initial laws governing the quality of medicines, but pharmacovigilance really started with the case reports of phocomelia attributed to thalidomide (McBride, 1961). These combined the typical characteristics of typical adverse drug reactions in their worse form: severe fetal malformations with multiple similar cases exposed to the same drug. From this disaster emerged national pharmacovigilance systems. Spontaneous reporting would iden-

tify adverse drug reactions that could justify or mandate regulatory action. These systems were set up in the 1970s with the famous British yellow card to report cases of suspected adverse drug reactions. In 1974, the term “pharmacovigilance” first appeared in the medical press (Lagier *et al.*, 1974; Dunlop, 1974). Other terms, such as postmarketing surveillance (Wilson, 1977) or adverse drug reaction monitoring (Fox, 1976; Lee and Turner, 1978; Moore *et al.*, 1985; Faich, 1986) have mostly disappeared. Cases started flowing in and needed to be assessed. Some cases seemed to be very much related to drug exposure, others less, but there was no systematic method to express the degree of association or causality. This led to the development of causality assessment. The 1980s were the golden age of imputability, with the creation of several dozen methods, each trying to be more reproducible or closer to the truth (Meyboom and Royer, 1992). Comparisons of the different methods were published (Pere *et al.*, 1986; Macedo *et al.*, 2003;

<sup>1</sup>Part of this chapter was used in Moore N. The past, present and perhaps future of pharmacovigilance: Homage to Folke Sjöqvist. *Eur J Clin Pharmacol*. 2013;69 Suppl 1:33–41.

<sup>2</sup>Conflicts of interest. Over the years, I have had the opportunity of working with most or all pharmaceutical companies and regulatory or public financing bodies. However, none of this, other than the experience accrued, has any relevance to the content of this paper.

Theophile *et al.*, 2010). Bayesian methods were proposed (Jones, 1987) but never really adopted because of the their complexity. New methods based on logistic regression are still being developed (Arimone *et al.*, 2006; Theophile *et al.*, 2010, 2012). However, few of these imputation methods are still regularly used, like the French method (Begaud *et al.*, 1985; Moore *et al.*, 1985), the WHO scale (<http://who-umc.org/Graphics/24734.pdf>; Edwards and Biriell, 1994), or the Naranjo method (Naranjo *et al.*, 1981). Their main merits may be to quantify the information in the case report and their use as training instruments.

Beyond individual case reports, case series were studied as entities (number of cases, similarity of cases – Tubert *et al.*, 1991; Begaud *et al.*, 1994; Abou Chakra *et al.*, 2010) or as a fraction of the actual number of cases that occurred over a given period of time, related to underreporting (Tubert and Begaud, 1991; Tubert *et al.*, 1992). Much energy was devoted in the 1990s to underreporting and how this could be used to derive real numbers of cases from the number of reports (Tubert-Bitter *et al.*, 1996; Moride *et al.*, 1997; Alvarez-Requejo *et al.*, 1998; Pierfitte *et al.*, 1999; Begaud *et al.*, 2002). In addition to the biases of spontaneous reporting, these reports also required an understanding of drug utilization patterns and exposed populations. These case-based approaches evolved over time towards what is now known as case-population methods, where all the cases in a given area are identified and compared with drug utilization data or the actual number of users (Capella *et al.*, 1998, 2002; Ibanez *et al.*, 2000; Theophile *et al.*, 2011a; Gulmez *et al.*, 2013a,b; Moore *et al.*, 2013a). This is especially valuable early in the marketing of a new drug (Moore *et al.*, 2013a,b).

During that time, large numbers of cases kept accruing in the national pharmacovigilance spontaneous reporting databases, and the tools to manage these large masses of information became increasingly more powerful and sophisticated. Data-mining tools were developed to identify or verify alerts based on disproportionality analyses: one might expect in the absence of a specific risk that events occurring randomly could be reported as adverse drug reactions. If the reporting were really random, all drugs might be associated with

reports of reactions in the same proportion, depending on the occurrence of the event in the drug's user population. If the association were not random, this might result in a greater than expected number of reports (Stricker and Tijssen, 1992). Different methods have been proposed. Some are quite simple, such as the reporting odds ratio (Moore *et al.*, 1993, 1997, 2005; Rothman *et al.*, 2004) or the proportional reporting rate ratio (Evans *et al.*, 2001; Waller *et al.*, 2004). More sophisticated methods, such as neural propagation networks (Bate *et al.*, 1998, 2002; Bate, 2007) or gamma Poisson shrinker Bayesian methods (Almenoff, 2003, 2006, 2007) have been developed. All methods give the same results if at least three cases of a given drug–reaction pair are reported (van Puijenbroek *et al.*, 2002).

The problem with this approach is that unfocused data mining of spontaneous reports will generate large numbers of spurious signals because most are well known drug–event associations and because this approach relies on spontaneous reports. It therefore combines all the difficulties of epidemiological methods and the choice of comparator populations (Moore *et al.*, 1997; Gregoire *et al.*, 2008) with the uncertainties of spontaneous reporting. Spontaneous reporting can be affected by a number of biases, such as relative overreporting (or asymmetrical underreporting), notoriety bias (a variant of the previous bias), contraindication bias, or dilution bias. Associations between drugs or events can modify apparent associations with other drugs, create spurious signals, or hide existing signals (Moore *et al.*, 1997, 2003; Pariente *et al.*, 2007, 2009, 2010, 2012; Gregoire *et al.*, 2008).

As these biases and difficulties with spontaneous reports became apparent, the progress in the availability of large or very large scale population databases made it feasible to test hypotheses, and maybe even generate alerts from actual population data rather than from spontaneous reports, so that the problem of underreporting or exposure denominators could be taken care of. This has led to the combinations of large databases in the EU-ADR, IMI-Protect, and US Sentinel programs (Platt *et al.*, 2009, 2012; Trifiro *et al.*, 2009, 2011; Behrman *et al.*, 2011; Coloma *et al.*, 2011; Forrow *et al.*,

2012). The use, advantages, and risks of these large databases are becoming apparent, and methods to counter the inherent biases and unmeasured confounders are being developed, such as instrumental variables and high-dimensional propensity scores (Dahabreh *et al.*, 2012; Gagne *et al.*, 2012a,b; Rassen and Schneeweiss, 2012; Rassen *et al.*, 2012; Garbe *et al.*, 2013). Just as the 2000s were the heyday of data mining in spontaneous reporting databases, the 2010s may be the time of data mining in large population databases.

Beyond that the crystal ball is clouded. Social media may play a role in the early identification of alerts, much as was proposed for questions to drug information centers long ago. Maybe Google Trends™ will be the future alerting system, much as was proposed for questions to drug information centres long ago (Begaud *et al.*, 1987). How individual medical files will be incorporated into the Cloud and made available remains uncertain. A certainty is that as computing power grows ever more powerful, the capacity to identify minute differences may overtake the capacity to identify or include biases, resulting in a distinct risk of being overwhelmed by statistically “significant” differences that are medically irrelevant. This might have the good effect of giving more importance to common sense and medical judgment.

However, increasing the capacity to detect minute changes will not alter the fact that most adverse reactions in clinical practice or leading to hospital admissions are well known adverse reactions to old drugs (Pirmohamed *et al.*, 2004). Detecting new alerts is not always more important than taking care of older problems.

## PHARMACOVIGILANCE AS A REGULATORY SCIENCE

Over these 40 years, the regulatory systems and requirements have changed too. The adverse reaction occurs at the patient level, and the initial interaction between the patient and a healthcare professional (HCP) leads to identification of the reaction and the decision to report or to query a drug information center before reporting. The patient or the HCP may or may not report to the

manufacturer of the suspect drug or to the regulatory authorities, directly or through a regional center (Moore *et al.*, 1985). The drug manufacturer and regulators exchange information on these adverse reaction reports. These, of course, have no effect on the actual reporting of events since they do not affect the real source of the reports: the patient–HCP interface. Regulators’ efforts to promote reporting have taken many faces, such as including yellow cards in drug formularies, adding black triangles to boxes for recently marketed medicines, and making it mandatory to report all cases or only serious and/or unexpected cases. This has little effect since prescribers are usually unaware of legal requirements. It would be difficult and counterproductive to try to enforce them legally. Drug information centers may contribute to the identification of cases. Cases can be retrieved when HCPs or patients call to ask for information on a drug-related problem. The HCP will call for problems they cannot solve by themselves or with Google, which skews the reporting towards interesting (unexpected) reactions. Patients tend to report less severe adverse reactions that are already on the labeling, or that they have heard of in the media or seen on the Internet with a distinct possibility of manipulation (Moore *et al.*, 2003; Pariente *et al.*, 2007, 2009; McLernon *et al.*, 2010). A recent paper, however, seems to suggest that patient reports can contribute useful information for signals (van Hunsel *et al.*, 2011).

Efforts from the regulators have been focused more on interactions with the pharmaceutical companies. There has been a major shift from a surveillance system based mostly on spontaneous reporting towards a more risk-based system. This evolution has been in parallel with the better understanding of the limits of spontaneous reporting, and the increasing availability of good pharmacoepidemiological resources. The industry has been required to provide a risk management plan when a drug is marketed to quantify the risks that have been identified or are suspected at the time the drug is put on the market, and to mitigate or minimize these risks. These risks can be based on actual risk data, such as experimental or toxicology data, or the results of premarketing clinical trials. They can also be pre-emptive, looking at risks common to the

drug class or the disease entity. For instance, whatever the results of clinical trials or preclinical data, one would not market a new nonsteroidal anti-inflammatory drug (NSAID), cyclooxygenase-2 (COX-2) selective or not, without preparing a careful assessment of a putative cardio-thrombotic risk. The risk might also be related to the disease domain. There have been a number of issues about cancer in diabetic patients, and type 2 diabetes seems to be a predisposing factor for cancer. No new drug for type 2 diabetes would be marketed without at least keeping an eye open for a possible cancer risk (Blin *et al.*, 2012). Each new drug approved by the European Medicines Agency or the FDA has to submit a risk management plan or risk evaluation and mitigation strategy describing how the known risks of the drug will be quantified, the methods that will be used to identify new risks, and how the company proposes to reduce these risks for users. Targeted and quantified monitoring, based on ad-hoc studies with specific objectives, will be accompanied by the nonspecific spontaneous reporting system monitoring, including ongoing continuous disproportionality analysis. Intensive monitoring or ad-hoc pharmacoepidemiological studies may also be required.

At the same time, much effort has been put into the development of preclinical and clinical safety in the International Conference on Harmonisation process, such as topics S7B and E14 putting forth the requirements for the exploration of the proarrhythmic potential of non-antiarrhythmic drugs (Aldariz *et al.*, 1986; Campbell, 1990; Doig, 1997; Haddad and Anderson, 2002; Shah, 2005; Titier *et al.*, 2005). Further efforts and considerable means are being put into the Innovative Medicines Initiative and similar programs to identify predictors of specific risks such as hepatotoxicity (EMA/CHMP, 2006).

There is also a shift beyond safety issues to an assessment of efficacy, effectiveness, or efficiency, or performance, within the risk–benefit paradigm. Until recently, most of the efficacy data came from the premarketing clinical trials. Risk was looked for post marketing. However, premarketing clinical trials may be uncertain predictors of postmarketing performance or benefit, for all kinds of reasons relating to patient selection, unnatural drug usage

patterns, and intense surveillance and monitoring during the trials. Actual real-life drug usage patterns may or may not be different from the clinical trials. For instance, though there have been many reports of hypothetical numbers of cases of upper gastrointestinal (GI) bleeding and deaths related to the use of NSAIDs (Singh, 2000; Tramer *et al.*, 2000), which were widely used to promote the use of selective or preferential COX-2 inhibitors, the usage pattern of NSAIDs in VIGOR or Class or other trials that were used to extrapolate the deaths can be found in fewer than 5% of all NSAIDs patients (Depont *et al.*, 2007; Duong *et al.*, 2014). The risk of GI bleeding seems to be up to 20–40 times lower in real life than in these clinical trials (Tramer *et al.*, 2000; Moore, 2001; Laharie *et al.*, 2010). These studies may be included in the risk management plans, required as commitments at the time of the marketing authorization or required by health insurance systems or health technology assessment organisms (such as the National Institute for Health and Care Excellence in the UK).

European authorities are preparing a guidance paper on postmarketing efficacy studies ([http://ec.europa.eu/health/files/pharmacovigilance/2012\\_11\\_28\\_pc\\_paes.pdf](http://ec.europa.eu/health/files/pharmacovigilance/2012_11_28_pc_paes.pdf)).

## PROPER DRUG USE TO AVOID ADVERSE REACTIONS

However well the drugs are studied and the summary of product characteristics (SPC) carefully written, the regulators attentive, and the pharmaceutical companies diligent and aware, this is of no avail if the drugs are poorly prescribed. Poor prescribing practises, more than anything else, are at the root of recent drug scandals, though this might be only an issue in France, of course (Aronson *et al.*, 2006).

Benfluorex (Mediator®), an appetite suppressant, was approved and marketed as an adjuvant in the treatment of type 2 diabetes. This might not be completely unreasonable, if the drug caused the patients to lose weight and reduce insulin resistance. After all, weight loss is a major element in the treatment of type 2 diabetes, and can suffice to control it. Unfortunately, this hidden ampheta-

mine, like its predecessor and closely related drug isomeride, can cause cardiac valve disease, resulting in heart failure or death (Weill *et al.*, 2010). Since the drug was in fact not really very effective, it was removed from the market, certainly later than it should have been. Among the elements of the scandal were that the drug might have been identified and removed at the same time as isomeride, or that the risk seems to have been noted 10 years before the drug was actually taken off the market. But the main element was that this drug was prescribed for slimming purposes to young persons who wanted to lose a few pounds and were in no case diabetic; clearly repeated instances of drug misuse. For some reason the authorities and the company were accused of malfeasance, but poor prescribing was barely mentioned.

Another recent scandal is the overuse of third-generation oral contraceptives (OC3s) resulting in cases of pulmonary embolism and deaths in young women. The main issue is that though these OC3s and fourth-generation oral contraceptives are clearly labelled as second-line drugs, to be used only when first- or second-generation oral contraceptives have been poorly tolerated, they are mostly used as a first-line choice. Recently, while giving a course in pharmacology to first-year medical students (average age 18), about half the young women who were on oral contraceptives were on OC3s, which had all been prescribed as a first choice. Again, a clear example of poor prescribing.

Other common causes of adverse reactions lead to excess mortality. Beyond the obvious reactions, such as bleeding with warfarin or other anticoagulants (Pouyanne *et al.*, 2000; Lacoste-Roussillon *et al.*, 2001; Pirmohamed *et al.*, 2004; Claudia *et al.*, 2011; Huhtakangas *et al.*, 2011; Subherwal *et al.*, 2012), there are more subtle effects that are also well known, such as for instance fatal falls with benzodiazepines, a class of drugs that are commonly misused by being prescribed long term to elderly persons with no clear benefit and clear risks (Lagnaoui *et al.*, 2004; Pariente *et al.*, 2008; Billioti de Gage *et al.*, 2012).

Other reports show evidence of widespread ignorance of SPC or changes in SPC, even when accompanied by Dear Doctor letters, Dear Health Care Professional letters, or Dear Healthcare Profes-

sional communications (Mol *et al.*, 2010; Bahri *et al.*, 2011; Theophile *et al.*, 2011b; Pieming *et al.*, 2012a,b; Ruiter *et al.*, 2012).

Since most of the relevant adverse reactions leading to patient harm are well-known adverse reactions to old medicines, and despite the major advances in pharmacovigilance, the proportion of patients admitted to hospitals because of adverse reactions has mostly not changed for 40 years (Einaron, 1993; Moore *et al.*, 1998; Pirmohamed *et al.*, 2004); certainly, the major issue is not so much the regulation of these drugs, but the training of prescribers and of patients (Aronson *et al.*, 2006).

The training of prescribers is a major concern in Europe. The number of hours available in medical schools to teach pharmacology to medical students has been dwindling, whereas the power and complexity of drugs is increasing. No wonder under-trained prescribers may not always use or prescribe drugs in the most rational way. The medical diploma has been likened to a "licence to kill." This obviously requires the appropriate training for proper prescribing (Birkett *et al.*, 2010). A European survey of clinical pharmacology, done under the aegis of the European Association of Clinical Pharmacology and Therapeutics ([www.EACPT.org](http://www.EACPT.org)) has found that in most European countries the standard of training is still very low (Orme, 2003). The number of hours used to train medical students in prescribing is small and in some countries not getting any better (Jaillon, 2006). There is obviously a need to rethink the training of physicians to ensure that they understand the basics of safe and effective prescribing, but also the mechanisms of adverse drug reactions, so they can be anticipated and prevented, as most could and should. This should start early in the medical career, and training in proper prescribing should be mandatory (Maxwell *et al.*, 2007; Heaton *et al.*, 2008; Sandilands *et al.*, 2011; Duncan *et al.*, 2012; Ross *et al.*, 2013). Much as a bus driver has to renew their driver's licence every few years, prescribers should have mandatory refresher training in prescription of new drugs to maintain their prescriber's licence. If anatomy is relatively stable over a lifetime, the drugs available for a prescriber will change rapidly over time. The drugs that are most prescribed now were not available 20 years ago (or

less), and physicians trained at the time will only have a very faint notion of what they are unless of course the pharmaceutical industry representatives trained them, which may not be ideal (Clark *et al.*, 2007). A poorly trained prescriber is much more dangerous for society than a poorly trained bus driver. Bus accidents may make the headlines more because more people are killed at once, but the effects of poor prescribing are cumulatively much greater.

Another driver of adverse drug reactions is patient lack of compliance or carelessness. This is encouraged by the constant repetition that drugs should be safe, and that it is in some way abnormal and a scandal that they are not completely without danger. They are not and cannot be. There is no such thing as a safe drug. All drugs are dangerous, though some may also be useful (Moore, 2005). Any chemical substance that directly or indirectly alters or modifies the body's chemistry or physiological response, whether through interaction with receptors, enzymes, direct chemical effect, or through the inhibition or stimulation of immunity, will have a potential for adverse reactions. The more effective or powerful the drug is, the greater the risk of adverse reactions. There are only more or less safe (or dangerous) ways of prescribing and using them. The illusion of drug safety is certainly a major reason for the continued rate of serious adverse reaction. Other equally dangerous environmental modifiers are recognized as dangerous. Cars are dangerous if driven. Drivers know not to drive drunk or tired, and use seatbelts (or should) (Blazejewski *et al.*, 2012). If they do not, they will be fined if caught. Even though flying is by far the safest way of traveling, each time you get on a plane you get a demonstration of seat belts and life jackets, to impress the risks of traveling. Patients should also be informed that drugs are dangerous. This should be written on each patient information leaflet, rather than a long and useless list of indiscriminate potential adverse reactions. There is a need for the training of patients and future patients in the proper use of drugs. A prolonged campaign for rational use of antibiotics has reduced the use of these drugs, and patient requests for them. Maybe just as children are taught in school safe-street procedures and how to cross streets, they

could be taught safe medication procedures and how to use medicines.

Finally, there are the unexpected modifiers of risks and effects, not so much concomitant diseases and drugs, which are known or should be known by the prescriber, but the genetic factors. These encompass the drug's pharmacokinetics, especially through variability in the cytochrome system (Hamberg *et al.*, 2010, 2013), but also the pharmacodynamics through altered receptors or ion channels. Both of these main types of pharmacogenetic variability may change the patient's individual risk/benefit ratio in a relatively straightforward way. In addition, other genetic traits may specifically change the patient's susceptibility to a given adverse reaction for specific drugs. A prime example is DRESS syndrome and abacavir, related to a human leukocyte antigen subtype (Phillips *et al.*, 2011; Pirmohamed, 2012). No doubt more of these will be discovered. In time, the one-dollar whole genome will be able to track individual susceptibility and provide patients with a map of their own strengths and weaknesses, but may not protect them against poor prescribing and dangerous patient behavior.

The very nature of medicines and their relationship and interactions with the prescriber and the patient need to be rethought. That is our only hope to go from just counting bodies to actually avoiding drug-related events and deaths.

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Plate 32.1 Exanthematous morbilliform eruption consisting of erythematous macules and papules of the trunk.



Plate 32.3 Bullous eruption of the arm corresponding to a phototoxic eruption on a sun-exposed area.



Plate 32.2 Urticaria with oedematous papules and plaques, which generally last a few hours.



Plate 32.4 Cutaneous necrotizing vasculitis, consisting of purpuric papules, which predominate on the lower extremities.



Plate 32.5 Acute generalized exanthematous pustulosis.



Plate 32.6 DRESS syndrome presenting as exfoliative dermatitis.



Plate 32.7 Fixed drug eruption, characterized by round, sharply demarcated erythematous plaques.

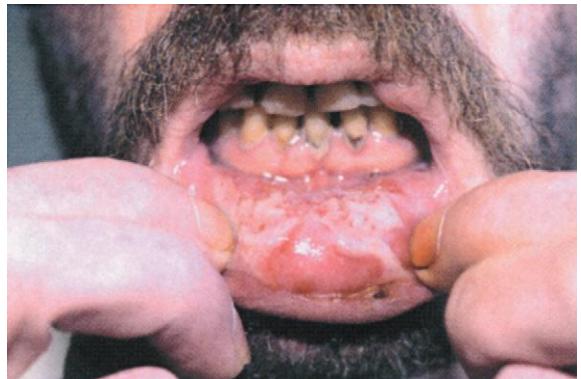


Plate 32.8 Drug-induced pemphigus with erosion of mucous membrane.



Plate 32.9 Toxic epidermal necrolysis characterized by skin necrosis, with flaccid blisters and epidermal detachment on the trunk.