

Editors

Ron Mann

Elizabeth Andrews

Pharmacovigilance

Second Edition



 **WILEY**

PHARMACOVIGILANCE

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Editors

RONALD D. MANN

ELIZABETH B. ANDREWS



John Wiley & Sons, Ltd

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Preface

Pharmacovigilance is the study of the safety of marketed drugs examined under the practical conditions of clinical use in what are usually large populations. Safety cannot, however, be considered except in relation to the efficacy of the drug, whether it is used in healthy or sick people, the pharmaceutical quality of the drug, the nature and seriousness of any side effects and the degree to which these can be treated, the threat posed by the disease that is treated with the drug and the rest of the complex of issues that comprise holistic patient care.

Much has happened in the world of pharmacovigilance since the first edition of this book was published in 2002. The legal basis of the subject in Europe has changed materially, the PSUR (Periodic Safety Update Report) has come to be recognized as a major means of undertaking a comprehensive re-assessment of the balance of safety and efficacy of the drug, the use of the MedDRA dictionary has become more established, the growth of regional monitoring centres has been found increasingly useful in the UK and especially in France, adverse drug reaction monitoring has been strengthened in Germany, the structure of the regulatory body in the UK has been revised, and there has been considerable emphasis on pharmacovigilance planning and the development of risk minimization action plans. There has been greater scrutiny of drug safety policy in the US than ever before, within the regulatory agency itself, by congress, and by committees of the Institute of Medicine.

There have also been reassessments of the place of some major drugs and drug classes in ther-

apeutics. Drugs have been withdrawn or their usage modified due to prolongation of the QTc interval and the threat of torsades de pointes, the place of the SSRIs (selective serotonin reuptake inhibitors) in young people has been much modified, the long-term use of HRT (hormone replacement therapy) has been restricted and among the non-steroidal anti-inflammatory agents the cardiovascular safety of long-term usage of the COX-2 (cyclo-oxygenase-2) inhibitors has been challenged.

All of these changes call attention to the need for yet more rigorous and proactive pharmacovigilance. The changes also highlight the need for greater transparency of the pharmacovigilance process to assure the public that regulators, health professionals, pharmaceutical companies and academics are continually reviewing risks and benefits of medicines in their fullest context.

These events have necessitated a second edition of this book which is now divided into five parts, thus:

1. The basis of pharmacovigilance
2. Signal generation
3. Pharmacovigilance and selected system–organ classes
4. Key current topics
5. Lessons and directions.

It is interesting that the latter section ends with an important chapter on pharmacogenetics – a road, along with the growth of the use of organized

databases, that many of us feel will provide much of the progress of the future.

The editors wish to express their considerable appreciation of the support received from Mrs Lucy Sayer of Wiley and Mrs Juliet Booker who has assisted her. Professor Mann wishes to acknowledge

the very extensive help he has received from his personal assistant, Mrs Susan Jerome.

Ronald D. Mann
Elizabeth B. Andrews
27 April 2006

Foreword

When I wrote the foreword to the first edition of this book in 2002, I little thought that I would be invited to repeat the exercise a mere four years later. The early publication of the second edition of a book such as this is an important event, signalling that the contents of the first edition have met with professional approval, have fulfilled an informational need and, as science moves on, the topics discussed need to be revisited.

So what of moment has occurred in the field of pharmacovigilance in the past four years? I would highlight four developments which to me seem significant.

First, from a regulatory standpoint, the fallout from the withdrawal of rofecoxib (Vioxx) by the manufacturers in September 2004 has cast the longest shadow. Regulatory agencies worldwide were forced to examine their approach to the safety of marketed medicines. The timely implementation in November 2005 of the new EU pharmaceutical directives into national legislation gave fresh emphasis to the importance of risk management strategies and risk minimisation plans for newly approved medicines. How these plans should be implemented and monitored remains the subject of intense debate in the light of earlier and largely unsuccessful attempts by regulators to encourage effective postmarketing surveillance by the sponsors of new medicines. Among the issues up for discussion is who should pay for studies which have been agreed and what penalties should be exacted for non-compliance.

Second, from a scientific standpoint, the contributions of the ‘omics’ to pharmacovigilance have perhaps been less than many had hoped for. The translation of the principles of pharmacogenomics to the practice of personalised medicine in the clinic remains an elusive goal, with the notable exception of oncology where long-standing genetic research is now

beginning to pay rich dividends. Innovations in diagnostic tests are an essential precursor to the successful adoption of personalised medicine and, again, intensive work in oncology illustrates the importance of this. The widespread development of safer and more effective medicines underpinned by pharmacogenetic principles remains tantalisingly distant in spite of our increasing knowledge base in the understanding of genetic polymorphisms of drug-metabolising enzymes, drug transporters and of receptors mediating drug response.

Pharmacoepidemiology is a third area worthy of comment and here I would highlight one study which provided new evidence of the clinical and economic importance of adverse drug reactions. Pirmohamed and colleagues (2004) reviewed some 18 820 patients admitted to two large general hospitals over a six-month period. 1225 patients (or 6.5% of the population) were admitted as a direct result of an adverse drug reaction. The overall fatality rate of these patients was 0.15% with a projected annual cost to the NHS of adverse drug reactions, based on these figures, of £466 million. Studies such as this give a clear indication of the clinical and economic burden that adverse drug reactions place on health-care systems.

A fourth area where the pace of debate has accelerated is the role of patients in all aspects of medicines regulation, including pharmacovigilance. For many years, patients were regarded as the passive recipients of medicines prescribed by health-care professionals, mainly doctors. This is no longer the case, and the sponsors of new drugs, regulators and prescribers ignore the views of patients at their peril. The public’s assessment of the risk–benefit balance of a medicine may differ markedly from that of the industry or the

regulator and attention must be paid to these views. The greater involvement of patients is an important and positive move. Implicit in this is the need to provide higher quality and clearer information on medicines for both prescribers and the public. This process has been set in train, but has some way to go and deserves further encouragement.

My foreword in 2002 expressed the wish that pharmacovigilance should focus more on extending knowledge on drug safety and less on finding evidence of harm, and further, more work on outcome measures (including surrogate markers and biomarkers) was needed. These

remain worthy aspirations and it will be interesting to see the progress which is made when the third edition of this valuable book comes to be written.

Alasdair Breckenridge

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Part I

THE BASIS OF PHARMACOVIGILANCE

1

Introduction

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'Not all hazards can be known before a drug is marketed'.

Committee on Safety of Drugs, Annual Report 1969, 1970.

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 1961–62. 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. Figure 1.1 shows a child with thalidomide-induced amelia of the upper limbs and phocomelia of the lower limbs fitted with the kind of prostheses available at that time. 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 39 licensed medicines withdrawn, after marketing, for drug safety reasons since the mid-1970s in the United Kingdom.

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 45 years since the thalidomide tragedy?

Partly, the problem is one of numbers. For example, the median number of patients contributing data to

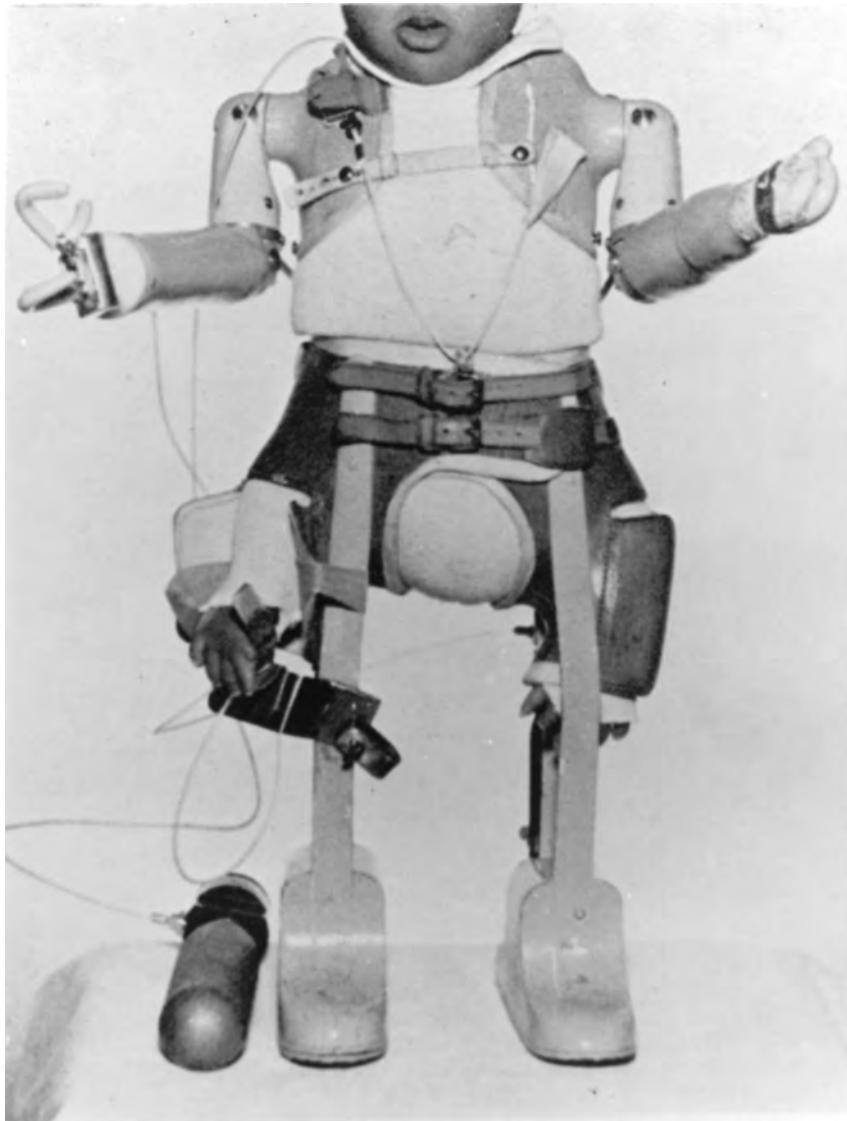


Figure 1.1. Child with thalidomide-induced deformities of the upper and lower limbs fitted with pneumatic prostheses.

the clinical safety section of new drug licensing applications in the United Kingdom 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

Table 1.1. Drugs withdrawn in the United Kingdom by the marketing authorization holder or suspended or revoked by the Licensing Authority.

Brand name (drug substance)	Year action taken	Major safety concerns
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, multi-system toxicity
Althesin (alphaxolone plus alphadolone)	1984	Anaphylaxis
Pexid (perhexilene)	1985	Hepatotoxicity, neurotoxicity
Suprol (suprofen)	1986	Nephrotoxicity
Merital (nomifensine)	1986	Haemolytic anaemia
Unicard (dilevalol)	1990	Hepatotoxicity
Glauline eye drops 0.6% (metipranolol)	1990	Uveitis
Halcion (triazolam)	1991	Psychiatric reactions
Micturin (terodiline)	1991	Arrhythmias
Teflox (temafloxacin)	1992	Multi-system toxicity
Centoxin (nebacumab)	1993	Mortality
Roxiam (remoxipride)	1994	Aplastic anaemia
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

different from the kinds of volunteers and patients in whom pre-marketing 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 paediatric 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 United States (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 post-marketing safety experience. This situation may well change as large comprehensive databases such as the General Practice Research Database (GPRD) 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 information, 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 35 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 United Kingdom 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 post-marketing surveillance (PMS) 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 United States since the mid-1970s. A series of events in the United States 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 timelines for FDA reviews. The shorter approval times lead to some medications being approved sooner in the United States than that 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, Pomeranz and Corey (1998) published the results of a meta-analysis that estimated that 106 000 fatal adverse reactions occurred in the United States in 1994. This and other articles (Wood, Stein and Woosley, 1998) stimulated considerable public, congressional and regulatory attention on reducing the societal burden of drug reactions and medication errors (Institute of Medicine, 1999; U.S. Food and Drug Administration, 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 centres. 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 United States and offers new challenges to pharmacovigilance professionals. In fact, the shift is not restricted to the United States as both the FDA and the EMEA in 2005 issued guidance documents for industry on signal detection, evaluation, good pharmacovigilance practice and recommendations for managing risks after the approval (EMEA, 2005; U.S. Food and Drug Administration, 2005a–c).

We have long recognized then that the safety of patients depends not only on drug licensing by regulatory bodies but also on post-marketing drug safety surveillance, pharmacovigilance. It is also important to note that the same post-marketing 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 adverse drug reactions. 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, haematopoietic 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 anaemia, 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 pharmacoepidemiology 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 ADR 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 United Kingdom, 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 United States, 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 under-reporting, and the data provide a ‘numerator’ (the number of reports of each suspected reaction) only. 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

This monitoring, abbreviated as PEM, as conducted in the United Kingdom and New Zealand, represents a ‘hybrid’ method, combining aspects of public health surveillance and spontaneous reporting with aspects of formal epidemiological studies. In the United Kingdom, 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. Six or twelve 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 his or her 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 90 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 United Kingdom and a similar programme in New Zealand are unique in providing a monitored-release programme that can detect or help refute new signals in the early life of a medicine.

Considerable interest centres 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 programmes, such as case-control surveillance of birth defects, conducted by the Sloane Epidemiology Center, screen for potential associations between birth defects and prescription and over-the-counter medications. Analytic methods that allow screening of enormous amounts of data for patterns that might deviate from expected – data mining techniques – are being applied to spontaneous reporting databases, databases on potential drug abuse and diversion and large population-based health records.

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 and 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, Shapiro and Mitchell, 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 current 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 United Kingdom) 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.

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 (RCTs) 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.

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 EMEA and FDA on pharmacovigilance planning and risk management. This emphasis on planning a pharmacovigilance programme 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 pharmacoepidemiology studies (International Society for Pharmacoepidemiology, 2004).

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Legal Basis – EU

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INTRODUCTION

Within the European Union (EU), the pharmaceutical industry is a highly regulated sector. The level of regulation reflects the potential hazards associated with the use of medicinal products. Subject to a limited number of exceptions, all medicinal products placed on the market within the EU must have a marketing authorisation. The grant of a marketing authorisation signifies that a medicinal product complies with the quality, safety and efficacy criteria set out in European medicinal product regulatory law. In 2004, a review of European pharmaceutical regulatory law took place, in what is referred to as the ‘EU Pharma Review’, and new legislation was issued. It is this new legislation that is discussed in this chapter.

Marketing authorisations for products to be placed on the EU market are granted:

- on a national basis by the competent authority of a Member State (where the product will be marketed in one Member State only); or
- through the mutual recognition procedure, where a marketing authorisation granted by the competent authority of an original ('Reference') Member State is accepted by the competent authorities of other Member States; and
- on an EU basis by the European Commission (the Commission) under the centralised procedure, in accordance with the provisions of Regulation (EC) No. 726/2004.

Pharmacovigilance requirements apply to all authorised medicinal products on the market in the EU and European Economic Area (EEA) states (Iceland, Liechtenstein and Norway). Both human use and veterinary medicinal products are subject to these requirements; this chapter outlines the requirements for human use medicinal products only.

The need for pharmacovigilance arises from the fact that, despite extensive clinical trials at the pre-licensing stage in support of a marketing authorisation application for a medicinal product, some safety hazards are only identified after wider use in the general population. The aim of establishing pharmacovigilance systems is to safeguard public health by taking measures for the intensive supervision of undesirable effects of authorised medicinal products so as to ensure the rapid withdrawal from the market of any medicinal product presenting a negative risk–benefit balance under normal conditions of use.

The key legal requirements for pharmacovigilance for human use medicinal products are set out in European legislation. For medicinal products authorised under national or mutual recognition procedures, the relevant legislation is Directive 2001/83/EC of 6 November 2001 on the Community Code relating to medicinal products for human use, as amended by Directive 2002/98/EC of 27 January 2003, Directive 2003/63/EC of 25 June 2003, Directive 2004/24/EC of 31 March 2004 and Directive 2004/27/EC of 31 March 2004. All references throughout this chapter to Directive 2001/83/EC are to the amended text. For medicinal products authorised under the centralised procedure, the relevant legislation is Regulation (EC) No. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (the ‘Agency’). For investigational medicinal products used in clinical trials, pharmacovigilance requirements are set out in the Clinical Trials Directive, Directive 2001/20/EC.

GUIDANCE

Both Article 106 of Directive 2001/83/EC and Article 26 of Regulation (EC) No. 726/2004 require the

Commission, in consultation with the Agency, the Member States and interested parties, to produce guidance on the collection, verification and presentation of adverse reaction reports so as to facilitate the exchange of pharmacovigilance information within the EU. All such guidance must take account of international harmonisation work on pharmacovigilance terminology and classification, and the Commission is required to publish a reference to an internationally agreed medical terminology.

In accordance with this requirement, the Commission provides guidance on the interpretation and implementation of pharmacovigilance requirements in Volume 9 of *The Rules Governing Medicinal Products in the European Union*. For ease of reference, it should be noted that although Volume 9 replaces all pharmacovigilance guidance published by the Commission before June 2004, there is presently a draft of Volume 9a that deals with the changes introduced by the EU Pharma Review.

The Agency is advised by a scientific committee, the Committee for Medicinal Products for Human Use ('CHMP'). A sub-division of this committee is the Pharmacovigilance Working Party, which has a mandate to provide a forum for discussion, consensus development and co-ordination of pharmacovigilance issues at EU level with which Member States are required to co-operate. The Pharmacovigilance Working Party produces documents which supplement the guidance in Volume 9; these are identified in Part IV of Volume 9.

DEFINITIONS

The definitions of key pharmacovigilance concepts apply to all European pharmacovigilance and are set out in Title I of Directive 2001/83/EC. The Commission provides guidance on their interpretation in Volume 9.

An ‘adverse reaction’ is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. Volume 9 advises that an adverse reaction, contrary to an adverse event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected.

A ‘serious adverse reaction’ means an adverse reaction which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly/birth defect. Volume 9 advises that a serious adverse reaction also includes serious adverse clinical consequences associated with use outside the terms of the Summary of Product Characteristics (including, e.g. prescribed doses higher than those recommended), overdoses or abuse. Important adverse reactions that are not immediately life threatening or do not result in death or hospitalisation, but may jeopardise the patient, should be considered as ‘serious’.

An ‘unexpected adverse reaction’ means an adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristics. Volume 9 advises that this includes reactions related to the class of products within which the particular product falls, which are mentioned in the Summary of Product Characteristics but which are not specifically described as occurring with the product.

For nationally authorised products, the relevant Summary of Product Characteristics is that approved by the competent authority in the Member State to whom the reaction is being reported. For centrally authorised products, the relevant Summary of Product Characteristics is that authorised by the European Commission.

‘Abuse of medicinal products’ means the persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

EUROPEAN PHARMACOVIGILANCE FOR MEDICINAL PRODUCTS AUTHORISED BY NATIONAL OR MUTUAL RECOGNITION LICENSING PROCEDURES – DIRECTIVE 2001/83/EC

Title IX of Directive 2001/83/EC deals with pharmacovigilance obligations imposed on the Agency, the Commission, marketing authorisation holders and the Member States for medicinal products authorised through national and mutual recognition procedures. Article 102 explains that:

‘In order to ensure the adoption of appropriate and harmonised regulatory decisions concerning the

medicinal products authorised within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use, the Member States shall operate a pharmacovigilance system. This system shall be used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically.

Member States shall ensure that suitable information collected within this system is communicated to the other Member States and the Agency. The information shall be recorded in the database referred to in [Regulation (EC) No. 726/2004] and shall be permanently accessible to all Member States and without delay to the public.

This system shall also take into account any available information on misuse and abuse of medicinal products which may have an impact on the evaluation of their benefits and risks.’

THE AGENCY

Article 105 requires the Agency, in collaboration with the Member States and the Commission, to set up a data-processing network to facilitate the exchange of pharmacovigilance information to enable all the competent authorities to share pharmacovigilance information at the same time. The development of the EudraVigilance facility is discussed further below.

THE COMMISSION

As discussed previously, the Commission has obligations under Article 106 in relation to the publication of pharmacovigilance guidance.

MARKETING AUTHORISATION HOLDERS

Article 104 of Directive 2001/83/EC sets out the obligations of marketing authorisation holders. Marketing authorisation holders must maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country. Save in exceptional circumstances, these reactions must be communicated electronically in the form of a report in accordance with the guidance in Volume 9. All suspected serious adverse reactions brought to the attention of the marketing authorisation holder

by health care professionals must be recorded and reported to the competent authority of the Member State where the incident occurred within 15 days of receipt of the information.

In addition, marketing authorisation holders are required to record and report all other suspected serious adverse reactions of which they can reasonably be expected to have knowledge and which meet the notification criteria set out in Volume 9. This addresses the fact that, in addition to adverse reactions reported by health care professionals, others will be identified in worldwide scientific literature or during post-authorisation studies.

Marketing authorisation holders must ensure that all suspected serious unexpected adverse reactions and any suspected transmission through a medicinal product of any infectious agent occurring in the territory of a third country are reported to the Agency and the competent authorities of the Member States where the product is authorised, within 15 days of receipt of the information. The format for these reports is set out in Volume 9.

Where a medicinal product has been authorised through the mutual recognition procedure, the marketing authorisation holder must ensure that all suspected serious adverse reactions occurring in the Community are reported in such a way as to be accessible to the Member State that first authorised the product ('Reference Member State') or to any competent authority acting as Reference Member State. The Reference Member State shall assume the responsibility of analysing and monitoring such adverse reactions.

All suspected adverse reactions must be submitted to the competent authorities in the form of a periodic safety update report ('PSUR') (including a scientific evaluation of the risk/benefit balance):

- immediately upon request or at least every 6 months after authorisation and until the placing on the market;
- immediately upon request, or at least every 6 months during the first 2 years following the initial placing on the market and
- once a year for the following 2 years.

After this period, the PSURs must be submitted at 3-year intervals or immediately upon request. Following the grant of a marketing authorisation, the marketing authorisation holder may request the amendment

of these periods. There is also a specific provision that states that a marketing authorisation holder may not communicate information relating to pharmacovigilance concerns about its products to the general public without giving prior or simultaneous notification to the competent authority. In any case, the marketing authorisation holder must ensure that all such information is presented objectively and is not misleading. If a marketing authorisation holder fails in this duty, the Member States are under an obligation to apply effective, proportionate and dissuasive penalties.

QUALIFIED PERSON

Article 103 of Directive 2001/83/EC requires marketing authorisation holders to have an appropriately qualified person, who must be resident in the Community and who is responsible for pharmacovigilance, permanently and continuously at their disposal. Volume 9 provides that this qualified person may be resident in the EEA, reflecting the fact that the pharmacovigilance legislation is not, in fact, limited to the EU. The qualified person is responsible for:

- establishing and maintaining a system which ensures that information about all suspected adverse reactions, reported to people within the company and medical representatives, is collected and collated at a single point within the Community;
- preparing the reports that the marketing authorisation holder is obliged to prepare (see p. 15) for the competent authorities, in accordance with national guidelines and Volume 9;
- ensuring a full and prompt response to any request from a competent authority for additional information (including information about volume of sales or prescriptions) necessary for a risk/benefit evaluation of a medicinal product; and
- providing the competent authorities with any other relevant information about the benefits and risks afforded by a medical product, including information on post-authorisation safety studies.

MEMBER STATES

Article 101 of Directive 2001/83/EC requires Member States to take all appropriate measures to encourage all

health care professionals to report suspected adverse reactions to the competent authorities. Member States can also impose specific reporting requirements on health care professionals, in respect of the reporting of suspected serious or unexpected adverse reactions.

Once notified of suspected serious adverse reactions, Article 105 requires Member States to ensure that they are brought to the attention of the Agency, the other Member States and the marketing authorisation holder within 15 days using the Agency's data-processing network. Where, following an evaluation of adverse reaction reports, a Member State decides that a marketing authorisation should be varied, suspended or revoked, Article 107 imposes an obligation to notify the Agency, other Member States and the marketing authorisation holder forthwith. In urgent cases, a Member State may suspend the marketing authorisation of a medicinal product on the condition that the Agency, Commission and other Member States are informed no later than the following working day.

EUROPEAN PHARMACOVIGILANCE FOR CENTRALLY AUTHORISED MEDICINAL PRODUCTS – REGULATION (EC) NO. 726/2004

Articles 57(1)(c)–(f) of Regulation (EC) No. 726/2004 make the Agency and particularly its committees responsible for the co-ordination of the supervision of medicinal products which have been authorised within the Community and for providing advice on the measures necessary to ensure the safe and effective use of these products. Title II Chapter 3 of Regulation (EC) No. 726/2004 deals specifically with pharmacovigilance relating to medicinal products for human use.

THE AGENCY

Article 22 requires the Agency to co-operate with the national pharmacovigilance systems, in order to receive all relevant information about suspected adverse reactions to authorised medicinal products. If necessary, the Agency's CHMP will provide opinions on the measures necessary to ensure the safe and effective use of particular medicinal products, which may

include amendments to the marketing authorisation granted.

EudraVigilance is a central computer database created by the Agency in December 2001, and it contains reports of suspected serious adverse reactions to medicinal products that have been authorised by the Community. These reports are received from the various competent authorities and from the pharmaceutical companies. This satisfies the Agency's obligation under Article 57(1)(d) to ensure the dissemination of information on adverse reactions to medicinal products authorised in the Community by means of a database permanently accessible to all Member States. In the future, health care professionals, marketing authorisation holder and the public will all have appropriate levels of access to these databases. This is because the Agency believes that those groups could benefit from receiving feedback based on information in EudraVigilance and that this could help improve treatment and prevent side effects.

As of 1 May 2004, EudraVigilance can also be used for reporting side effects from clinical trials.

The Agency is also responsible for collaboration with the World Health Organisation (WHO) on matters of international pharmacovigilance, and must take any steps necessary to submit appropriate and adequate information promptly to the WHO regarding the measures taken in the EU which may have a bearing on public health protection in third countries (Article 27).

THE COMMISSION

The Commission's obligations under Article 26 in relation to the publication of guidance are discussed above.

MARKETING AUTHORISATION HOLDERS

Article 22 requires marketing authorisation holders to ensure that all relevant information about suspected adverse reactions to centrally authorised products is brought to the attention of the Agency and also importantly states that patients should be encouraged to communicate any adverse reaction to health care professionals.

Article 24 requires holders of centralised marketing authorisations to ensure that all suspected serious

adverse reactions to one of their products occurring within the Community that are brought to their attention by a health care professional, are recorded and reported to the Member States where the incidents have taken place within 15 days of receipt of the information. Marketing authorisation holders must also ensure that all suspected serious unexpected adverse reactions and any suspected transmissions through medicinal products of any infectious agents occurring in the territory of a third country are reported to the Agency and all the Member States within 15 days of receipt of the information.

As with holders of marketing authorisations granted under national or mutual recognition procedures, holders of marketing authorisations for centrally authorised products are required to maintain detailed records of all suspected adverse reactions occurring within or outside the EU reported to them by health care professionals.

Subject to the specific terms of a marketing authorisation, all suspected adverse reactions must be submitted to the competent authorities in the form of a PSUR (including a scientific evaluation of the risk/benefit balance):

- immediately upon request or at least every 6 months after authorisation and until the placing on the market;
- immediately upon request or at least every 6 months during the first 2 years following the initial placing on the market; and
- once a year for the following 2 years.

After this period, the PSURs must be submitted at 3-yearly intervals or immediately upon request. There is a specific provision that states that a marketing authorisation holder may not communicate information relating to pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the Agency. In any case, the marketing authorisation holder must ensure that all such information is presented objectively and is not misleading. If a marketing authorisation holder fails in this duty, the Member States are under an obligation to apply effective, proportionate and dissuasive penalties.

As can be seen, the considerations for a marketing authorisation holder are effectively the same, whether the product is authorised centrally or nationally/mutually recognised.

QUALIFIED PERSON

Article 23 of Regulation (EC) No. 726/2004 is similar to Article 103 of Directive 2001/83/EC and requires holders of centralised marketing authorisations to have an appropriately qualified person, responsible for pharmacovigilance, permanently and continuously at their disposal. This qualified person shall reside in the Community (or EEA, according to Volume 9) and is responsible for:

- establishing and managing a system which ensures that information about all suspected adverse reactions, reported to people within the company and medical representatives, is collected, evaluated and collated so that it may be accessed at a single point within the EU;
- preparing the reports required of the marketing authorisation holder for the competent authorities and the Agency;
- ensuring a full and prompt response to any request from the competent authorities for additional information (including information about volume of sales or prescriptions) necessary for a risk/benefit evaluation of a medicinal product; and
- providing the competent authorities with any other relevant information about the benefits, and risks of a medicinal product, including information on post-authorisation safety studies.

MEMBER STATES

Article 22 requires the competent authorities of Member States to ensure that all relevant information about suspected adverse reactions to centrally authorised products are brought to the attention of the Agency. Where the suspected adverse reactions are classified as serious, Article 25 requires the Member States to record and report them to the Agency and the marketing authorisation holder within 15 days of receipt of the information.

CLINICAL TRIALS DIRECTIVE

In addition to the pharmacovigilance requirements for authorised medicines, Directive 2001/20/EC on the

approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use introduced reporting requirements for adverse events and serious adverse reactions that occur during clinical trials. Investigators are required to report all serious adverse events immediately to the sponsor, other than those that the protocol or investigator's brochure identify as not requiring reporting. The sponsor shall keep detailed records of all adverse events that are reported to him by investigators, and these records shall be submitted to the Member States in whose territories the clinical trials are being conducted, if the Member States so request.

The sponsor shall ensure that all information related to suspected serious unexpected adverse reactions that are fatal or life threatening is recorded and reported as soon as possible to the competent authorities in all Member States concerned, and to the ethics committee, no later than 7 days after the sponsor receives such information, and any relevant follow-up information should be communicated within an additional 8 days. Other suspected serious unexpected adverse reactions should be reported to the competent authorities concerned and to the ethics committee within 15 days of first knowledge of the sponsor. The sponsor shall also inform all investigators.

Once a year throughout the clinical trial, the sponsor should provide the Member States in whose territories the clinical trials are being conducted, and the ethics committee, with a listing of all suspected serious adverse reactions which have occurred over the period, and a report of the subjects' safety. Member States shall ensure that all suspected unexpected serious adverse reactions to investigational medicinal products are entered into a central database.

EUROPEAN PHARMACOVIGILANCE LEGISLATION – MEMBER STATE IMPLEMENTATION

European Directives are not directly binding on Member States, but must be implemented nationally through domestic legislation. European Regulations have a direct effect on Member States, and no further

procedural action is required for them to bind Member States.

UNITED KINGDOM

The European pharmacovigilance requirements have been implemented in the United Kingdom by the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994, as amended (the '1994 Regulations') (see Appendix 6 at <http://www.opsi.gov.uk>). Schedule 3 of the 1994 Regulations creates certain criminal offences for non-compliance with European pharmacovigilance requirements. In addition, the Medicines for Human Use (clinical trials) Regulations 2004 (the '2004 Regulations') (see Appendix 7 at <http://www.opsi.gov.uk>), which implemented Directive 2001/20 relating to the implementation of good clinical practice in the conduct of clinical trials, imposes specific pharmacovigilance obligations on clinical trial investigators and sponsors in respect of reporting suspected unexpected serious adverse reactions arising in clinical trials. Regulation 49 of the 2004 Regulations makes it a criminal offence to fail to comply with those obligations.

The UK competent authority responsible for medicinal product pharmacovigilance is the Medicines and Healthcare products Regulatory Agency ('MHRA'), an executive agency of the Department of Health.

The MHRA's post-licensing division, together with the Commission on Human Medicines ('CHM'),¹ runs the 'Yellow Card' scheme for the reporting of all suspected adverse drug reactions (the name of the scheme derives from the colour of the standardised reporting forms, see Appendix 8 at <http://www.opsi.gov.uk>). Voluntary reports are accepted by the MHRA/CHM from both health care professionals and members of the public.² In addition, reports are received from marketing authorisation holders in accordance with their legal obligations.

For established products, the MHRA requests that health care professionals report only serious suspected

¹ The Commission on Human Medicines was established on 30 October 2005, combining the functions of the former Medicines Commission and Committee on Safety of Medicines.

² Yellow card reporting used to be available only to health care professionals. A pilot scheme for patient reporting was launched in January 2005, and now all patients can report suspected adverse reactions using this scheme.

adverse reactions. For newer products, for which relatively limited safety information will be available, the MHRA/CHM encourages the reporting of all suspected adverse reactions. New products are identified with an inverted black triangle symbol ‘▼’ in the relevant professional publications and advertising material. In addition, the MHRA/CHM has a particular interest in adverse reactions in children and the elderly – delayed drug effects, congenital abnormalities and herbal remedies.

In accordance with the requirements of the Data Protection Directive 95/46/EEC (as implemented in the United Kingdom by the Data Protection Act 1998, as amended, see Appendix 9 at <http://www.opsi.gov.uk>) and with common law confidentiality requirements, personal details, such as the name and date of birth of a patient, are no longer requested for Yellow Cards completed by health care professionals. Instead, reporters include the patient’s age, sex and a reference number to enable identification of the particular report in any further correspondence. For Yellow Cards submitted by patients, personal details are requested so that the MHRA can get in contact with the person if more information is needed.

All reports are entered into the MHRA’s Adverse Drug Reactions On-Line Information Tracking (ADROIT) database. The MHRA evaluates the reports to assess the causal relationship between the drugs and reported reactions, and to identify possible risk factors contributing to the occurrence of the reactions. Marketing authorisation holders may subscribe to the MHRA’s ADROIT Electronically Generated Information Service (AEGIS), enabling electronic exchange of pharmacovigilance data.

On rare occasions, if the MHRA determines that the risks of a product outweigh its benefits, it may be necessary to withdraw the product from the market. Alternatively, and as is more usual, the MHRA may require that warnings be included in the product information or on the package label or that the indications for the use of the medicine be restricted.

The MHRA communicates with health care professionals and patients to warn about adverse effects and to provide information. It sends doctors and pharmacists *Current Problems in Pharmacovigilance*, a bulletin providing alerts to problems identified with particular medicines. For urgent medicinal product

hazard warnings, ‘Dear Health care Professional’ letters are sent to all doctors and pharmacists by post or electronic cascade. Fact sheets are also produced for both health care professionals and patients, and safety alerts are published on the MHRA’s website.

ITALY

The European pharmacovigilance requirements have been implemented in Italy by Legislative Decree n. 178 of 29 May 1991 and Legislative Decree n. 44 of 18 February 1997 which has been partially amended by legislative Decree n. 95 of 8 April 2003.

The Italian authority responsible for pharmacovigilance is the Department for the Evaluation of Medicinal Products and Pharmacovigilance of the Agenzia Italiana del Farmaco (AIFA) (the ‘Italian Agency of Pharmaceuticals’).

The AIFA liaises with regional health authorities, with the national pharmacovigilance authorities of other Member States and with international institutions, such as the WHO. In accordance with European requirements, all pharmaceutical companies must appoint a ‘qualified person’ responsible for pharmacovigilance, on a continuous and permanent basis. Pharmaceutical companies must:

- maintain detailed records of all suspected adverse reactions that occurred in Italy, in the European Community or in any other third country;
- record and notify to the competent health authority and/or to the AIFA all suspected serious reactions that occurred in Italy and that were brought to their attention by health care professionals immediately and in any case within 15 days following the receipt of the information;
- ensure that all serious and unexpected adverse reactions that occurred in a third country and were brought to their attention by a health care professional are reported to the AIFA immediately and in any case not later than 15 days following receipt of relevant information;
- report to the AIFA any suspected serious adverse reaction that occurred in the European Community, when the medical products were authorised according to the mutual recognition procedure and for which Italy acts as the Reference State.

Doctors and health care professionals shall submit all suspected adverse reactions of which they are informed immediately to the person responsible for pharmacovigilance in the health institution to which they belong, who in turn shall transmit electronically, immediately and in any case not later than 7 days from receipt of the information, the above information to both the holder of the marketing authorisation and to the AIFA. Health care professionals must notify any and all suspected adverse reactions (serious, not serious, expected and unexpected) to vaccines and medicines that are under intensive control and included in lists published periodically by the AIFA.

Public health institutions and scientific institutions shall appoint a person responsible for pharmacovigilance, who must take care of the connection to and registration with the national electronic system for the management of pharmacovigilance issues. Private clinics satisfy their pharmacovigilance obligations through the individual responsible for pharmacovigilance at the public institution.

Adverse event reports are submitted online. Registration on the national electronic system takes place through a very simple procedure laid down by the AIFA itself. The reporting form is in Appendix 10 (<http://www.opsi.gov.uk>).

The Decree n. 95/2005 abolishes the criminal sanctions that were provided for violations of the obligation to notify medicinal adverse reactions by doctors, pharmacists and health care professionals and introduces higher administrative sanctions against pharmaceutical companies that do not comply with the law relating to the registration and notification of serious and adverse reactions. Moreover, the decree also provides for disciplinary sanctions against health care professionals at public health institutions.

In case of violation of the pharmacovigilance obligations set out above, the following sanctions may be applied:

- a fine from €30,000 to €18,000 may be levied against the holder of the marketing authorisation. This amount is increased by an amount between 0.1% and 1% of the revenue generated by the sale of the product to which the information relates;
- a fine from €20,000 to €120,000 levied against the person responsible for pharmacovigilance at the holder of the marketing authorisation; and

- the submission of the person responsible for pharmacovigilance at the public institutions to disciplinary proceedings, according to law.

FRANCE

The European pharmacovigilance requirements have been implemented into French law by a Decree n. 95–278 of 13 March 1995. This decree was later amended by the Decrees n. 99–144 of 4 March 1999 and n. 2004–99 of 29 January 2004. The relevant provisions regarding pharmacovigilance are now codified in Articles R.5121-150 *et seq.* of the French Public Health Code. In addition, on 28 April 2005, the Health Ministry published guidelines for good application of pharmacovigilance rules (*'Bonnes Pratiques de Pharmacovigilance'*).

The competent authorities responsible for pharmacovigilance are the French Agency for the Sanitary Safety of Health Products ('AFSSAPS'), the National Pharmacovigilance Commission ('Commission Nationale de Pharmacovigilance'), the Technical Committee ('Comité Technique') and, at a regional scale, the regional pharmacovigilance centres (there are 31 centres).

The French Public Health Code provides for reporting obligations on health care professionals. In particular, it requires medical doctors, dental surgeons and midwives to report any serious or unexpected adverse reactions in relation to a medicinal product, whether or not they have actually prescribed the product. Pharmacists are also obliged to report serious or unexpected adverse reactions relating to the products they have dispensed. Reports are filed in a prescribed form at the nearest regional centre, which forwards the data to the AFSSAPS (see Appendix 11 at <http://www.opsi.gov.uk>). Voluntary reporting of adverse reactions which are not serious or unexpected may also be filed at the nearest regional centre. The Technical Committee is responsible for co-ordinating and evaluating the data provided by regional centres. Regional centres are obliged to forward information relating to serious adverse reactions to the AFSSAPS directly.

Reporting obligations are also imposed on companies pursuant to the provisions of Article R.5121-178 of the French Public Health Code. In particular,

pharmaceutical companies are required to appoint a qualified person responsible for pharmacovigilance ('*responsable de pharmacovigilance*'), whose function is to report every serious adverse reaction to the AFSSAPS.

Pursuant to the provisions of Article R.5121-171 of the French Public Health Code, any company which markets a medicinal product is required to record and report all suspected serious adverse reactions which are brought to its attention by a health care professional or of which it can reasonably be expected to have knowledge. It must also report any serious and unexpected adverse reaction occurring in the territory of a third country which is brought to its attention.

GERMANY

The EU pharmacovigilance requirements have been implemented in the German Drug Act (*Arzneimittelgesetz*, AMG). All individuals or businesses involved in the marketing of medicinal products, including manufacturers, wholesalers, physicians and pharmacists, are bound by an ongoing pharmacovigilance duty to ensure that no unsafe drugs enter the market (s. 5(1) AMG).

According to the legal definition, a drug is to be considered 'unsafe' if the current state of scientific knowledge suggests and gives rise to reasonable concerns that the adverse side effects of the properly applied drug outweigh its benefits (s. 5(2) AMG). This ban on the marketing of (purportedly) unsafe drugs applies irrespective of whether a marketing authorisation for the product concerned has been granted but not yet revoked. Possible legal sanctions for violations of this duty can be severe, with fines and terms of imprisonment of up to 3 years or 1 year in the case of simple negligence. In particularly severe cases, for example, if the conduct has endangered the health of a vast number of individuals this may lead to up to 10 years of imprisonment (s. 95 AMG).

The holder of a German national marketing authorisation must report any serious adverse reactions within 15 days of learning of the effects to the competent German authority. This is generally the Federal Institute for Medicinal Products and Medical Devices, '*Bundesinstitut für Arzneimittel und Medizinprodukte*' (BfArM) unless either the Federal Agency for Sera and Vaccines, '*Paul Ehrlich Institut*' (PEI), or the

Federal Agency for Health Protection of Consumers and Veterinary Medicine is competent in the area of that product (s. 77 AMG).

The applicant must also make all related documentation available together with a scientific evaluation of the adverse reactions (s. 29(1) AMG). All adverse reactions, other than serious ones, must be recorded and reported at regular intervals. The reporting forms are in Appendix 12 (<http://www.opsi.gov.uk>).

Both BfArM and the district governments of the German states are vested with far-reaching powers to protect public health against hazards resulting from medicinal products by imposing certain restrictions on a medicinal product and/or withdrawing the product from the market. BfArM may restrict, suspend or revoke the marketing authorisation of the drug in question (s. 69 AMG), whereas the state authorities have competence for all other issues. As always in German public law, each acting authority must establish that the measure taken is appropriate and reasonable under the particular circumstances of the case.

In cases where practical experience or scientific research leads to a new risk-benefit assessment of medicinal products on the market, BfArM may order a so-called Phased Plan Procedure (PPP, *Stufenplanverfahren*; ss 62 and 63 AMG). The goal of the PPP is to arrive at an amicable solution for addressing and responding to health risks which come to light after the medicinal product concerned has been approved for circulation on the market.

If the available data and information support reasonable concerns that a certain drug is creating a health hazard, the competent authority must initiate the PPP by calling meetings where all parties concerned (including the manufacturers) are represented and can put forward their arguments. If no consensus can be reached or if the majority recommendations are not voluntarily complied with, the authority may revert to its general supervisory powers and impose the above-mentioned measures, including informing the public of health hazards caused by certain medicinal products.

Each pharmaceutical company is legally obliged to appoint a PPP Officer ('*Stufenplanbeauftragter*', s. 63a AMG), whose duty is to comply with the reporting requirements of the AMG and to co-ordinate and implement pharmacovigilance activities within the company.

APPENDICES OF REFERENCE MATERIALS

EUROPEAN COMMISSION

1. Directive 2001/83/EC of 6 November 2001 on the Community Code relating to medicinal products for human use, as amended, available at <http://pharmacos.eudra.org>
2. Regulation (EEC) No. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, available at <http://europa.eu.int/>
3. The Rules Governing Medicinal Products in the European Union, Volume 9: *Pharmacovigilance*, available at <http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm>
4. Draft Volume 9a of *The Rules Governing Medicinal Products in the European Union*, available at http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/12-05/draft%20of%20Volume%209a_12_2005.pdf
5. Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, available at <http://europa.eu.int/>

UNITED KINGDOM

6. The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994, as amended, available at <http://www.opsi.gov.uk>
7. The Medicines for Human Use (Clinical Trials) Regulations 2004, available at <http://www.butterworths.co.uk/legislation/index.htm>
8. UK Yellow Card reporting forms for patients and health care professionals, available at <http://www.yellowcard.gov.uk>
9. Data Protection Act 1998, as amended, available at <http://www.butterworths.co.uk/legislation/index.htm>

ITALY

10. Pharmacovigilance reporting form.

FRANCE

11. Pharmacovigilance reporting form, also available at <http://www.sante.gouv.fr/cerfa/efindes/abvitot.pdf>

GERMANY

12. Pharmacovigilance reporting forms.

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Legal Basis – United States

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INTRODUCTION

During the decade of the 1990s, pharmaceutical regulation in the United States was dominated by a determined focus to develop a more timely and efficient drug approval process. This emphasis was advanced by an usual confluence of interest by Congress, patient groups and the Food and Drug Administration (FDA).

By contrast, the initial years of the twenty-first century have focused on drug safety, perhaps in part a reaction to what occurred in the 1990s. Risk-management plans, product monitoring, post-marketing surveillance and accelerated withdrawals have become the new focus of that same confluence of interests. Although innovative solutions are being discussed, and some will be embraced, pharmacovigilance has been, and will remain, at the heart of drug safety.

This chapter will describe the legal basis and requirements for pharmacovigilance in the United States with regard to drugs and biological products. This chapter will then review how the FDA enforces these requirements and the penalties for non-compliance. For purposes of this chapter, pharmacovigilance means the collection, analysis and submission to the FDA of adverse experiences and other safety information related to drugs and biological products.

BACKGROUND

The legal requirements for the development, approval and marketing of drugs in the United States are contained in the Federal Food, Drug and Cosmetic Act (FDCA) (Pub. L. No. 75-717, 52 Stat. 1040 (1938)), as amended (codified as amended at 21 U.S.C. §§ 301 *et seq.*). Biological products (e.g. vaccines, blood, cellular derived products and most products derived from biotechnology) are approved (licensed) pursuant to the Public Health Service Act (PHSA) (Ch. 288, 37 Stat. 309 (1912)), as amended (codified as amended at 42 U.S.C. § 262). Biological products are also subject to the legal requirements for drugs during the developmental stage as well as the post-approval marketing stage. For purposes of this chapter, when there is a discussion of drugs, the reader must assume that the same requirements apply to biological products unless specifically identified otherwise.

A pharmaceutical company must look to three sources of information to determine the legal standards for pharmacovigilance in the United States: laws, regulations and guidance documents. If a manufacturer, sponsor or individual violates standard in the law, then they are subject to the penalties described in such laws. These laws, however, are often relatively general (i.e. manufacturers shall keep records and make reports). Often the FDA must publish

regulations that further define the more generalized standards in the law. The FDA develops regulations by publishing a proposed rule in the *Federal Register*, taking public comment and then publishing a final rule that takes into account comments received. Once a final regulation takes effect, it is published in the US government's Code of Federal Regulations (CFR). Assuming the FDA regulations are properly developed, they set legally binding standards. If a company violates a regulation, then it is the same as if the company has violated the law itself and the company is subject to the penalties described in the law. Guidances are a third source of information about the FDA's standards. Guidance documents are informal communications from the FDA that provide the agency's current thinking about how to comply with various legal requirements. Guidance documents, however, do not have the force and effect of law. Therefore, if a company violates or otherwise does not comply with the conduct described in a guidance, then the company is not automatically violating the law or subject to penalties.

The FDA adds the following disclaimer to all guidance documents it publishes:

This guidance has been prepared by the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on [the topic of the respective guidance]. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

Conduct that is contrary to an FDA guidance represents a risk, however, that the FDA will consider such conduct a violation of law and attempt to bring an enforcement action.

LAW

The specific law that governs pharmacovigilance requirements in the United States for drugs is section 505 of the FDCA (21 U.S.C. § 355). Section 505(i) of that law gives the FDA the authority to regulate investigational drugs. As part of that authority, the FDA must, by regulation, require 'the

establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug . . . as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application . . .' (21 U.S.C. § 355(i)(1)(C)). Biological products are regulated as drugs during the investigational stage; as such, this provision forms the legal basis for safety reporting for biological products as well (21 C.F.R. § 312.2(a); § 601.21). The details of what must be reported are set forth in the regulations and guidance documents discussed below.

For approved drugs, the basis in law for pharmacovigilance is section 505(k) of the FDCA (21 U.S.C. § 355(k)). That provision states, in part, for approved drugs that 'the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained . . . as the Secretary may by general regulation, or by order with respect to such application, prescribe' to determine, among other things, whether the drug should be withdrawn from the market due to safety concerns. As with investigational drugs, the law merely gives the FDA the authority to require such records and reports. It is the regulations and guidance, as discussed below, which set forth the specific standards.

For biological products approved under the PHS Act, the FDA has been given the legal authority to set standards for such products to 'insure the continued safety, purity and potency of such products . . .' (42 U.S.C. § 262(d)). The standards, according to the law, must be set forth in regulations. The FDA gathers further legal support for these legal requirements from the drug misbranding provisions of the FDCA (21 U.S.C. §§ 352(a) and (f)(1)). As with drugs, it is the underlying statute that provides the general legal authority to require pharmacovigilance activities for biological products, whereas the specific standards are set forth in the regulations and guidance documents discussed below.

REGULATIONS

The FDA regulations contain provisions establishing a system for reviewing reports of adverse events and

submitting them to the FDA. Only certain reports must be sent to the FDA, depending on the nature of the event and the source of the information. The regulatory requirements for reporting adverse events related to investigational and marketed products are largely the same and are intended to be consistent with international standards. On 14 March 2003, FDA published a proposed regulation that would amend pre- and post-marketing safety reporting regulations (68 Fed. Reg. 12406). One primary objective of the proposal was to further harmonize the FDA requirements with evolving international standards. Notably, the proposed regulation would create a new requirement that manufacturers collect and report information to FDA regarding medication errors (*Id.*). The proposed rule generated much comment from industry and other stakeholders. As of late 2005, no further action has been taken on the proposed rule, and the existing regulations remain in effect.

FOOD AND DRUG ADMINISTRATION REPORTING STANDARDS FOR INVESTIGATIONAL DRUGS AND BIOLOGICAL PRODUCTS

Review of Adverse Events

FDA regulations require the sponsor of an Investigational New Drug (IND) to ‘promptly review all information relevant to the safety of [a] drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations . . .’ (21 C.F.R. § 312.32(b)). The safety information that sponsors receive from clinical investigations often is in the form of reports relating to experiences of the clinical study subjects.

An investigator has no obligation to report adverse events to the FDA and is only required to report adverse events to the sponsor. Under FDA regulations, investigators evaluate adverse experiences based on two criteria: whether the event is serious and whether it was caused by the drug. Investigators are required by the FDA’s regulations to ‘promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately’ (*Id.* at § 312.64(b)).

Depending on several criteria discussed below, FDA regulations provide two mechanisms for sponsors to report adverse event and other safety information about investigational drugs to the agency. Sponsors report adverse experiences to the FDA either as an expedited report or as part of an IND annual report (21 C.F.R. §§ 312.32–33). Adverse experiences that are not reported to the FDA under one of these two mechanisms are usually included in listings submitted to FDA as part of a final study report.

Expedited Reports – Written and Telephone Investigational New Drug Safety Reports

The goal of expedited safety reporting is to ensure timely communication to the FDA of the most important new information about the safety of investigational drugs (52 Fed. Reg. 8798, 8815 (1987)). Expedited reports are required for adverse events experienced by subjects taking investigational drugs if the event is (1) ‘serious’, (2) ‘associated with the use of the drug’ and (3) ‘unexpected’. The regulatory standards for these three criteria are discussed below. Expedited safety reports also are required when the sponsor receives reports of pre-clinical findings that suggest significant risk to human subjects including reports of mutagenicity, teratogenicity or carcinogenicity (21 C.F.R. § 312.32(c)(1)(i)(B)).

There are two types of expedited reports: written IND safety reports and telephone IND safety reports (21 C.F.R. § 312.32(c)). The type of expedited safety report that is required depends upon the seriousness of the event. A written IND safety report informs the FDA of an event associated with the study drug that is serious and unexpected (*Id.* at § 312.32.(c)(1)). IND sponsors must submit written IND safety reports within 15 calendar days after the sponsor’s initial receipt of the reportable information (*Id.*). A telephone IND safety report is required when an adverse event is fatal or life threatening (*Id.* at § 312.32(c)(2)). IND sponsors must make such a report to the agency as soon as possible but in no event later than 7 calendar days after the sponsor’s initial receipt of the reportable information (*Id.*).

Serious Adverse Events

FDA regulations define a ‘serious adverse event’ for subjects receiving investigational drugs as one that

results in any of the following outcomes: death, a life-threatening adverse drug 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 to be serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (21 C.F.R. § 312.32(a)).

Because adverse events that are fatal or life threatening are included in the definition of a ‘serious’ event, they must be submitted to the FDA as a written report in addition to a telephone report.

Unexpected Adverse Events

Telephone and/or written IND safety reports are required only for adverse events that are ‘unexpected’. FDA regulations define an unexpected adverse drug experience with an investigational drug as one for which

the specificity or severity . . . is not consistent with the current investigators’ drug brochure or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended (*Id.*).

Associated with the Use of the Drug

An expedited IND safety report is *not* required for an adverse event unless the event is associated with the use of the drug. For purposes of IND safety reporting, an event is ‘associated’ with the use of a drug if ‘there is a reasonable possibility that the experience may have been caused by the drug’ (*Id.* at § 312.32(a)).

Follow-Up Reports

In addition to promptly reviewing adverse safety information that it receives, an IND sponsor must also ‘promptly investigate’ *all* safety information, regardless of whether the information meets the criteria for submitting an expedited safety report (*Id.* at

§ 312.32(d)). If the investigation reveals additional ‘relevant’ follow-up information, then the information must be submitted to the FDA as soon as it is available (*Id.*). The preamble to FDA’s final rule sheds light on whether additional information must be submitted:

Determining the relevance of information is invariably a matter of judgment. In this case, relevant information is information that explains or clarifies the circumstances of the reported adverse experience. For example, each follow-up might include reports of autopsy findings or reports of their results of additional blood tests (52 Fed. Reg. 8798, 8818 (1987)).

If a sponsor initially determines that safety information does not meet the criteria for expedited reporting, but a subsequent investigation reveals that the information should be reported to the FDA, then the sponsor must report the information as soon as possible ‘and in no event later than 15 calendar days after the determination is made’ (21 C.F.R. § 312.32(d)).

Annual Reports

As part of the IND annual reports, sponsors report *all* adverse experiences with investigational drugs and preclinical findings suggesting a significant risk for human subjects to the FDA. Food and Drug Administration regulations require IND sponsors to submit a summary of the status and progress of investigations each year, within 60 days of the anniversary date on which the IND went into effect (*Id.* at § 312.33). One purpose of the requirement for submitting annual reports is to provide both sponsors and the FDA with insight into the status and progress of the studies conducted under an IND (52 Fed. Reg. at 8819). In furtherance of this purpose,

FDA believes it is important periodically to aggregate all [adverse] experiences, whether or not the individual events are thought to be drug related, for review and analysis. Such groupings may show an increased incidence of an adverse experience or other problem that would not be readily ascertainable in a review of single, discrete adverse events (*Id.*).

The regulations require that annual reports include a brief summary of the status of each clinical study that is in progress or completed (21 C.F.R. § 312.33(a)).

The information must include, at a minimum, the total number of subjects initially planned for inclusion in the study, the number of subjects entered into the study as of the report's date, the number who have completed the study as planned and the number who have dropped out of the study for any reason (*Id.*).

Annual reports must also include a narrative or tabular summary of the most frequent and most serious adverse experiences by body system and a list of preclinical studies completed or in progress during the previous year (*Id.* at § 312.33(b)). Food and Drug Administration regulations and the preamble to those regulations do not specify what the agency expects sponsors to include among the most frequent and most serious events. The FDA has, however, issued guidance on good risk-assessment practices, including the generation, acquisition, analysis and presentation of pre-marketing safety data [FDA CDER/CBER Guidance for Industry, Premarketing Risk Assessment (March 2005)]. Sponsors also must list in the annual report all patients who died during participation in the investigation and all who discontinued the study in association with any adverse experience, regardless of any conclusions about whether the event was related to the drug (*Id.* at §§ 312.33(b)(3)–(4)). Annual reports must also include a summary of all IND safety reports submitted during the preceding year (*Id.* at § 312.33(b)(2)).

FOOD AND DRUG ADMINISTRATION REPORTING STANDARDS FOR MARKETED DRUGS AND BIOLOGICAL PRODUCTS

Collection, Review and Recordkeeping of Adverse Product Experience Information

Three separate regulatory provisions govern the review and reporting of safety information related to marketed drugs and biologics. Separate provisions govern the review and reporting of (1) drugs marketed pursuant to a New Drug Application (NDA) or an Abbreviated NDA (ANDA), (2) biological products and (3) drugs that are lawfully marketed without an approved NDA (21 C.F.R. §§ 314.80, 314.98, 600.80, and 310.305), respectively. Only sponsors of an approved application or biologics license are required to report safety information to the FDA. Physicians and other healthcare professionals have no

legal obligation to report safety information to the manufacturer, to the sponsor or to the FDA.

As with investigational drugs, any applicant or licensed manufacturer holding an approved application or a biologic license must promptly review all adverse experience information pertaining to its product (21 C.F.R. §§ 314.80(b), 314.98, 600.80(b)). This requirement covers information obtained or received from any foreign or domestic source, including information derived from commercial marketing experience, post-marketing clinical investigations, post-marketing epidemiological/surveillance studies, reports in the scientific literature and unpublished scientific papers (*Id.*). Prescription drug products marketed for human use without an approved drug application must meet these requirements as well (21 C.F.R. § 310.305).

Applicants or licensed manufacturers also must establish and follow written procedures for the surveillance, receipt, evaluation and reporting of post-marketing adverse product experiences (21 C.F.R. §§ 310.305(a), 314.80(b), 314.98, 600.80(b)). The regulations require applicants or licensed manufacturers to retain records of all adverse product experiences, including raw data and any related correspondence, for 10 years (21 C.F.R. §§ 310.305(f), 314.80(i), 314.98, 600.80(i)).

Although licensed biological products are generally covered by these standards (21 C.F.R. 600.80), there are some product-specific differences. Licensed blood and blood components (21 C.F.R. § 606.3(c)) are exempt from these requirements. Instead, adverse reaction records for these types of products must be retained and made available to the FDA upon request (21 C.F.R. § 606.170(a)). Any fatal ‘complication of blood collection or transfusion’ must be communicated to the FDA as soon as possible, followed by a written report within 7 days (21 C.F.R. § 606.170(b)).

Vaccines must comply with the requirements of 21 C.F.R. § 600.80 as set forth below. In addition, certain childhood vaccines are also regulated under the National Childhood Vaccine Injury Act (NCVIA) of 1986 (section 2125 of the PHS Act) (42 U.S. § 300aa-25). This law requires certain vaccine manufacturers and healthcare providers who administer such vaccines to make reports to a separate programme known as the ‘Vaccine Adverse Event Reporting System’ (VAERS). The VAERS programme

is co-administered by FDA and the Centers for Disease Control (CDC), which is a separate unit of the federal Department of Health and Human Services. If a vaccine falls under the jurisdiction of NCVIA, then any adverse event is to be reported only to the VAERS programme. Nonetheless, these manufacturers must meet the other requirements of 21 C.F.R. § 600.80.

REPORTING ADVERSE PRODUCT EXPERIENCES FROM MARKETED PRODUCTS

The regulations specify two mechanisms for reporting post-marketing adverse product experiences: 15-day alert reports and periodic reports. A 15-Day Alert Report must be submitted by an applicant or licensed manufacturer within 15 days after receiving information regarding a domestic or foreign ‘serious’ and ‘unexpected’ adverse product experience (21 C.F.R. §§ 310.305(d), 314.80(c)(1)(i), 600.80(c)(1)(i)). A periodic report is submitted for any adverse product experience that is not ‘serious’ and ‘unexpected’ (21 C.F.R. §§ 314.80(c)(2)(i), 314.98, 600.80(c)(2)(i)).

All domestic adverse product experience reports for both drugs and biological products (unless treated differently as discussed above) should include a completed FDA Form 3500A for each individual patient or attached publication. If the adverse product experience is foreign, then either a Form 3500A or a Council for International Organizations of Medical Sciences (CIOMS) I is acceptable (21 C.F.R. §§ 314.80(f), 600.80(f)). If the product is a vaccine, then a VAERS form should be used (21 C.F.R. § 600.80(f)). Applicants or licensed manufacturers may use computer-generated forms or an alternative format, such as a computer-generated tape or tabular listing, if the alternative format contains the same information as Form 3500A and if the appropriate FDA department agrees to the alternate format in advance (*Id.*).

The FDA has proposed a regulation requiring the reporting of adverse product experiences in electronic format but has not yet taken final action on the matter (63 Fed. Reg. 59,746 (1998)). In the interim, the agency has offered guidance for applicants and licensed manufacturers that wish to file such reports electronically [FDA CDER/CBER Draft Guidance on Providing Regulatory Submissions in Electronic Format – Postmarketing Periodic Adverse Drug Experience Reports (June 2003)].

15-Day Alert Reports

An applicant or licensed manufacturer must submit a ‘15-Day Alert Report’ to FDA within 15 calendar days of receiving information of a ‘serious’ and an ‘unexpected’ domestic or foreign adverse product experience (21 C.F.R. §§ 310.305(d), 314.80(c)(1)(i), 600.80(c)(1)(i)).

The definition of ‘serious’ for purposes of reporting post-marketing adverse product experiences is identical to that for IND adverse product experiences discussed above (21 C.F.R. §§ 310.305(b), 314.80(a), 314.98, 600.80(a)). The definition of ‘unexpected’ for post-marketing adverse product experiences is similar to that for the IND adverse product experiences. An adverse product experience is ‘unexpected’ if the experience is not listed in the current labelling for that product (21 C.F.R. §§ 310.305(b), 314.80(a), 314.98, 600.80(a)). An adverse product experience is ‘unexpected’ even if it could have been anticipated from the pharmacological properties, of the product so long as it is not listed in the labelling (*Id.*). This definition includes events that are symptomatically and pathophysiological related to events listed in the labelling but that differ because of greater severity or specificity (*Id.*). As an example of an event that is ‘unexpected’ due to greater severity, the regulations cite hepatic necrosis when the labelling refers only to elevated hepatic enzymes or hepatitis and cerebral thromboembolism and cerebral vasculitis when the labelling refers only to cerebral vascular accidents (*Id.*).

Unlike the criteria for expedited reporting of adverse events in investigational drugs, the regulations regarding reporting spontaneous post-marketing events do not require an assessment of causality. It is the FDA’s view that when a report regarding a drug is made spontaneously, causality is implied, because the reporter otherwise would not have taken the time to transmit the information to the applicant or to a regulatory authority.

15-Day Alert Report Follow-Ups

Applicants or licensed manufacturers are also required to promptly perform a ‘follow-up’ investigation into the adverse product experience and to separately report any new information to the FDA as a ‘15-Day Alert Report Follow-Up’ within 15 calendar days receiving that information (21 C.F.R. §§ 310.305(c)(2),

314.80(c)(1)(ii), 314.98, 600.80(c)(1)(ii)). If the applicant or licensed manufacturer performs an investigation but is unable to uncover any additional information, then the applicant or licensed manufacturer is expected to maintain a record of the steps taken to seek additional information; however, a follow-up report need not be submitted (*Id.*).

15-Day Alert Reports Based on Scientific Literature

Fifteen-day alert reports must be filed when ‘serious’ or ‘unexpected’ adverse product experiences are reported in case reports or in the results of formal clinical trials published in scientific or medical journals (21 C.F.R. §§ 314.80(d), 314.98, 600.80(d)). When a 15-day alert report is based on information obtained from an article in a scientific or medical journal, a copy of the article must be included with the report (*Id.*).

Exceptions to the 15-Day Alert Report Requirements

A 15-day alert report is not required for information regarding an adverse product experience that was obtained from a post-marketing study, including a study conducted under an IND application, unless the applicant or licensed manufacturer concludes that there is a ‘reasonable possibility’ that the product caused the experience (21 C.F.R. §§ 310.305(c)(1)(ii), 314.80(e), 314.98, 600.80(e)). When reports of adverse product experiences obtained during a post-marketing study are reported in any context, they should be marked to indicate that they were so obtained (*Id.*).

PERIODIC REPORTS

Any post-market adverse product experience that is not ‘serious’ and ‘unexpected’ must be reported to the FDA in a periodic report (21 C.F.R. §§ 314.80(c)(2)(i), 314.98, 600.80(c)(2)(i)). Periodic reports must contain a ‘narrative summary and analysis’ of the information in the report, including an analysis of all 15-day alert reports filed during that period (21 C.F.R. §§ 314.80(c)(2)(ii), 314.98, 600.80(c)(2)(ii)). Periodic reports must also include a

completed FDA Form 3500A for each adverse product experience not reported in a 15-day alert report during the period as well as an index consisting of a line listing of patient identification numbers and adverse reactions terms (*Id.*). Finally, periodic reports must include a history of actions taken in response to adverse product experiences during the period, such as labelling changes or the initiation of studies (*Id.*).

Quarterly v. Annual Periodic Reports

During the first 3 years after the date of approval or licensing of a product, periodic reports must be submitted quarterly, beginning on the date of approval of the application (21 C.F.R. §§ 314.80(c)(2)(i), 314.98, 600.80(c)(2)(i)). Each quarterly report must be filed within 30 days of the close of the quarter (*Id.*). After 3 years, applicants or licensed manufacturers need only submit annual reports, which must be filed within 60 days of the anniversary of approval or licensing (*Id.*). The FDA may require an applicant or licensed manufacturer to submit quarterly reports for a period longer than 3 years (*Id.*).

Follow-Up Investigations for Periodic Reports

Follow-up investigations for adverse product experiences that are not ‘serious’ and ‘unexpected’ are not required. If the applicant or licensed manufacturer chooses to perform an investigation, then it may submit any information that it discovers in the next periodic report rather than filing a separate ‘follow-up’ report (21 C.F.R. §§ 314.80(c)(2)(i), 314.98, 600.80(c)(2)(i)).

Exceptions to Periodic Reporting Requirements

Periodic reports need not contain adverse product experience information obtained from reports in scientific literature or from foreign marketing experience or post-marketing studies (including studies conducted under IND applications) (21 C.F.R. §§ 314.80(c)(2)(iii), 314.98, 600.80(c)(2)(iii)). Thus, the only adverse product experiences that must be included in periodic reports are spontaneous reports from domestic sources that have not been included in a 15-day alert report.

ANNUAL REPORTS

In addition to the periodic safety reports that applicants must submit to the FDA, annual reports are also required for holders of drug approvals. Although these reports primarily provide ancillary information about the product, such as distribution data and manufacturing changes, annual reports must also include safety information in the form of copies of unpublished reports of new clinical and preclinical findings (21 C.F.R. §§ 314.81(b)(2)).

MULTIPLE REPORTS, APPLICATIONS OR PRODUCTS

Applicants and licensed manufacturers are not required to report adverse product experience information that has already been reported to the FDA. Thus, no report should contain adverse product experiences that occurred in clinical trials if those experiences were previously submitted as part of an approved application (21 C.F.R. §§ 314.80(g), 314.98, 600.80(g)). Similarly, an applicant or licensed manufacturer is not required to file a report if the FDA itself was the source of the adverse product experience information and no additional information was uncovered during the ‘follow-up’ investigation (21 C.F.R. §§ 310.305(c)(5), 314.80(b), 314.98, 600.80(b)).

Reporting requirements apply to all entities identified on the product’s label as a manufacturer, packer or distributor (21 C.F.R. §§ 310.305(c)(1)(i), 314.80(c)(1)(iii), 314.98, 600.80(c)(1)(iii)). To avoid duplication in reporting, however, these entities may submit any adverse product experience information to the applicant or licensed manufacturer for inclusion in the applicant’s or licensed manufacturer’s 15-day alert report (21 C.F.R. §§ 310.305(c)(3), 314.80(c)(1)(iii), 314.98, 600.80(c)(1)(iii)). This submission must occur within 5 calendar days of the entity’s receipt of the information (*Id.*). If the entity elects this method, then it must keep a record that includes a copy of each adverse product experience report, the date the report was received, the date that the report was submitted to the applicant or licensed manufacturer and the name and address of the applicant or licensed manufacturer (*Id.*).

PATIENT PRIVACY

The names and addresses of patients should not be included in any reports submitted to the FDA (21 C.F.R. §§ 310.305(e), 314.80(h), 314.81(c)(2), 314.98, 600.80(h)). Instead, the applicant or licensed manufacturer should create a unique code number of less than eight characters for each report (*Id.*). The applicant or licensed manufacturer must include the name of the person who reported the adverse product experience (*Id.*). The applicant or licensed manufacturer also must maintain sufficient patient identification information to permit the FDA to identify the name and address of individual patients (*Id.*).

PHYSICIAN/CONSUMER REPORTING: THE FOOD AND DRUG ADMINISTRATION MEDICAL PRODUCTS REPORTING PROGRAM (MEDWATCH)

In addition to receiving mandatory adverse event information from drug manufacturers and distributors, the FDA also receives voluntary adverse event reports from the medical community and consumers through its MedWatch programme. This programme provides a system for healthcare professionals and consumers to report adverse events to the FDA with respect to drugs, biologics, medical devices and nutritional products such as medical foods, dietary supplements and infant formulas. Food and Drug Administration’s website permits healthcare professionals to voluntarily transmit adverse event information electronically, and the FDA also has designed a specific MedWatch adverse event reporting form that can be submitted by mail or fax. In addition, the FDA has a toll-free telephone number for reporting adverse experiences.

GUIDANCE DOCUMENTS

Over the last decade, FDA has published a series of guidance documents that further articulate its views about how IND sponsors and NDA or Biologics License Application (BLA) applicants can comply with the regulations and statutes governing adverse event review and reporting. Many of these guidance documents address or incorporate by reference the applicable international standards.

In June 2002, the United States Congress re-authorized the Prescription Drug User Fee Act III (PDUFA III) for the second time. In the context of the PDUFA re-authorization, the FDA agreed to satisfy certain performance goals, including producing guidance for industry on risk-management activities for drug and biological products.

Unlike statutes and regulations, however, agency guidance documents do not have the force and effect of law; instead, they represent the agency's current thinking and recommendations on particular topics. Thus, if a company does not comply with the conduct described in a guidance document, then the company's behaviour is not automatically unlawful and subject to penalties. Conduct that is contrary to an FDA guidance presents a risk, however, that the FDA will consider such conduct a violation of law and will attempt to bring an enforcement action. It is important, therefore, for companies to understand these guidance documents and to make carefully informed judgments, so that any action that does not comply with policies expressed in a guidance document will nonetheless meet the requirements of applicable law and regulations. In any event, guidance documents do provide IND sponsors and NDA applicants with a clear idea of what FDA considers to be lawful conduct, and therefore, familiarity with them is critical. Current FDA guidance documents can be found on the agency's website at <http://www.fda.gov>.

RISK MANAGEMENT – PRE- AND POST-MARKET

To fulfil its commitment to produce guidance for industry on risk management, and in response to increasing concerns about drug safety, in 2004, the FDA initiated a public process to develop the following final guidance documents. Each of the three documents focuses on one aspect of risk management:

- CDER/CBER, Guidance on Premarketing Risk Assessment (March 2005).
- CDER/CBER, Guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005).
- CDER/CBER, Guidance on the Development and Use of Risk Minimization Action Plans (RiskMAP) (March 2005).

The first two guidance documents address pre- and post-marketing risk assessment, respectively, providing information on the data and systems that are necessary or advisable for reporting adverse events to FDA. The guidance on risk minimization discusses the development of objective plans to utilize specific tools to minimize a known risk associated with the use of a particular product (i.e. education/outreach or registered access programmes to minimize *in utero* exposure to teratogenic drugs). The agency notes that a RiskMAP could also be considered as a selectively used type of Safety Action Plan as defined in the 'International Conference on Harmonization (ICH) guidance E2E: Pharmacovigilance Planning'.

Food and Drug Administration has also issued a guidance document explaining the agency's new Drug Watch system [CDER Guidance on FDA's 'Drug Watch' for Emerging Drug Safety Information (May 2005)]. The agency plans to make information available on its website to consumers and healthcare professionals about drugs for which the agency is actively evaluating early safety signals.

INTERNATIONAL CONFERENCE ON HARMONIZATION

In recent years, FDA has been supportive of international efforts to harmonize reporting requirements and standards. In general, FDA's policy on international standards states that

[w]here a relevant international standard exists or completion is imminent, it will generally be used in preference to a domestic standard, except when the international standard would be, in FDA's judgment, insufficiently protective, ineffective, or otherwise inappropriate (60 Fed. Reg. 53077, 53084 (1995)).

To that end, the FDA has issued many ICH or ICH-influenced documents as guidance for industry, including the following:

- CDER/CBER, Guidance on E2B(M): Data Elements for Transmission of Individual Case Safety Report, ICH Revision 2 (March 2005).
- CDER/CBER, Guideline for Industry-E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1995).

- CDER/CBER, Guidance on E2E Pharmacovigilance Planning (April 2005).
- CDER/CBER, Guidance for Industry-Post-Marketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report (1997).
- CDER/CBER, Guidance for Industry-E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (1997).

ENFORCEMENT

Generally, the FDA evaluates compliance with these safety reporting standards through inspections of manufacturers, sponsors and clinical investigators and of relevant records maintained by such entities (FDCA § 704; 21 U.S.C. § 374; PHSA § 351(c); 42 U.S.C. § 262(c)). Under the law, it is a prohibited act to fail to ‘establish or maintain any record, or make any report, required under section . . . 505(i) or (k) . . . or [to refuse] to permit access to or verification or copying of any such required record’ (FDCA § 301(e); 21 U.S.C. § 331(e)). By committing this prohibited act or causing someone else to do so, a manufacturer, sponsor (including any culpable individuals) or clinical investigator may be found liable under either the civil or the criminal penalties of the FDCA and the PHSA (FDCA § 303(a); 21 U.S.C. § 333(a); PHSA § 351; 42 U.S.C. § 262).

Food and Drug Administration has several enforcement steps that can be taken if the agency determines that an entity or individual is not submitting required safety information, is submitting false information or is otherwise not in compliance with the applicable laws and regulations. Generally, the first step is to send the entity or individual a warning letter briefly describing what the FDA investigation has found and concluding that the conduct violates one or more provisions of the law. The FDA will ask for prompt action to correct the conduct described by the agency and will usually note that if prompt action is not taken, then further regulatory action may result. In most such letters, the FDA identifies product seizure (FDCA § 304; 21 U.S.C. § 334) and/or injunction (FDCA § 302; 21 U.S.C. § 332) as two possible actions that could be taken without further warning. Since the early 1990s, FDA has issued more than a

dozen warning letters in the area of safety reporting. In virtually every instance, the entity or person subsequently took the necessary corrective action to ensure future compliance with safety reporting standards. These warning letters are available on the FDA website.

Food and Drug Administration may also revoke an approved NDA for a drug or the approved license for a biological product if a manufacturer does not comply with its safety reporting obligations (21 C.F.R. §§ 314.150(b)(1), 601.5(b)(iv)).

In addition, FDA can initiate a criminal prosecution, regardless of whether the agency has sent a warning letter or whether the recipient has implemented corrective action. Violations of the FDCA subject any culpable entity or individual to both misdemeanour and felony criminal convictions that can involve substantial fines and prison sentences. If records are kept or submitted that are knowingly false and they are material to the FDA’s compliance assessment, then the entity or individual may also be in violation of several provisions of the general federal criminal code, including the False Statements Act (18 U.S.C. § 1001). Such criminal violations are felonies with substantial monetary penalties and jail sentences. In the late 1980s, the FDA brought several criminal prosecutions against pharmaceutical companies for violations of pharmacovigilance reporting laws and regulations.

CONCLUSION

Compliance with the FDA requirements for pharmacovigilance reporting is essential. It is also complex. As this brief summary makes clear, there are laws, regulations and guidance documents that must be understood and adhered to. These standards – particularly the regulations and guidance documents – change with relative frequency. Thus, it is important that companies and individuals charged with pharmacovigilance compliance ensure that they have the most current versions of all applicable standards. Therefore, although this chapter provides a reasonable framework of the legal requirements pertaining to pharmacovigilance activities, close scrutiny of the laws, regulations and guidance documents on adverse event and other safety reporting standards is essential.

4

Ethical Oversight, Consent and Confidentiality

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INTRODUCTION

We put money that we do not spend in the bank – not under the mattress or in a hole in the back yard. We are not bankers, and neither of the authors has any special expertise in economics or bank regulation. However, sometime early in childhood, we learned to believe that the bank would safeguard every penny, would pay a modest rate of interest and would give our money back to us on request. Eventually (maybe by watching Jimmy Stewart save the Bailey Savings and loan each Christmas), we figured out that even though we could always get our money back, it was not in the vault and that people who receive loans are being given ‘our’ money. At some level, we recognize that by collecting, protecting and circulating the money of significant numbers of people, banks provide the lifeblood of the local economy, creating and sustaining a public good while protecting the very personal financial interests of the individuals whose money is being used.

This chapter is not about the economy, but it is about something that is just as vital to our quality

of life: the epidemiologic and outcomes research that anticipate and addresses public health needs, sustains quality and fuels innovation in our health care system. Information is the lifeblood of twenty-first century health care, whether the information and analyses that researchers provide clinicians and public health officials or information about individuals’ health and routine health care made available to researchers for analysis. However, few ordinary citizens are aware of the critical role played by their health information – maintained and used in confidence – for sustaining quality and innovation in our health care system and for protecting the population from public health risks such as new flu viruses, other communicable diseases, teratogens and biological weapons. In fact, far too many ordinary people have an unfounded belief that the anonymous use of information about their health and health care for these purposes is risky to them as individuals. To some extent, this fear is mirrored in the US state and federal regulations.

The US state and federal medical privacy regulations, promulgated by the Department of Health and Human

Services,¹ were authorized as part of the ‘administrative simplification’ section of the Health Insurance Portability and Accountability Act (HIPAA).² They establish the infrastructure for protecting individuals’ personal privacy interests in seeking medical care or health benefits while ‘banking’ their medical information to make it available for determining their course of treatment and for administration of health benefits. The regulations do not apply to researchers. Rather, the regulations restrict the conditions under which researchers may have access to medical records for epidemiology and outcomes research. Moreover, the dominant approach to individual privacy taken by this regulation (and by most state laws affecting research) is comparable with encouraging each individual to stuff money in a mattress or dig a hole and to lend very, very carefully.³ As discussed more fully below, the HIPAA medical privacy regulation also appears to be affecting interpretation of the established Common Rule⁴ provisions governing data research in ways that are detrimental to epidemiologic and outcomes research.

The HIPAA approach to the data-only research is a hybrid of two philosophically disparate approaches. The secondary approach, added just before the regulation became effective in 2003, is the ‘data use agreement’. As discussed more fully below, this approach has promise, but because of limitations resulting from the influence of the dominant approach, its utility for

certain types of research is severely limited. The dominant approach is irrevocably and, we argue, mistakenly rooted in the authorization of each individual for *each* research use of his or her health information.⁵ The same is true of the European Union’s Data Privacy Directives although the Directive arguably allows for more flexibility in implementation than the HIPAA regulations.⁶ The consent/authorization model is grounded in a system of ethics that values autonomy over community.⁷ This can be seen as a natural outgrowth of American individualism, but in this context, it does erect potentially significant barriers to epidemiologic research. As discussed more fully below, with respect to archival or records research, a consent-based model is entirely unsuited to protecting individuals’ privacy interests and has resulted in some extremely wasteful research practices that also are not privacy enhancing. This chapter reviews the roots of the current regulatory approaches and offers preliminary thoughts regarding the parameters of a model more suited to protecting the privacy interests of individuals while encouraging the secure use of medical archives and other databases in epidemiologic and outcomes research.

CONFIDENTIALITY ISSUES IN EPIDEMIOLOGY STUDIES

For some of the epidemiologic challenges, such as anticipating the spread of new viral strains and drug-resistant bacteria, we are likely to face consent-based models that are scientifically inappropriate for the research questions being asked. Validity depends on the characteristics of the sampling criteria used in compiling the database: if data subjects are self-selected, each epidemiologic analysis will likely

¹ Department of Health and Human Services, Standards for Privacy of Individually Identifiable Health Information, 65 Federal Register 82 463 (28 December 2000, as amended in 31 May 2002 and 14 August 2002), hereinafter ‘privacy regulations’, adding parts 160 and 164 to Title 45 of the Code of Federal Regulations (CFR).

² Pub. L. No. 104-191 (21 August 1996), amending the Social Security Act (SSA) by adding Part C of Subchapter XI, codified at 42 U.S.C. §§ 1320d *et seq.* (HIPAA).

³ By comparison, the laws for protecting our personal financial interests from banking risks are built on the assumption that money is collected, invested and loaned while protecting individuals’ interests by insuring deposits and establishing strong incentives for banks to comply with strict regulations.

⁴ The US federal regulatory framework for the protection of human research subjects is known as the Common Rule. It has been codified, in some cases with slight modifications, by 17 different federal agencies at 7 C.F.R. Part 1c; 10 C.F.R. Part 745; 14 C.F.R. Part 1230; 15 C.F.R. Part 27; 16 C.F.R. Part 1028; 21 C.F.R. Part 56; 22 C.F.R. Part 225; 28 C.F.R. Part 46; 32 C.F.R. Part 219; 34 C.F.R. Part 97; 38 C.F.R. Part 16; 40 C.F.R. Part 26; 45 C.F.R. Part 46; 45 C.F.R. Part 690 and 49 C.F.R. Part 11. See, 56 Fed. Reg. 28 002 (18 June 1991), implementing Pub. L. No. 95-622, 92 Star. 3412, Title III, Section 301 (9 November 1978).

⁵ As discussed more fully below, the regulation establishes specific criteria that a committee, after debating the relative value of the specific research proposal and the privacy risk to the individual, may apply to decide whether or not to waive individual authorization as to the specific research project. 45 C.F.R. 164.512(i)(1)(i).

⁶ European Union Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, 25 July 1995, available at http://ec.europa.eu/justice_home/fsj/privacy/law/index_en.htm

⁷ See Barefoot (1998) (describing the argument that respect for individual autonomy demands a consent/authorization model, even when there is a societal need for access to personal health information).

require a separate analysis of the impact of the self-selection factors on the research findings. In some cases, this will mean that it is not possible to obtain a valid answer to an important research question.

Research using information collected for other purposes, such as health care delivery or health benefits administration, is critically important as we enter the century of discoveries based on genomic science. Pinpointing differences in health or health care quality based on geography, demography, health history or co-morbidities will become ever more important for clinical research, for public health planning and for ensuring access to appropriate care. We do not have the luxury of time and resources to collect consents and obtain data from volunteers and evaluate the validity of the sample for testing every unique data hypothesis.

Public health surveillance is typically conducted under specific laws authorizing or requiring the collection of certain types of data in the public interest (See, e.g. Chapter 1). The new medical privacy regulations, for example, have explicit exemptions from the prohibitions on disclosure where the data are being collected under various public health surveillance laws.⁸ In enacting the mandatory reporting laws, the state legislature has been persuaded that the individual's interest in privacy can be achieved in other ways that are not anathema to the public interest in pharmacovigilance and other public health surveillance. They have required public health authorities and regulated entities to simultaneously protect the privacy interests of individuals while making the requisite reports and appropriately using and safeguarding the collected data.

But most epidemiologic studies do not have the legislatively protected status of public health surveillance. With respect to follow-up studies of drug safety, many registries and outcomes research more generally, confidentiality issues generally are subject to the informed consent and authorization laws, and not the spontaneous and/or mandatory reporting laws applicable to pharmacovigilance. The challenge in North America and the European Union is to create a system in which patient needs for confidentiality protections can be achieved while also facilitating important public health research. If society moves too far in the direction of providing absolute protection to

seal off access to health information from secondary uses, such as formal studies of drug safety, then we are at risk of eroding the information foundation that supports public health planning and health care quality, including societal judgements on the benefits and risks of medications.

Follow-up studies of drug or medical device safety fall into the broad general category of 'research', which is defined in US laws regulating research (discussed below) as 'a systematic investigation . . . designed to develop or contribute to generalizable knowledge'.⁹ As noted above, instead of an exemption from the prohibitions on use or disclosure of patient data, the HIPAA medical privacy regulation subjects disclosure or use of information for research purposes to an additional, entirely new patient authorization process.¹⁰ The same attention to the public interest in *both* privacy and research results that is seen in event reporting laws is not evident in US laws regulating data access for epidemiologic and outcomes research.

Admittedly, the 'worst case' damage to a given individual from a security breach and misuse of personal information may be highly significant. Yet, the potential damage or risk from the non-research misuse of personal information is precisely the same risk that adheres to pharmacovigilance and public health reporting. Indeed, with respect to the types of conditions that often are the subject of mandatory public health reporting – sexually transmitted diseases (STDs), child abuse, substance abuse – the potential damage from stigmatization or prejudice arguably is at its greatest.

Arguably, what is required is some mechanism for evaluating (1) the researcher's bona fides and (2) the arrangements for securing the data from unauthorized use by employees and/or contractors and from external security breaches. However, neither of these can be found in existing law.

EXISTING LAW

Three separate categories of US laws govern confidentiality issues in epidemiologic and outcomes research: the Federal Common Rule, the new federal medical

⁸ 45 C.F.R. § 164.512.

⁹ 45 C.F.R. § 46.102.

¹⁰ 45 C.F.R. § 164.508.

privacy regulations promulgated under HIPAA, and the laws of various states.

COMMON RULE

As discussed more fully below, the Federal Common Rule¹¹ was designed to be a mechanism for protecting the interests of human subjects in federally funded or regulated research. Congress did not enact a law regulating research under its power to regulate matters affecting interstate commerce or even under its authority to safeguard the rights and liberties of individuals under the Constitution. Rather, the law is an expression of a federal policy not to spend federal money on research that is not consistent with certain social values. As a result, the applicability of the Common Rule, and the scope of authority of the administering agencies, is somewhat odd. It applies to

- research conducted by the 17 agencies that have adopted the rule;
- recipients of federal research grants as a condition of awarding the grant;
- research that is included in an application submitted to the Food and Drug Administration (FDA) for approval of a drug, biologic or certain devices and
- all research conducted in or by an employee of an institution that has filed an ‘assurance’ with the Department of Health and Human Services, whether or not a specific project is federally funded.

Thus, research conducted in private clinics or institutions that do not have federal grants or an assurance appears to fall outside the scope of the Common Rule, as does research conducted by commercial research organizations that will not be used in a regulatory submission, e.g. many epidemiologic and outcomes studies. But, because the records of interest in epidemiologic research often are those collected by institutions subject to the Common Rule, the would-be researcher faces a tremendous catch-22: the research is not subject to the regulation, and under the law, the researcher has no claim on the time or resources of

an IRB for obtaining review of the project or waiver of consent. However, each of the multiple academic medical centres from which the researcher wishes to obtain data is subject to the rule and must have the proposal reviewed by its own IRB. For example an epidemiologic researcher who wishes to analyze data from Johns Hopkins, Duke, M.D. Anderson and Stanford University Medical Centers will have the project reviewed by four separate IRBs each of which must approve the project and waive individual consent for it to go forward. In reality, if the researcher is not affiliated with the institution, it may be very difficult to get the IRB to review the proposal without forming a collaborative relationship with someone affiliated with each institution who can get the project on the IRBs’ schedules or confining one’s research to those institutions that already have such collaborative arrangements. Neither is particularly compatible with sampling considerations for epidemiologic research.

Moreover, it is not clear that legal – and organizational – responsibility for review of large, multisite epidemiologic studies appropriately should be delegated and diffused in this manner, rather than being assumed by the research entity that is accountable for use and security of the data.

HIPAA MEDICAL PRIVACY LAW

The federal privacy regulations under HIPAA establish that ‘covered entities’ may not use or disclose ‘protected health information’ except as permitted by the privacy regulation.¹² The regulation defines ‘covered entities’ to include health care providers (e.g. doctors, hospitals, laboratories, pharmaceuticals and clinics), health plans and health care clearinghouses.¹³ By requiring certain contractual terms in all covered entities’ contracts with vendors, suppliers and anyone else who may process or come into contact with protected health information in performing services for the covered entity, the regulation indirectly applies to business associates of covered entities as well.¹⁴

¹² See 45 C.F.R. § 164.502(a).

¹³ 45 C.F.R. § 160.103; 45 C.F.R. § 160.102(a).

¹⁴ 45 C.F.R. § 160.103, 164.502(e), 164.504(e).

¹¹ *Supra* note 4.

Under the privacy regulation, only the following categories of uses and disclosures of protected health information are permitted:

- for purposes of treatment, payment and certain health operations related to the individual's treatment or payment, with notice of these routine uses¹⁵;
- for purposes unrelated to treatment, payment or health operations, with the prior written authorization of the individual¹⁶;
- for certain specific purposes enumerated in the regulation, including protecting the public health and conducting research under a waiver of authorization, provided that applicable conditions are met.¹⁷

In fact, the law expressly prohibits a covered entity from obtaining a blanket authorization for future research use of records of health care or health benefits; it also prohibits a covered entity from making the signing of any authorization a condition of treatment of the individual. Moreover, even with respect to permitted uses and disclosures, a covered entity may use or disclose only the minimum necessary information to accomplish the intended purpose.¹⁸ Unless every use or disclosure of information fits within one of these permitted categories, the provider or health plan would be exposed to potential civil and criminal penalties for supplying information to a researcher.¹⁹

De-Identified Information

Many people have suggested that the regulation should not affect epidemiologic and outcomes research because it generally does not require access to 'individually identifiable' information. The statute says that 'individually identifiable health information' is any information, including demographic information collected from an individual, that (1) is created or received by a health care provider, health plan, employer or health care clearinghouse and (2) relates to the past, present or future physical or mental health or condition of an individual, the provision of health care to an individual, or the past, present or future

payment for the provision of health care to an individual and (1) identifies the individual or (2) with respect to which there is a reasonable basis to believe that the information can be used to identify the individual.²⁰ Under the statute, information that does not fall within the category to be considered 'individually identifiable' is not subject to the statutory, or regulatory, requirements.

Congress, the US Department of Health and Human Services Regulatory, privacy advocates, the research community and others have wrestled with the definition of what characteristics of data create a 'reasonable basis to believe' that it could be used to identify the individual. What would be a reasonable standard? On one extreme are researchers and public health advocates who might argue that all data should be considered exempt if the key 'direct identifiers' are removed. From this perspective, the importance of research using these data outweighs the low probability that these data might be used (or misused) to re-identify individual patients. On the other end of the spectrum are experts in database manipulation who advise that any database, even with the complete removal of identifiers, could potentially be overlain with other data sources and through probability matching on certain information fields, *could* be used to re-identify some percentage of individuals. These assertions, together with the fears of some privacy advocates, have led some to conclude that even if the researcher has no interest in knowing the patients' identities, no intent to link the files to other files for this purpose and establishes physical and procedural safeguards to make it difficult or impossible for employees to do so, the mere possibility that files could theoretically be linked to re-identify patients is a privacy risk to society that should not be permitted.

For its part, in implementing this definition, the Department of Health and Human Services seems to have listened to the database experts and created an extremely high standard for information to be considered as falling outside the category of individually identifiable health information. It specifically defined such information as 'de-identified'. It chose to use statistical probability – as determined by a statistician – to establish the permissible practices that can be used to establish a 'reasonable basis to believe'.

¹⁵ 45 C.F.R. § 164.506(a).

¹⁶ 45 C.F.R. § 164.508.

¹⁷ 45 C.F.R. § 164.512

¹⁸ 45 C.F.R. §§ 164.502(b), 164.514(d).

¹⁹ Social Security Act (SSA) § 1177; 42 U.S.C. 1320d-2.

²⁰ SSA § 1171(6); 42 U.S.C. 1320d(6).

The agency's approach is firmly grounded in the art and science of database manipulation. It does *not* ask whether a reasonable person looking at the data fields on an individual record could discern who the person is or how to contact him or her. The regulation does not take into consideration who will use the data, for what purpose or the security arrangements for protecting the data from being accessed by unauthorized individuals or from being used to identify individuals. Rather, it asks whether the data fields that appear in a data set also appear in databases that are generally available and which therefore *could be used by someone who is attempting to identify data subjects*. Examples of such generally available databases include state drivers license data, voter registration lists, the telephone book, birth records, credit reports and so on. Because the construction and renting of databases of all kinds has been prevalent in US society, this approach to de-identification presents considerable challenges.

The regulation offers a 'safe harbour' method in which the covered entity must (1) have no actual knowledge that the information could be used alone or in combination with other information to identify participants and (2) *all* of the following must be removed from the data:

- names;
- all geographic subdivisions smaller than a state, including street address, city, county and precinct;
- zip code and their equivalent geocodes (the initial three digits of zip codes may be used if the resulting geographical area contains more than 20 000 people or, for areas with less, the initial three digits of the zip code must be changed to 000);
- all elements of date (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death and all ages over 89 and all elements of dates indicative of such age, unless aggregated into a single category of age 90 or older;
- telephone and fax numbers;
- e-mail addresses;
- social security, medical record, health plan beneficiary and account numbers;
- certificate and license numbers;
- vehicle identifiers and serial numbers, including license plate numbers;

- device identifiers and serial numbers;
- web universal resource locators (URLs);
- Internet protocol (IP) address numbers;
- biometric identifiers, including finger and voice prints;
- full face photographic images and any comparable images and
- any other unique identifying number, characteristic or code.

Some of the data fields in the list, such as social security number, e-mail address, telephone number and the like, offer a fairly ready way to find out who a data subject is.²¹ The other fields chosen for stripping appear a list of fields that a database expert would find to be useful for triangulating databases to zero in on identified cases. Removal of all the fields listed in the regulation is the only 'safe harbour' for any data to be outside the regulation's prohibitions on use or disclosure.

The only alternative to the safe harbour is for a 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' (42 C.F.R. 164.514(a)(1)(i)). Under this 'statistical' method, a database can be considered 'de-identified' if

- [a] person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable:
 - (i) Applying such principles and methods, determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information; and
 - (ii) Documents the methods and results of the analysis that justify such determination.²²

²¹ The irony, of course, is that within a set of health care or health benefits data, even the patient's name, address and telephone number are not necessarily adequate to know that one is looking at the same individual in different records of health encounters. The same household or neighborhood may have many individuals named John Smith, Maria Hernandez or Sally Wong. As a result, date of birth or social security number – or some other unique code that is known to be associated with a single individual over time – is almost always needed for health information systems to perform at an acceptable level of accuracy in identifying individuals.

²² 45 C.F.R. § 164.514(b)(1).

As the rule is constructed, the inclusion of a patient-related date of any kind in a data set appears automatically to transform the data into protected health information. As a result, unless a statistician makes the risk finding, transmission of data including dates to anyone would be a technical violation of the regulation. Likewise, ‘county’ and ‘zip code’ are in the list of fields that are automatically considered to be ‘identifiers’ that must be removed for data to fit the de-identification ‘safe harbour’. In fact, unless each patient authorizes the disclosure or unless a statistician renders a risk opinion, an overly strict reading of the regulation would make the disclosure of a table of frequencies that includes any of the suspect fields a disclosure of protected health information, particularly if the cell sizes are modest. Unfortunately, responsibility for deciding whether data meet these criteria is placed on the physicians, hospitals and health plans that are subject to enforcement penalties if they wrongfully disclose protected health information. As a result, unless statisticians develop a robust new business of delivering opinions regarding the probability of re-identification of databases that include various dates, data that meet the de-identification safe harbour are virtually useless for sound and informative epidemiologic or outcomes research.

Authorization for the Use and Release of Identifiable Information

The privacy regulation prohibits covered entities from using or disclosing protected health information for research purposes without an individual’s written authorization or a waiver of authorization in accord with the regulation. The regulation explicitly provides that using information for research is not one of the activities that is permitted under the arrangements for using and disclosing information for treatment, payment and health care operations. ‘Authorization’ to use information for research is required – in *addition* to the requirements under the Federal Common Rule relating to ‘informed consent’ of the subject to participate in the research protocol – as discussed more fully below. Likewise, the criteria for waiver of authorization under the privacy regulation are different from and in addition to the criteria for waiver of informed consent under the Common Rule.

Authorization for Research

The privacy regulation specifies the required element for a valid authorization. To be effective, an authorization must include, among other elements

- a specific description of the information to be used or disclosed;
- specific identification of the person or entity with whom or to whom the covered entity may make the requested use or disclosure;
- an expiration date;
- a specific description of the purpose of the use or disclosure;
- an explanation of how the individual may revoke the authorization;
- a statement that the information disclosed may be subject to redisclosure by the researcher and no longer protected by the federal regulation and
- whether the covered entity will receive either direct or indirect remuneration from a third party for making the disclosure, a statement to this effect.

The authorization must contain all the elements specified in the privacy regulation,²³ as well as any disclosures or elements required by any applicable state law, unless an IRB or privacy board grants a waiver of authorization or of the form of authorization with respect to one or more elements in accord with the regulation’s waiver criteria.²⁴

Waiver of Authorization Requirement

In lieu of asking individuals to authorize the disclosure of their protected health information, the covered entity may seek waiver of the authorization requirement from an IRB established in accordance with the Common Rule or from a specially constituted privacy board.²⁵ Either entity may grant a waiver of authorization if the research protocol meets the privacy regulation’s waiver criteria. These criteria resemble the Common Rule criteria for waiver of informed consent, discussed more fully below.²⁶ However, the

²³ 45 C.F.R. § 164.508(c).

²⁴ See *id.* at 82 816–17 (codified at 45 C.F.R. § 164.512(i)).

²⁵ 45 C.F.R. § 164.512(i). Likewise, omission of any one of the required elements of a valid HIPAA authorization may be waived by an IRB in accord with the criteria specified in the regulation.

²⁶ 45 C.F.R. § 164.512(i)

differences in type of risk and the findings, as well as the different purposes served by informed consent as opposed to the HIPAA authorization, have proved to be a significant source of confusion and administrative complexity for IRBs.

The medical privacy regulation became effective as of 14 April 2001. Because the regulation supplements but does not supersede the Common Rule, all data-only research that also is subject to the Common Rule must comply with requirements to have an IRB consider *both* a waiver of informed consent to participate in research and a waiver of authorization under the privacy regulation.²⁷

Research with Records of Deceased Individuals

Under the Common Rule, deceased individuals are not considered ‘human subjects’.²⁸ Absent state laws or institutional policies to the contrary, research using the records of deceased persons does not require IRB approval or an IRB waiver of informed consent. The privacy regulation, in contrast, includes deceased persons as ‘individuals’, whose privacy is protected by the regulation. The regulation states that a covered entity can provide access to records of deceased individuals only if it obtains representations from the researcher that the information sought will be used only for research purposes and is necessary for these purposes.²⁹ In addition, the covered entity, at its discretion, may require the researcher to document the death of the individuals whose protected health

²⁷ 45 C.F.R. § 164.512(i)(2)(iv)(A). To waive the authorization requirement, an IRB or privacy IRB must determine that (1) the use or disclosure of the protected health information involves no more than minimal risk to the proposed research subjects; (2) the proposed research could not practicably be conducted without the waiver and (3) the research could not practicably be conducted without access to and use of the health information. The finding of “minimal risk” in item 1 is based on a finding that at least the following three elements are present: (1) there is an adequate plan to protect personal identifiers from improper use and disclosure; (2) an adequate plan to destroy such identifiers at the earliest opportunity consistent with the conduct of the research (unless there is a health or research justification for retaining the identifiers or if retention is otherwise required by law) and (3) there are ‘adequate written assurances’ that the identifiable health information will not be reused or disclosed to any third party except as required by law, for oversight of the research project, or for other research for which the use or disclosure would be permitted by the regulation.

²⁸ 45 C.F.R. § 46.102(f) (2000).

²⁹ 45 C.F.R. § 164.512(i)(1)(iii).

information is sought.³⁰ Alternatively, an IRB or privacy board could waive authorization with respect to deceased individuals under the regulation’s criteria for waiver.³¹

Data Use Agreement

In promulgating the final HIPAA medical privacy rule, the Secretary of Health and Human Services established an additional provision for data research using medical records in which ‘facially de-identified data’ could be made available for research and public health purposes under a data use agreement in which the researcher promises to protect the privacy of the data subjects and safeguard the data from use or disclosure for impermissible purposes.

When this proposed modification was announced, many in the research community applauded the possible revisions as achieving a more appropriate balancing of the public interest in research and public health with the public interest in protecting the privacy of data subjects. However, some expressed concern that even these arrangements for de-personalized, confidential use of facts compromise the privacy interests of the data subjects. In effect, the data use agreement binding the researcher was not believed to be adequate legal protection from the potential privacy risk that might result from a researcher’s violation of the provisions of the data use agreement.

As a result, the final regulation was a compromise: it is a hybrid of the protection provided by de-identification and the protection provided by the data use agreement binding the researcher not to use or disclose the data for purposes other than those specified in the agreement. Unfortunately, the regulation specifically prohibits the use of this mechanism for research if a medical device serial number is included in the record to be reviewed – even if the agreement prohibits the researcher from using or disclosing the serial number in a way that would identify individuals. Thus, although this approach holds promise as

³⁰ 45 C.F.R. § 164.512(i)(1)(iii)(B).

³¹ Although an IRB might be inclined to grant such a waiver under the Common Rule criteria (particularly since deceased individuals are not ‘human subjects’), the privacy regulation provides a process for obtaining authorization from the executor of an individual’s estate or other personal representative, so it is not clear how these new rights and responsibilities may affect the deliberations of IRBs.

a foundation for workable privacy protections that permit bona fide research, the HIPAA framework and authority is too fragmented to provide the necessary legal foundation.

STATE LAWS

The requirements of the HIPAA regulation expressly do not preempt state laws unless it is ‘impossible to comply’ with both the state and federal requirements.³² If it is impossible to comply with both, then the federal law preempts the state law only if the state law is less stringent than the federal law.³³ Moreover, the informed consent provisions of the Common Rule state that ‘The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective’.³⁴ Some states, such as Minnesota, have laws that directly regulate research.³⁵ These state laws are not preempted by the Common Rule, and so long as the federal and state requirements are not inconsistent with one another, the rule is that one should comply with all applicable laws.

Virtually, all states have some form of law or law specifying what constitutes consent, and the above provision of the Common Rule indicates that IRBs and researchers are obliged to comply with them. In practice, complying with the informed consent requirements of medical privacy laws has not been an insurmountable impediment to epidemiologic research because states typically do not have provisions regarding the waiver of consent; thus the affirmative federal policy has been assumed to govern. In recent years, however, many states have considered legislation that is more restrictive than the Common Rule with respect to waiver of consent.³⁶ As these laws are implemented, IRBs may find that fewer

³² Pub. L. 104–191 § 263(c)(2); 45 C.F.R. § 160.202 (defining ‘contrary’).

³³ *Id.* One law is more stringent than another if it is more protective of the privacy rights established by the HIPAA regulation, including more specific with respect to the ‘form, substance, or need for express legal permission’. 45 C.F.R. § 160.202 (defining ‘more stringent’).

³⁴ 45 C.F.R. § 46.116(e).

³⁵ See, for example, Minn. Stat. Ann. § 144.335(3a)(d).

³⁶ See, for example, 2001 Tex. Sess. Law Serv. ch. 1511 (S.B. 11 (Vernon)).

epidemiologic protocols meet the criteria for waiver of consent.

An even more troubling set of problems for research stems from the increasingly prevalent state laws regulating informed consent and information disclosure when genetic testing or genetic information is involved. As health care interventions increasingly use genetic analyses for diagnostic purposes and for selection of appropriate pharmaceutical interventions, it will be increasingly unlikely that any medical record can be presumed not to include genetic information. State genetic laws typically define ‘genetic information’ very broadly, so that carrier status, single gene diseases, multiple gene diseases and genes that merely indicate a susceptibility for a disease are all encompassed by the definition. As a result, records containing such information generally become subject to state law requirements regarding disclosure of such information. Unless federal regulators and institutions sponsoring IRBs are attentive to the implications for epidemiologic research, the social sensitivity of genetic information (popularly thought of in more narrowly predictive terms than the states’ broad definitions) may very well be construed as making any records that include information regarding the results of genetic tests ineligible for expedited review. That is, as discussed below, under the 1998 notice from the FDA and the National Institute of Health (NIH),³⁷ research using data that might be used to disadvantage the data subject is not to be deemed ‘minimal risk’ research for purposes of an IRB’s expedited review policy. Thus, the breadth of state laws protecting genetic information raises the possibility that routine data-only research will have to be approved and considered by the full IRB, with the potential for fractious ‘research vs. privacy’ debates that may result in the approval of only a fraction of important protocols.

The net result of the three bodies of US law is that there are many sources of legal requirements that impact researchers’ access to data for purposes of epidemiologic research. And because responsibility for complying with these requirements generally focuses on the data source, any one of multiple laws can become a roadblock to the conduct of research. In effect, there is no legal or organizational framework that holds the plethora of laws together in a way that offers straightforward principles for protecting the

³⁷ *Infra* note 43.

public interest in the conduct of epidemiologic and outcomes research while protecting the data subjects' privacy interests.

RESEARCH ETHICS

ROOTS IN INTERVENTION AND MANIPULATION

Almost every paper or book on research ethics includes a cautionary reference to atrocities committed in the name of science or abuses resulting from a researcher's crass objectification of research subjects. Lurking in the background of the calls for more laws protecting human subjects are memories of the abuses at Auschwitz and in the Tuskegee and Willowbrook studies. Contemporary research ethics is grounded in the desire to protect the individual from unknown and at some level unknowable risks. Both the Declaration of Helsinki³⁸ and the 'Common Rule'³⁹ (which forms the basis for laws protecting human subjects in the United States) reflect a philosophical framework that prioritizes individual autonomy, well-being and just distribution of burdens and benefits in the conduct of research, as well as the subject's beneficence and contribution to benefit others.

Under the Common Rule, there are two different types of protection for research participants:

- review of specific research protocols by an Institutional Review Board (IRB) to identify the risks to participants presented by the specific research protocol and
- consent of each research participant which is informed by disclosure of the risks and benefits of the research.

The two protections become co-mingled because US regulations assign the IRB two different tasks. In addition to identifying and weighing the risks presented by the protocol and deciding whether it can go forward

or needs modification, the IRB also reviews the forms and documents used to inform the subject and to obtain consent, *and* under certain limited circumstances, is authorized to waive the consent requirement with respect to a given research protocol. All things considered, this approach has been quite effective in protecting human participants from risk in research that involves intervention or manipulation of health care, such as clinical trials and other experimentation.

REVIEW OF RESEARCH RISK VERSUS NON-RESEARCH RISK

As clinical interventions become more complex and involve newer scientific approaches, it is increasingly clear that competent and independent IRB analysis and review are indispensable for identifying and evaluating the desirability of subjecting individuals to the known and unknown risks of a researcher's proposed protocol.

With respect to research using medical archives, however, the research risks are essentially the same in every study: all of the risks stem from the privacy interests of a data subject and the potential damage from potential *non-research* misuses of personal information in our society. The risk to the data subject from the research, therefore, is a direct function of the arrangements for data security and the potential for breaches of the security arrangements or dishonest behaviour by a researcher in using or disclosing information for non-research purposes. Assuming that the researcher is obliged to use information only for research and to maintain adequate security to protect it from further disclosure or unauthorized use, none of the privacy risks stems from any specific research protocol itself. Rather, to the extent that different data analyses appear to involve more or less risk, the differences can be traced to social values and attitudes towards the *subject matter* of the investigation.

For example most people would say that research relating to HIV or genetics involves greater privacy risk than research on the common cold. This perceived difference in the risk of the *research* is an illusion. Assume that a single database, maintained under tight security arrangements, is made available to two different researchers under confidentiality agreements

³⁸ Declaration of Helsinki, World Medical Association, Inc, adopted by the 18th World Medical Association General Assembly in June 1964 and revised most recently in October 2000. The Declaration is a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects, including research on identifiable data.

³⁹ *Supra* note 4.

that bind the two investigators to the same obligations regarding use and protection of the data. One is studying HIV infection, and the other is studying staphylococcus infection. The privacy risks in both cases are the same; they stem from the adequacy of data security arrangements and the obligations imposed on the investigators. The appearance of differential risk stems from the current cultural perceptions of HIV and that people or institutions – other than the researcher – might misuse the information to embarrass or harm the data subject *if* they were to gain access to the information. Similarly, test results from the various breast cancer genes only appear to be more sensitive than information about a family history of breast cancer. In fact, both could be misused in precisely the same way *if* they were to fall into the wrong hands. The fact that there are persons in our society who, if unchecked, might discriminate against individuals in violation of the law, or misuse information to disadvantage or harm a data subject, does not vary based on the subject matter of the research. Rather, the perceived differences among data projects reflect differences in the potential for social, psychological or financial *damage* to the data subject in our society, assuming that there is a negligent or intentional failure of data security arrangements.⁴⁰

Unlike the approach IRBs take in interventional research involving physical manipulation or intervention in the subject's care, nothing in the research design in a data-analysis project can control, eliminate or mitigate these societal risks. In a data study, one cannot modify the dosing, the subject selection criteria or the laboratory tests used to monitor the effect of the research manipulation on the individual. The events to be examined in the research have already occurred. The epidemiologic or outcomes researcher

is an active observer of natural processes that have been recorded in the history of an individual's health care and health benefit interactions. An epidemiologic study, by definition, seldom can be shown to have a potential benefit to the individuals who are the data subjects. Rather, because the observed events and interventions have already occurred in the natural course of events, the benefit of the *research* is to the public health in general or to succeeding generations that may benefit from innovations that may be developed. Accordingly, when, as is required by the Common Rule, the Review Board attempts to determine whether the '[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result from the research'⁴¹ the Review Board is not being asked to weigh the risks the protocol poses to an individual in relation to the importance of the knowledge to be gained. Rather, the Review Board is being asked to consider the potential sociopsychological damage to an individual in our society based on the fact that he or she evidences the character under investigation, *assuming* that there is a breach of data security that results in a disclosure of data outside the research context where the data are used for an impermissible purpose.⁴²

As a result, the 'weighing' question posed to the Review Board with respect to archival research misses the mark entirely. It largely becomes a philosophical question about the importance of the knowledge that might be gained in comparison with the IRB's beliefs about how badly US society discriminates or misuses the particular characteristics that are under study. By comparison, for interventional research, the Review Board evaluates the risk of the research protocol and proposes modifications to minimize the risk posed by the research. The Board evaluates the *research* risk in relation to benefits to the participant and the importance of the potential knowledge. The risk equation does *not* include consideration of the possibility that a negligent or intentional action that is *not* a part of the research protocol – for example an auto accident on the way to the clinical trial site – could result in the death or serious bodily harm of a participant.

⁴⁰ We see this directly in the fact that consideration of the danger from external factors rather than the research itself has crept into agency interpretations of the concept of risk under the Common Rule. In 1998, in discussing revisions to the categories of research eligible for 'expedited review' the Department [through both the Food and Drug Administration (FDA) and the National Institute of Health (NIH)] stated that expedited review was impermissible where 'identification of subjects or their responses would place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasions of privacy and breach of confidentiality are not greater than minimal'. 63 Fed. Reg. 60 355, 60 366.

⁴¹ 45 C.F.R. § 46.111(a)(2).

⁴² Under the Common Rule, data security is a separate issue from the issue of the relative risk and value of interventional research. Compare 45 C.F.R. § 46.111 (a)(1) and (2) with § 46.111(a)(7).

The critical problem is that as formulated, the Common Rule's risk equation – when applied in review of a data-only project – is almost certain to devolve into a referendum on the value of the researcher's hypothesis. In fact, the vast majority of IRBs appear to avoid such tangled debates by establishing procedures under which most data-only studies fall into the category posing 'minimal risk' to data subjects. The categories of studies eligible for expedited review under the Common Rule are specified in a guidance document promulgated by the Office for Human Research Protections.⁴³ Under this guidance, where there is a risk of discrimination based on disclosure of the subject's responses or data, the research is *not* eligible for expedited review *unless* 'reasonable and appropriate protections will be implemented'.⁴⁴

The Department's introduction of 'reasonable and appropriate protections' in evaluating the risks inherent in data-only studies hints at the underlying issue that, in our view, *should* be of concern in any Board Review of a data study: does the study design appropriately limit use and disclosure of personal identifying information? And, does the researcher have adequate arrangements for data security?⁴⁵ However, as currently formulated, this decision is made only in considering whether or not to *have* a full Board review of a study. The review itself is still premised on a risk-value enquiry that does not address the real questions about the risk posed by the research, i.e. the risk that identifying data might be used or disclosed for non-research purposes.

INFORMED CONSENT AND CONTROL

The concept of consent is critical in interventional research because the physical risks and rigors of the research will directly affect the individual and his or her health and well-being. The informed consent process helps to minimize the potential for coercion and for ensuring that the individual maintains control over what is done to him or her in the research protocol. In effect, it is a recognition of the value our society places on an individual's physical integrity

⁴³ Categories of research that may be reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure, 63 Fed. Reg. 60 355-67 (Nov. 9, 1998).

⁴⁴ 63 Fed. Reg. 60 355, 60 366.

⁴⁵ See, for example, Lowrance (1997).

and autonomy. A properly informed individual may decide to accept fairly significant risks. However, only in rare circumstances where the risk is judged to be minimal would our values and our current laws permit a researcher or Board to decide to subject others to physical risks without their knowledge; never would we expect an IRB to permit experimentation on human beings against their will.

ANOMALY: Consent in Archival Research

In the context of archival research, where the researcher will access only information in existing records, the role of informed consent is conceptually different from consent to physical participation. As discussed above, assuming adequate data security arrangements and protection of direct identifiers, the research itself does not pose a risk to the data subject. Epidemiologic and outcomes research is concerned not with a specific individual but with populations.

At best, therefore, any 'informed consent' discussion with individual data subjects is little more than an explanation of the researcher's hypotheses and research interests and his or her promises and arrangements regarding the safeguarding of data. Because epidemiologic researchers are concerned with populations and not individuals, both of these discussions could be addressed in a more general manner, such as a researcher's data practices, and more effective communication to the public regarding research topics and how data archives are used in investigating them. A discussion between a researcher and an individual data subject may elicit sympathy or the 'beneficence' of the data subject and a motivation to permit the records to be used. However, to the extent that the data subject dislikes the topic or the philosophical underpinnings of the research question, consent is little more than an invitation for the data subject to exert control over the researcher's inquiry by denying access to data.⁴⁶ If this very natural exercise of

⁴⁶ Some have maintained that an individual's privacy interests justify his or her refusal to allow information to be used in research. To once again make the analogy to the banking world, this is analogous to the argument that I do not want you to lend my money to individuals, industries or activities that I find morally repugnant. In the financing case, the objection is rooted in the concept of unjust enrichment. Arguably, the situation is somewhat different where the

power can be expected to occur fairly systematically (e.g. those who favour the researcher's point of view or value the subject matter consent to use of their records and those who do not, decline to consent), then the records sample available for analysis of any kind is systematically biased and may not meet the criteria to be considered a valid sample for conducting the research.

Suppose that the discussion of the research topic is more neutral to minimize adverse selection and the informed consent documents seek merely to inform the individual of the risks. As discussed above, the risks to the individual from data-only studies are from the potential misuses of information by *non*-researchers who obtain it through illegal or negligent activities. As such, the risk statement is a statement about the society in which we live and not about the research, *per se*. In fact, a full statement of the 'risks' might very well detail the various possible illegal acts that could cause damage to the individual's reputation, employment, insurability and so on. But these are not research risks. The individual has little or no way of estimating or evaluating the probability of these occurrences. Arguably, this is what the Review Board should have done in evaluating the researcher's data security arrangements. The prudent individual, when confronted with a catalogue of abuses that *might* occur if the information found its way outside the research lab, would be hard pressed to find a reason why he or she *should* authorize the information to go to the laboratory in the first place.

As a practical matter, in institutions where data-only studies are subject to the Common Rule, it is widely understood that the rule 'works' only because these

researcher's endeavour is designed to contribute to the quality and innovation in health care and health care delivery. In this context, the reason that data pertaining to an individual are in the archives is because the individual already has availed him or herself of the resources of the health care system, and is, therefore, an unwitting, direct beneficiary of the quality improvement and innovation that has gone before. In this case, the equities, benefits and distribution of burdens of the research process arguably warrant secure, confidential use of data without each individual's authorization. To say 'I do not want to know about that subject, and I do not want anyone else to learn about that subject' runs counter to the freedom of inquiry on which our research and scholarly activities are based. Particularly where the researcher does not know or have access to information identifying individual subjects, it is difficult to make the case for the opposition other than as a differential value for free scientific inquiry.

studies typically are considered to be eligible for expedited review, and the IRB's reviewer decides to waive the requirement for obtaining the consent of data subjects. Any additional requirement that threatens to disrupt this accommodation, either by requiring the Board to debate and review the relative merits of the research question and society's potential for discrimination and privacy invasion, can do little more than increase the probability that the existing regulatory scheme may threaten the viability of valid epidemiologic and outcomes research.

ANOMALY: Consent to Future Use of Research Data

Since the promulgation of the HIPAA medical privacy regulations, a very troubling phenomenon has started occurring at several clinical research sites in the United States. In part because of a fusion and confusion of the HIPAA authorization requirements and the Common Rule's informed consent requirements, some IRB administrators and/or privacy officers advising IRBs at clinical research sites are prohibiting the inclusion of provisions in the informed consent that govern future use of the research data created in a clinical trial.

Under the Common Rule, the consent signed by the individual is the vehicle for informing the individual of the potential physical and personal risks of the research as well as of the potential uses and disclosures of the data. It is important to note that in a research institution acting in accord with best research practices, the data are not the same as the clinical record of care rendered to the clinical trial participant. With respect to the research site, the data are extracted from the more comprehensive record of care at the site and are disclosed to the researcher and/or research sponsor. Typically, direct personal identifiers and contact information are not furnished to the researcher/sponsor, although best clinical practices necessitate some sort of code number or other arrangement under which the specific research participant can be linked to the data, such as for follow-up on adverse findings or other matters of concern to the individual and/or to the integrity of the research, and of course, medical device serial numbers must be included in data reports. The informed consent traditionally has provided both for the disclosure by

the research site to the researcher/sponsor and the purposes or uses of the data by the researcher/sponsor, including any limitations on future use or publication of the data.

Where an IRB chooses to prohibit or limit the researcher's ability to obtain informed consent to future research use of the data created from an individual's participation in the clinical trial, we think this is in part due to two problematic developments. First, there is great confusion surrounding a new prohibition under the HIPAA medical privacy regulation.⁴⁷ HIPAA prohibits providers (and health plans) from obtaining blanket authorizations to research use of medical records or the conditioning of treatment or health benefits on the signing of such authorizations. This formerly occurred with some regularity as part of the consent to admission for treatment in some medical facilities. Second, we think that this is further evidence of the same troubling phenomenon we have seen with respect to the criteria for waiver of consent for epidemiologic and outcomes research using medical archives. In effect, there is an increasing tendency of some IRBs to substitute an *in loco parentis* decision by the IRB regarding the 'societal risk/value' of the researcher's use of the data for the individual's role in giving consent to use of the data from the clinical trial.

Although this result is not required by law, no law prohibits it either. The IRB has broad discretion under the Common Rule to determine what is to be included in the informed consent protocol. However, over time, this type of decision by IRBs could significantly increase the cost of research in the United States, as it could preclude the otherwise secure and confidential use of the research database by the researcher for purposes of formulating future hypotheses, looking back for evidence of unexpected adverse events, looking for new correlates or patterns in the data that were not part of the initial research protocol and other valid epidemiologic and outcomes hypotheses. Given the cost of obtaining clinical trial data, such a practice, over time, would likely make facilities whose IRBs elect to impose such limitations on the use of research data undesirable, unaffordable sites for clinical trials.

Ironically, some of the privacy officers advising IRBs have urged them to instead inform researchers

that they should rely on one of the mandatory assertions in the HIPAA authorization for research – that information disclosed under a HIPAA authorization may be redislosed by the recipient and that it is not subject to the protections of the HIPAA rule. This is not a solution at all for researcher, who wishes to review a clinical database for evidence of untoward effects or anomalies that may have been undetected in the original analysis.

IMPLICATIONS AND NEXT STEPS

In our view, there are several key aspects of the existing legal scheme that are cumbersome impediments to the conduct of large-scale epidemiologic studies. To make this scheme workable, we will need to

- engage in significant education of data sources and IRBs to integrate the new privacy authorization requirements with the existing Common Rule process for waiver of consent. Timely education will be key to avoiding IRB gridlock as the compliance date approaches.
- engage in significant education of the public regarding the value of epidemiologic research and the protections routinely used to protect individuals' privacy interests.

Because the privacy regulation also provides ordinary persons with access to information about all the people who have had access to their records – including researchers who access information under a waiver of authorization – there is a danger of public backlash if individuals are merely given a list of third parties that conduct research programs without an understanding of the purpose and importance of such uses and how the privacy of individual data subject is protected.

- Assist in developing de-identification strategies that will meet epidemiologists' data needs and monitor the use of resources invested in building an information infrastructure to ensure that the public interest in research is protected in a cost-effective manner.

At a more basic level, we must return to the more fundamental policy issue that a consent-based regulatory model (with waiver by a Review Board) is

⁴⁷ 42 C.F.R. § 164.506(b), 164.508.

little more than an abdication of the government's responsibility for using its power to protect both privacy and the public interest in research. Although this may be an ethically sound model in interventional research where a specific individual is being asked to subject him or herself to risks in the name of scientific curiosity, the ethical issues arguably are entirely different in data studies undertaken for public health and health care quality purposes. The consent model shifts responsibility to the individual: if the individual consents, then the individual assumes the risk of loss. As implemented under the new federal regulation, government authority is used merely to ensure that each individual is appropriately warned of the risks, and that those who nonetheless attempt to persuade individuals to consent, keep records of those warnings and of the consent, and are accountable for the inappropriateness of their procedures. From a legal perspective, waiver of consent by an IRB may be construed as an indication that the IRB or its institutional sponsor is accepting this responsibility on behalf of the individual. In our litigious society, this is not a legal model that over the long run will make it economically viable for hospitals, doctors and health plans to provide data to researchers under a waiver.

To bring the discussion full circle, if this approach had been used as the framework for monetary regulation, it would be analogous to forsaking the secure, regulated banking system for one more like venture capital: bankers would have to poll the public for funds, and each would-be investor would bear responsibility for approving the subject matter of each project and, having signed the forms, bear the risk of loss. In our view, the public interests in privacy *and* in the quality of health care that research makes possible argue for a more equitable approach to assuring that the burdens of research are shared by those who benefit and that government and/or private oversight is used to minimize risks to all by establishing data security standards and holding individuals accountable for violations.

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5

Pharmacovigilance-Related Topics at the Level of the International Conference on Harmonisation*

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INTRODUCTION

Authorisations for the marketing of medicinal products need to be based on the universal criteria 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 authorisation. Such an application includes all data and is assessed through the process of marketing authorisation 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 authorisation in different countries of the world at the same time and 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 organised regularly by the World Health Organization (WHO) for their member countries as a forum to strengthen international collaboration between their authorities.

ICH was established with the objective of harmonised interpretation and application of technical

* Disclaimer: The views expressed in this chapter are those of the authors and not necessarily represent the official views of the European Medicines Agency (EMEA).

guidelines and requirements for marketing authorisation, 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 harmonisation are

1. new types of medicinal products,
2. lack of harmonisation of current technical requirements,
3. transitions to technically improved testing procedures,
(all three requiring 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.

ICH covers the three regions, European Union (EU), Japan and the United States of America, where most pharmaceutical innovations have been developed and consists of the so-called ‘Six Parties’, i.e. the authorities and associations of innovative industry in these three ICH regions:

1. the European Commission, representing the 25 Member States of the EU,¹
2. the European Federation of Pharmaceutical Industries and Associations (EFPIA),
3. the Ministry of Health, Labour and Welfare of Japan (MHLW),
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).

¹ In addition, the European Commission represents Iceland, Liechtenstein and Norway, i.e. the three countries that are Members of the 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.

In addition, there are three ICH observers:

1. the WHO,
2. the European Free Trade Area (EFTA, 1999) represented by the Swiss authority Swissmedic² and
3. Canada represented by the Canadian authority Health Canada.

These Six Parties develop scientific consensus through discussions between experts from the authorities and industry. The draft consensus ICH guidelines or 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.

The ICH SC also comprises a subcommittee, the ICH Global Cooperation Group (GCG), which is set up from one representative from each ICH party, the ICH Secretariat, WHO, EFTA, Health Canada and from five regional harmonisation initiatives, namely the Asian-Pacific Economic Cooperation (APEC), the Association of Southeast Asian Nations (ASEAN), the Gulf Cooperation Countries (GCC), the Pan-American Network on Drug Regulatory Harmonization (PANDRH) and the South 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 harmonisation initiatives to facilitate the regional and global harmonisation related to ICH guidelines and recommendations. Their observership at SC level has been increased accordingly.

So far, ICH has published 53 guidelines in the three areas, quality, safety and efficacy,³ and provides in

² EFTA consists of the four members, Iceland, Liechtenstein, Norway and Switzerland, out of which Switzerland is the only country who is not a member of the EEA.

³ 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.

addition 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: Timing of Pre-Clinical Studies in Relation to Clinical Trials,
- M4: CTD – Common Technical Document for marketing authorisation applications and
- M5: Data Elements and Standards for Drug Dictionaries.

THE ICH STEP PROCESS

A new topic for harmonisation 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 contact point for the party he belongs 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 2 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 organisations, 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: START OF REGULATORY ACTION

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 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 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 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 the consultation are presented by the ICH Regulatory Rapporteur to the ICH SC for consideration as to whether the

Table 5.1. Overview of pharmacovigilance-related ICH guidelines.

Code	Topic	Adoption by ICH SC
ICH-E2A	Clinical Safety Data Management – Definitions and Standards for Expedited Reporting	October 1994
ICH-E2B(M)	Clinical Safety Data Management – Data Elements for Transmission of Individual Case Safety Reports	July 1997, amended in November 2000, revision of May 2005 of Step 3
ICH-E2C	Clinical Safety Data Management – Periodic Safety Update Reports for Marketed Drugs	November 1996
ICH-E2D	Post-Approval Safety Management – Definitions and Standards for Expedited Reporting	February 2003
ICH-E2C Addendum	Addendum to Clinical Safety Data Management – Periodic Safety Update Reports for Marketed Drugs	November 2003
ICH-E2E	Pharmacovigilance Planning	November 2004

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.

THE PHARMACOVIGILANCE-RELATED ICH TOPICS

So far, pharmacovigilance-related topics entered the ICH process in two waves. The first wave resulted in adoption of the ICH Topic ICH-E2A in 1994 with an extension to this work in the form of E2B and E2C,

finalised between 1996 and 1997. The second wave started in 2002 with three further ICH topics, E2D, E2C Addendum and E2E, finalised between 2003 and 2004 (Table 5.1).⁴

TOPIC ICH-E2A (STEP 5): CLINICAL SAFETY DATA MANAGEMENT – DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

This ICH guideline, 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-authorisation phase, it has also been used in the post-authorisation environment (Table 5.2). Reasons for this may have been the absence of an ICH guideline for the post-authorisation 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).⁵ The guideline also incorporated definitions agreed within the framework of the International

⁴ Whilst Table 5.1 provides a chronological overview, in the main text the guidelines are ordered by their contents.

⁵ The CIOMS is an international, non-governmental, non-profit organisation set up in 1949 under the auspices of WHO and UNESCO, 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 5.2. Key points addressed in the ICH-E2A guideline.

Definitions for AE and ADR in the pre-authorisation 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

Drug Monitoring Programme established by WHO for pharmacovigilance of marketed medicinal products.

ICH-E2D TOPIC (STEP 5): 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 (2003a) guideline on ADR case reports specifically for the post-authorisation phase (Table 5.3). Therefore, the ICH-E2D guideline was finalised in 2003 at ICH Step 4, formalising the application of relevant elements of ICH-E2A in the post-authorisation phase and responding to further harmonisation needs with regard to the definitions and management of case reports for expedited reporting in this phase. Such further harmonisation needs had previously been discussed in the CIOMS V Report (CIOMS, 2001), which therefore formed an important basis for ICH-E2D.

ICH-E2B(M) TOPIC (STEP 5): 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)

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

Definitions for AE and ADR in the post-authorisation 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 authorised 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-authorisation 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 authorisation holder despite any contractual relationship in place

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 (syn.: 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 (ICSR, syn.: ADR case report). With the mandate to further improve the definitions and specifications 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) (Table 5.4). A related questions and answers document is being kept updated by the EWG, 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 was initiated and the revised ICH-E2B(M), now called ICH-E2B(R3), was signed off at Step 2 in May 2005 (ICH, 2005a).

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

Description of all data elements of ADR case reports: 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

ICH-E2C TOPIC (STEP 5): CLINICAL SAFETY DATA MANAGEMENT – PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

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. This guideline describes the specifications for format and content of periodic safety

Table 5.5. Key points addressed in the ICH-E2C guideline.

Inclusion of all product presentations in one PSUR
Concept of international birthdate of a product, determining 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 authorisation 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 to the CCSI versus unexpected in comparison with locally authorised product information)
Presentation of individual case history
Formats of ADR line listings and summary tabulations
Presentation of exposure data
Overall safety evaluation and conclusion: analysis and discussion of data by marketing authorisation holder with a view to possible safety-related action
Explanation on responsibilities of marketing authorisation holders in contractual relationship
Annex of medically unconfirmed ADR case reports to be submitted as requested locally

update reports (PSURs) reflecting the safety profile based on worldwide data and concluding upon need for action (Table 5.5). Also ICH-E2C was based on the work achieved by CIOMS, i.e. the CIOMS II and CIOMS III reports (CIOMS, 1992, 1995).

ICH-E2C ADDENDUM TOPIC (STEP 5): ADDENDUM TO CLINICAL SAFETY DATA MANAGEMENT – PERIODIC SAFETY UPDATE REPORTS FOR MARKETED DRUGS

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 (Table 5.6) (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 drafting ICH-E2C Addendum. This guideline was adopted at Step 4 in 2003.

Table 5.6. 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
The organisation of some PSUR parts by system organ class
Risk management programmes, if in place for the product, 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 harmonisation towards international birthdate; clarifications for such harmonisation
Clarification on restart of PSUR submission frequency
New concept of summary bridging report supporting submission of a set of single PSURs
New concept of 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 (STEP 5): PHARMACOVIGILANCE PLANNING

This guideline 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 United Kingdom 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 programme of communication between marketing authorisation 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 authorisation 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', summarising identified, potential and unknown risks for the medici-

nal product. Various methods for data collection may be used, and ICH-E2E therefore provides, in addition to a format for pharmacovigilance plans, harmonised terminology for methods of active and passive surveillance as well as principles for the conduct of pharmacoepidemiological studies of non-experimental design (syn.: observational studies, non-interventional studies) (Table 5.7). ICH-E2E is a framework for the formal preparation of pharmacovigilance in the pre-authorisation assessment phase as well as for a continued proactive approach throughout the post-authorisation phase. Although ICH-E2E is not a summary of risk minimisation 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 minimisation 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 minimisation tools.

DISCUSSION AND CONCLUSIONS

The ICH initiatives in the area of pharmacovigilance have to be seen not only given the background of 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.

At the time of the first wave of pharmacovigilance-related ICH guidelines, the main focus was on gathering worldwide data in 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 paper work and facilitate data sharing and database entries. Its implementation is still ongoing, given the major technical change it represents for marketing authorisation holders and authorities. However, the future possibilities of sharing detailed case data in structured data fields are considered of major benefit. With a view to signal identification and risk-factor identification, algorithms and statistical methods have already been applied to data available

Table 5.7. 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 synchronisation of timetable with regulatory timetable for post-authorisation assessment, such as PSUR assessment or marketing authorisation 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

in other electronic formats using efficient, automated analysis by computer (data mining) (Clark, 2002; Clark, Klincewicz and Stang, 2002; Evans, 2002; Edwards *et al.*, 2002; van Puijenbroek, 2001). In accordance with EU legislation (Article 1(7), 2000; Article 51(c), 1993), the data processing network and management system EudraVigilance has been made available by the European Medicines Agency (EMEA) for expedited reporting and data storage in accordance with ICH-E2B(M) as well as MedDRA. Data mining tools for this system are under development. Electronic expedited reporting using EudraVigilance will become mandatory in the EU by legislation in November 2005. EudraVigilance allows networking and work sharing between the authorities in the EU, a necessity for the EU regulatory system. Aspects of ICH-E2A relevant to the post-authorisation phase have been implemented in the EU in Volume 9 of the Rules Governing Medicinal Products in the EU since its first version of 1997 (European Commission, 1997–2004), and ICH-E2D has been integrated in the revision of Volume 9A scheduled for finalisation in 2006. In the United States, the FDA developed their Adverse Event Reporting System (AERS), likewise based on ICH-E2B(M) and MedDRA and enabling electronic reporting. ICH-E2A and ICH-E2D have been incorporated by the FDA in their Proposed Rule on Safety Reporting Requirements ('Tome') (Raczkowski, 2003), and pharmaceutical industry hopes that current inconsistencies with regard to ICH-E2A, E2D and E2C will be cleared in the final rule (Khan, 2004). In Japan, electronic submission of ADR case reports, in accordance with ICH-E2B(M) and MedDRA/J (Japanese translation of MedDRA), was implemented in October 2003 and covered already after 6 months 55% of all submissions. Otherwise, ADR case reports are submitted on disks in accordance with ICH-E2B(M), so all ADR case reports are included in the database of the Japanese authorities on the basis of ICH standards (K Tamiya, personal communication, 17 June 2004). The fact that marketing authorisation holders can submit ADR case reports to the authorities in the three ICH regions according to the same technical standards represents major work facilitation.

The PSUR 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 adden-

dum during the second wave of pharmacovigilance-related ICH guidelines. ICH-E2C Addendum opened further opportunities for the useful application of the PSUR. In the United States, both these ICH guidelines were published in the Federal Register Notice, but the PSUR has not yet become the required format for periodic reporting. Since 2001, a waiver request may be submitted by marketing authorisation holders who want to use the PSUR, and in 2003, the PSUR format was included by the FDA in their Proposed Rule on Safety Reporting Requirements ('Tome') (Chen, 2003; Khan, 2004). Again, the availability of an agreed standard should allow marketing authorisation holders to submit the same PSUR in the three ICH regions at the same point in time and also promote co-operation between authorities. However, some legal issues in relation to harmonisation of data lock points and submission dates remain to be solved. On the other hand, the EU has successfully piloted work sharing and peer review between authorities in relation to PSUR assessment for products that otherwise fall outside the established structures of EU co-ordination (i.e. for purely nationally authorised products not subject to the centralised, mutual recognition or decentralised procedure) or for active substances subject to more than one authorisation procedure. This work sharing requires harmonisation of data lock points that go beyond the product, i.e. agreeing substance birth dates. This example shows how an ICH concept can be used for an even higher degree of harmonisation, as appropriate for a particular region. Moreover, from an EU perspective, it has to be said that the pharmacovigilance-related ICH guidelines as a whole have formed the basis for the processes as they are in operation in the pharmacovigilance system of the EU today.

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 at their regular meetings from 1999 onwards and expressed interest in increased co-operation 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 co-operation beyond personal contact.

The second wave of pharmacovigilance-related ICH guidelines was then prepared by the Japanese Ministry in 2000, at the same time when they strengthened the

Japanese pharmacovigilance system. The measures taken in Japan included the concept of EPPV described above.

In the United States, 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 authorised in 2002, the FDA finalised, following public consultation, three guidance papers in 2005 on risk assessment during the pre-authorisation phase, risk minimisation action plans as well as good pharmacovigilance practices and pharmacoepidemiologic assessment (FDA, 2005a-c).

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 optimise data collection processes in pharmacovigilance. Furthermore, welcoming proposals from the EMEA, the Heads of Medicines Agencies Ad Hoc Working Group (2003, 2005a,b) in the EU started developing a risk management strategy in 2002. More specifically with regard to products centrally authorised by the European Commission, the EMEA (2004b) established a procedure for assuring high-quality pharmacovigilance in both the pre-authorisation and the post-authorisation phase. Further initiatives are announced in the EMEA Road Map to 2010 (EMEA, 2004a), taking into account the revised legislation (Directive 2004/27/EC, 2004; Regulation (EC) No 726/2004, 2004) and the needs expressed by patients (EMEA/CHMP Working Group with Patient Organisations, 2005). The revised legislation introduces the concept of risk management systems to be put in place by marketing authorisation holders, and guidance has been included in the revised Volume 9A (European Commission, 2006). Needs expressed by patients include a proactive approach in pharmacovigilance.

All these activities in the three ICH regions reflect the high demand for strengthening pharmacovigilance from a public health, political as well as public point 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.

A possible third wave of pharmacovigilance-related ICH guidelines is therefore currently under consideration. In October 2006, the ICHSC adopted a new ICH topic on safety update reports for the development phase of medicinal products (E2F).

Looking furthermore at the importance of pharmacovigilance and drug safety beyond the three ICH regions, one needs to note the work of the Uppsala Monitoring Centre (UMC): With the aim to support world health in the field of drug safety, the UMC manages the WHO's Programme for International Drug Monitoring and provides an international networking structure as well as many services for their 81 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 guideline, and although it uses the ADR terminology WHO-ART, it also accepts cases coded in MedDRA (UMC).

Looking at drug safety from a global perspective and in particular not neglecting the needs of developing countries, the following needs to be considered.

Efficacious and safe use of a medicinal product depends on the product, the patient with his/her 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, pharmacovigilance and health services need reliable information on efficacious and safe use of medicinal product from elsewhere while making all efforts to improve their systems and taking into account local public 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 as well as 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-authorisation phase.

However, there is more work to be done in this respect, such as epidemiological, health priority, health service, pharmacogenetic, drug utilisation and medical-anthropological research. This will be a major future challenge for risk minimisation and its evaluation, when working towards worldwide access to medicines and providing medicines to multiethnic populations. In any case, co-operating within regional and international structures is of key importance for all countries with the aim of high-quality risk assessment and minimisation as well as efficient use of resources.

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6

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 harmonised 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 Harmonisation 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 programmes and benefit–risk analyses. The PSUR has now been adopted in many European countries, Japan and the United States. It is emerging as a gold standard of safety evaluation for marketed drugs and an important pharmacovigilance tool.

PURPOSE OF THE PSUR

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 authorised and to indicate whether

changes should be made to product information to optimise 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. After approval, a drug becomes so 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.

PSUR – GENERAL PRINCIPLES

ONE REPORT FOR PRODUCTS CONTAINING ONE ACTIVE SUBSTANCE AUTORISED TO ONE MARKETING AUTORISATION HOLDER

Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance for medicinal products authorised to one marketing authorisation 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 AUTORISED TO MORE THAN ONE MAH

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 is reported to the regulatory authorities, respective responsibilities for safety reporting should also be clearly specified.

COMBINATION PRODUCTS

For combinations of substances which are also authorised 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 non-clinical safety data should cover only the period of the report (interval data), with the exception of regulatory status information on authorisation 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 hospitalisation or prolongation of existing hospitalisation, 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 PSURS ACCORDING TO THE IBD

Each medicinal product should have as an IBD the date of the first marketing authorisation for the product granted to any company in any country in the

world. For administrative convenience, if desired by the MAH, the IBD can be designated as the last day of the same month. 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 harmonisation. Fortunately ICH E2C reverted to the IBD for scheduling reports, so now the European birth date is the same as the IBD for medicinal products first authorised in the European Union (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. 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 authorisations at different times in different countries. It is during this early period that harmonisation 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 separate 6-month or yearly PSURs covering 5 years, together with a PSUR bridging summary report, are required.

RESTARTING THE CLOCK

Approvals beyond the initial approval for the active substance may be granted for reasons including new indications, dosage forms, routes of administration or populations beyond those for which the active substance was initially authorised. 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 authorisation.

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 labelled or unlabelled. If the ADR reported is found in the approved product information for a given country, the event is considered labelled. If not, it is unlabelled. The European Summary of Product Characteristics (SPC) or locally approved product information continues to be the reference document upon which labelledness (or expectedness) is based for the purpose of local expedited post-authorisation safety reporting, so labelledness 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). MedDRA was developed in the early 1990s under the auspices of the ICH and is an important step towards the standardisation of terminology regarding the registering, documenting and safety monitoring of medical products. Its use in spontaneous reporting systems is now a regulatory requirement in some countries, and it is widely used in the preparation of PSURs. In November 1997, the 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 terminology. 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 Food and Drug Administration (FDA) has also introduced periodic reporting requirements based on ICH E2C, and it published a 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 authorisation, annually for the three following years and then five yearly after the first renewal;
- in the United States, the FDA requires quarterly reports during the first 3 years, then annual reports and
- in Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorisation. Systematic information on this cohort, taking into account a precise denominator, must be reported annually. Regarding other marketing experience, adverse reactions which are non-serious, but both mild in severity and unlabelled, must be reported every 6 months for 3 years and annually thereafter.

PSUR CONTENT

The amendment to ICH E2C stipulates that the MAH should submit a PSUR to the competent authority

Table 6.1. Contents of the periodic safety update report (PSUR).

Section number	Section
	Executive summary
1.1	Introduction
1.2	Worldwide market authorisation
1.3	Update on regulatory authority or marketing authorisation 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 authorisation status
Appendix 3	Line listings of case reports
Appendix 4	Summary tabulations of events (complement to Appendix 3)

of the country or region in question with succinct summary information and a benefit–risk analysis in the light of new or changing post-authorisation information. Specifically, the contents of the PSUR should be as laid out in Table 6.1. The rest of this section describes an overview of a model PSUR.

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 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 authorisation 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 MAH ACTIONS TAKEN FOR SAFETY REASONS

The *update on regulatory authority or MAH actions taken for safety reasons* refers to

- marketing authorisation, withdrawal or suspension;
- failure to obtain a marketing authorisation 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. ‘Dear Doctor’ letters).

CHANGES IN REFERENCE SAFETY INFORMATION

The *changes in reference safety information* section refers to changes in the CCSI. 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). 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 which 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 catalogue or describe all the studies.

OTHER INFORMATION

Other information may include risk management programmes 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, e.g. 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 organised 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 which 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.

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 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 are scheduled according to the local approval date. Moreover, not all companies will have synchronised 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 PSUR 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 labelledness 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 are the key to a thorough medical review and risk assessment. The sections of the PSUR which 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 which 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.

The PSUR process can be illustrated by the standard operating procedure (SOP) of H. Lundbeck A/S in this context. There are five stages to Lundbeck's procedure:

- data collection;
- PSUR writing;
- approval;
- archiving and
- distribution.

The data is collected from the following sources:

- Access to safety data: a tool for searching, reporting and extracting data from the pharmacovigilance database;
- Regulatory Affairs Division and Regulatory Central Archive of Lundbeck;
- International Clinical Research – Psychiatry and/or International Clinical Research – Neurology and Mood Disorders divisions of Lundbeck;
- Financial services of Lundbeck and
- Literature.

The data is then analysed and a first draft of the PSUR written. That draft is reviewed by relevant parties internal to Lundbeck and corrected to produce a second draft. Following a review by the safety

board, the document is approved, archived, distributed to Lundbeck subsidiaries and finally submitted to the competent authorities. Lundbeck usually prepares 6-month PSUR during the first 5 years after the IBD. For products older than 5 years, the company prepares yearly PSURs.

Events concerning population often not studied during the phase II and III studies (pregnant women, elderly and children) are discussed separately in the PSUR and the data are collected in our Lundbeck database with standard phrases [especially for pregnancies (trimester of exposure, retro or prospective case report etc.) to allow a quick overview on the course and outcomes of these pregnancies].

BEST METHODS OF COMPLIANCE

The Committee for Medicinal Products for Human Use (CHMP) of the European Agency for the evaluation of medicinal products (EMEA) has published a position paper on compliance with pharmacovigilance regulatory obligations (CPMP, 2001). This paper, which came into effect in January 2002, emphasises the importance of compliance with periodic reporting and lists the forms that non-compliance 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 standardised 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 and
- *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 recent paper, 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 maximise the efficiency of their procedures for producing PSURs, avoid potential pitfalls and ensure full compliance (Klepper, 2004):

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) which 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, which 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. As in the Lundbeck SOP, 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. Summary bridging reports and addendum reports require additional resources. When allocating resources to the PSUR process, companies should also be aware that the same departments will be called upon to produce the clinical trial annual reports required under the EU Clinical Trials Directive (see *Clinical Trial Annual Report*). 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-prioritising 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 ADRS

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 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 that book, Ronald Mann, former director of the University of Southampton's Drug Safety Research Unit, emphasises 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

Table 6.2. Some medically important adverse drug reactions (ADRs).

Acute liver failure
Acute renal failure
Acute respiratory failure
Agranulocytosis
Anaphylaxis
Aplastic anaemia
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

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 summarised in Table 6.2. 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:

- *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 (see ‘STANDARDISED AND HARMONISED MEDDRA CODING’).

STANDARDISED AND HARMONISED MEDDRA CODING

One of the characteristics of MedDRA that distinguishes it from traditional dictionaries is its extreme specificity or granularity. Slightly different verbatim terms are prone to be coded to different preferred terms and even entirely different SOCs, with important implications for subsequent statistical analyses. The quality of the term used by the reporter (verbatim term) drives the coding process. A high quality verbatim term is likely to autoencode, whereas a poor quality term is more likely to require manual assignment of a MedDRA term, which in turn increases the potential for inconsistencies. To ensure coding consistency for global companies where it is likely that cases will be entered remotely into the MAH’s central database, a global coding convention should be created, maintained and revised as necessary. This document could include, for example, the *Points to consider* developed by the Maintenance and Support Services Organization for MedDRA (MSSO, 2006), as well as other conventions. An example of a coding convention would be the establishment of a ‘rule’ that states that for any surgical procedure, the ADR that led to the surgery will be coded rather than the procedure itself, e.g. ‘gallstones’ rather than ‘cholecystectomy’.

PRESPECIFIED SEARCH CRITERIA

Prespecified search criteria for data retrieval should be developed, used and documented. This will ensure consistent and reproducible data retrieval.

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. It is also advisable to set up an in-house safety review committee, as Lundbeck has done. The medical reviewer responsible for a given medical product 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 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 summarised in Table 6.3.

Table 6.3. Examples of metrics of the periodic safety update report (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 autoencoded 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). Reproduced by permission of Lundbeck SAS.

CLINICAL TRIAL ANNUAL REPORTS

Clinical trial annual reports are a requirement of the 2001 European Union Clinical Trials Directive which came into effect on 1 May 2004. The manufacturer or sponsor is required to report both to the competent authority 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 authorisation status in any member state or whether they are used under the conditions of marketing authorisation. 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 post-marketing ADRs, the introduction of this European directive, along with the proposed regulations in the US 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.

PSUR AND RISK MANAGEMENT

The ‘Guideline on risk management systems for medicinal products for human use’ from the EMEA, adopted in November 2005, clearly states that risk management plan (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 authorisation. 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 a 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 utilisation 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 these information from multiple sources.

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 regulating authorities, an indicator for the need for risk management initiatives as well as a tracking mechanism for monitoring 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 numerous countries, for example a finding of an ADR of interest across many 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 – that is information from clinical trials, observational studies and spontaneous reporting, as well as pre-clinical studies. The consistency (or lack of it) of a potential signal across all these information sources can be extremely valuable to a 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, for example by shifting the promotional programme and product literature away from encouraging exposure in what seem to be vulnerable groups. 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 risk and seeks to protect its patients and products.

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Non-Clinical Safety Evaluation and Adverse Events in Phase I Trials

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INTRODUCTION

Non-clinical safety evaluation plays a key part in the development of novel pharmaceutical products, and the requirement for this can, in part, be attributed to drug-induced toxicities and serious adverse reactions. Governments worldwide legislate to protect the population against unsafe medicines, and much of the legislation has been enacted as a result of disasters caused by serious adverse reactions to medicinal products such as thalidomide. The resulting regulations allow governments to exercise control over medicinal products by compelling pharmaceutical companies to obtain authorisation to market their products. The effect is that, in the major pharmaceutical markets of the world, Sponsor companies are required to submit data demonstrating the quality, safety and efficacy of medicinal products to regulatory bodies which, subject to a positive review of the data, will grant a marketing authorisation or licence for the product.

The non-clinical safety data presented in such applications are gathered predominantly in the early stages of product development for use in assessing product

safety prior to administration to humans in clinical trials. The aims of the non-clinical studies include

- Identification of target organ toxicities
- Identification of dose-response relationships
- Assessment of systemic exposure and relationship with pharmacological and toxicological responses
- Assessment of reversibility of effect
- Provision of a basis for assessment of safe starting dose for human trials
- Identification of parameters for safety monitoring in human trials.

In summary, the non-clinical studies aim to build a profile of the potential effects of the product on humans, allowing the trials to be designed with an appropriate dose regimen and with safety monitoring to allow early detection of potential target organ toxicities.

NON-CLINICAL TESTING REQUIREMENTS

Historically, the regulatory control of clinical research has been different in Europe, the United States and

Japan. In Europe, the Clinical Trial Directive (Directive 2001/20/EC) came into force on 01 May 2004. Although the Directive has set the same regulatory framework for the control of clinical trials across Europe, there are differences between Member States in their transpositions of the Directive, resulting in some diversity in the regulatory mechanisms and requirements. Similarly, there has been no harmonisation on the precise extent of pre-clinical testing (toxicology and pharmacology) required before conducting the first study of a new drug in man. Various official (FDA, 1968) and unofficial (PMA, 1977; ABPI, 1985) guidelines have provided details of the basic studies that should be conducted in advance of a Phase I study. A partial consensus was reached on the non-clinical testing required with the publishing of the ICH M3 guideline, which came into operation in March 1998 (EMEA, 1998). However, even the latest revision of this guideline (November 2000a) shows areas of non-agreement in the data expectations of the EU, United States and Japan during the various phases of clinical development (e.g. duration of toxicology testing and timing of reproduction toxicology studies).

Although certain classes of therapeutic agents and drugs for the treatment of certain types of life-threatening or serious disease may warrant a more flexible approach, the general guidance is that, before initiating studies in humans of a pharmaceutical agent, the following studies should be undertaken:

- Acute toxicity studies in two mammalian species.
- Repeat-dose toxicity studies in two mammalian species (one non-rodent), the duration of which should equal or exceed the duration of the proposed human clinical study (see details below).
- Safety pharmacology studies to include the assessment of effects on the cardiovascular, central nervous and respiratory systems.
- *In vitro* evaluation of genotoxicity to include evaluation of mutations and chromosomal damage before Phase I with additional tests required before Phase II.
- Studies to evaluate the absorption, distribution, metabolism and excretion (ADME) of drugs in animals. Results of these studies should be available by the completion of the Phase I studies and before beginning patient studies.

- When appropriate, local tolerance studies in animals using the proposed route of administration for human studies. Such evaluations may be included as part of other toxicity studies.
- Reproduction toxicity studies appropriate for the population to be studied. For example, in the EU, embryofoetal development studies are required before the inclusion of females of childbearing potential in Phase I studies. If a male-only population is to be studied at Phase I, it is usually sufficient to include appropriate examination of the reproductive organs in the repeated dose toxicology studies. Studies of fertility, early embryonic development, pre- and post-natal development and development will be required before extending the participant population and the duration of administration in the clinical studies.
- Carcinogenicity studies are not normally required in advance of the conduct of clinical trials but on occasions may be warranted, for example if genotoxicity studies identify a potential risk.

In addition to describing the type of non-clinical studies that should be performed before administration to humans, the ICH M3 guideline addresses the duration of repeated-dose toxicology studies required to support human administration. Study duration should be based on the intended clinical use and dosage regimen. The non-clinical data required to support early human studies are of limited duration; in the US, single-dose toxicology studies with extended examinations can support single-dose human trials, but in Europe 2 weeks repeated dosing in two species, one rodent and one non-rodent, is required for administration of a single dose. This will also support up to 14 days repeated administration of a standard new chemical entity. For longer-term human administration, the required duration of non-clinical testing varies somewhat across the ICH regions, as noted in the ICH M3 guideline. For a simple daily-repeated dosing regime, however, 6-month rodent data and 9-month non-rodent data are widely acceptable to support Phase III clinical trials longer than 3 months.

Thus, although a relatively limited package of data on a product may be sufficient to allow the administration of single doses, a more extensive package of studies will be required subsequently, in order to facilitate assessment of the safety of longer-term studies in

more mixed populations. Progress through the various stages of drug development will require continued assessment of human safety data with the possibility of further non-clinical studies being required, depending on the information generated.

The basic battery of non-clinical safety studies is intended to be adequate for the identification and characterisation of potential toxic effects, which may be relevant during the early phase of clinical development. For some types of product, however, a 'standard' non-clinical programme may not be appropriate; abbreviated or extended testing programmes may be required and must be justified on a case-by-case basis. For example, it is generally not appropriate to perform genotoxicity assays for proteins and peptides unless there are concerns over impurities in the product. It may also be appropriate to reduce the repeated dose toxicology testing of such products, performing studies only in a single relevant species, rather than using a second animal species that is unresponsive to the test material. Conversely, extension of non-clinical programmes may be appropriate where there are special concerns over issues such as immunotoxicity, when special monitoring of immune responses should be included in the toxicology studies. In any case, the non-clinical programme should be designed and, if necessary, adjusted to provide data that will fulfill the aims of non-clinical testing and allow a reasoned assessment of product safety before administration to humans.

USE OF ANIMALS TO PREDICT HUMAN TOXICITIES

Animals are not perfect models for humans but there is, currently, no alternative means of assessing the effects of product administration on the whole organism. Some non-clinical safety assessments are performed using *in vitro* methods, for example potential for genotoxicity is partly assessed using a bacterial cell mutagenicity assay and a chromosomal aberration assay in mammalian cells. Many of the parameters examined in safety pharmacology, metabolism and toxicity studies are, however, functions of the whole animal.

The use of animals in safety studies is necessitated by regulatory requirements and assumes that animal toxicities are generally predictive of hazard to

humans. This assumption is the result of experience, which indicates that toxicology studies in laboratory animals yield data that are predictive of human toxicities. It is, however, essential to review this fundamental assumption for both scientific and political reasons. Only if we can be confident that animal models yield data that is predictive of human toxicities can we be confident that safety assessments are useful and justify the test systems. The consequences of poor prediction include inappropriate use of animals, unforeseen toxicities and unwarranted restrictions on potentially useful drugs, which may limit their therapeutic benefits.

The concordance of the toxicities of pharmaceuticals in animals and humans is, then, fundamental to the use of animal study data in safety assessments prior to human administration. Commercial confidentiality limits the availability of data on this subject, but there are some literature reports on the subject. In a survey of 139 drugs approved in Japan from 1987 to 1991 (Igarashi, 1994), animal toxicity data were drawn from 468 repeated dose studies, mainly in rats and dogs but with a few in mice and monkeys. Forty-three percent of clinical toxicities from 69 marketed drugs were not predicted from animal studies. The best predictability was for cardiovascular events and the poorest was for skin and hypersensitivity reactions. More recently, a multinational survey of 12 pharmaceutical companies was reported, in which data from 150 compounds that produced human toxicity events were reviewed, and the human toxicities related to the non-clinical findings (Olson *et al.*, 2000). When toxicities in rodent and non-rodent species were examined together, there was a concordance rate of 71% with the human toxicities. The concordance rate for non-rodent species was 63%, whilst for rodents alone it was 43%. Ninety four percent of these concordances were first observed in studies of 1-month duration or less. The human toxicities that showed the highest concordance with non-clinical data were haematological, gastrointestinal and cardiovascular effects. The lowest concordance rate was in cutaneous toxicities.

The two reviews both indicate that cardiovascular toxicities observed in clinical studies are likely to have been observed first in animals and that cutaneous toxicities also seem to be less apparent in non-clinical than in clinical studies. On the surface, it appears that the Japanese data from marketed drugs and the

multinational data from products in clinical trials had similar rates of concordance between non-clinical and clinical findings. The Japanese data indicated that 43% of toxicities in marketed drugs could not have been predicted from the non-clinical results, whilst the rate of concordance for drugs where human toxicities were observed during development was 71%. Presumably 29% of toxicities could not have been predicted from the non-clinical data. Caution should be exercised in correlating these figures because a number of those products which caused toxicities in clinical trials will not have reached the market. In addition, some rare toxicities may not be detected in clinical trials and may only be revealed when the product is on the market and used by a much larger and more mixed population. Olson *et al.* cited reviews of clinical toxicity resulting in withdrawal from marketing; only 4 of 24 cases and 6 of 114 cases could have been predicted from animals. This poor rate of prediction is considered to be unsurprising because late-onset toxic effects are usually idiosyncratic and therefore inherently of low incidence, are not dose related and are not related to the drug's pharmacology.

It may be impossible to improve the rate of prediction of rare and idiosyncratic human toxicities from non-clinical studies, but care should be taken to maximise the rate of prediction for those toxicities related to the metabolism of the test material or to its pharmacological actions. The choice of animal model is very important in this; inter-species differences in metabolism influence the metabolite profile, the route and rate of clearance of xenobiotics, whilst differences in the specificity and/or distribution of receptors give rise to differences in pharmacological responses to a given pharmaceutical. In order to maximise the usefulness of the non-clinical data in safety assessment, the species used for toxicity testing should be chosen based on their similarity to humans with regard to pharmacokinetic profile. Additionally, the chosen species should be responsive to the primary pharmacodynamic effect of the substance wherever possible, and in some cases studies in disease models may be warranted (EMEA, 2000b).

Apart from species differences, there are several other factors that may increase the rate of incorrect predictions of toxicity when moving from animals to man. These include differences in the way the toxicity is observed and recorded (eliciting verbal accounts of

symptoms is not possible in animals), the presence or absence of concomitant medication, pharmacokinetic and metabolic differences, age (animals are young and humans may be old), state of health (animals are free from disease), the small numbers and homogeneity of the animals studied compared with the heterogeneity of the humans, dose differences, housing and nutrition (optimal in animal studies) as well as timing differences.

Overall, the published data suggest that between one-half and two-thirds of pharmaceutical toxicities in humans can be predicted from non-clinical data, thus supporting the use of *in vivo* toxicology data in assessing the potential for human toxicity. Recently, however, the importance of choosing the most appropriate animal models and tests and of applying their results in the most appropriate way during safety assessments has come into sharp focus. This has been highlighted by the severe, life-threatening side effects suffered by six healthy volunteers in a Phase I, first-in-human, clinical study in the UK. The medicinal product administered, TGN1412, is a monoclonal antibody that was being developed as an immunomodulator and is one of a new generation of medicinal products which are being developed as technology allows the identification and targeting of more complex biological systems.

Repeated dose testing of the antibody had been performed in cynomolgus monkeys and it had been well tolerated by the animals following repeated dosing at doses of up to 50 mg/kg/week for 4 consecutive weeks. This dose level was therefore taken as the no observed adverse effect level (NOAEL) and was used as the basis for calculating the starting dose for the clinical study. The method of calculation followed draft guidelines that are frequently applied to investigational products (FDA, 2002; see also following section) whose mechanisms of action and secondary effects may be better understood than those of the new generation products such as TGN1412. Having applied safety factors and allometric correction factors to scale between the monkey and humans, the human starting dose was selected at 500 times less than the monkey NOAEL. The devastating effects caused in the volunteer subjects clearly demonstrates that use of the no observed adverse effect level obtained from the repeated dose cynomolgus monkey study did not provide a sufficient margin of safety for human dosing of this product.

Examination of this case and of the wider implications for safety assessment of medicinal products – with specific reference to (1) biological molecules with novel mechanisms of action; (2) new agents with a highly species-specific action; (3) new drugs directed towards immune system targets – is ongoing (Duff *et al.*, 2006). Further comment here is therefore inappropriate.

The investigations into this case seem likely to result in new guidance on the safety testing and assessment of such products. Whatever the outcome, the case has highlighted the fact that, whilst standard toxicological testing has had a good record in predicting the safety of new chemical entities and biologicals whose activities and targets are well understood, new strategies are required to assess the newer generation of products that are designed to modulate more complex biological systems. For more conventional products, however, current toxicology testing strategies and safety assessments remain useful although it is pertinent to examine their role and success in predicting human toxicities. This chapter therefore focuses on these types of assessment.

ESTIMATION OF SAFE STARTING DOSE AND SAFETY ASSESSMENT AND RISK–BENEFIT ANALYSIS

In addition to allowing identification of target organ toxicities, the aim of non-clinical safety studies is to yield data that will provide the basis for estimating the safe starting dose for clinical trials. The data should also inform the choice of dose regimen and dose escalations in early phase clinical trials and form the basis of risk–benefit analyses for clinical trial protocols.

Traditionally, selection of doses for first-into-human clinical trials has been based on the no observed effect level (NOEL) or no observed adverse effect level (NOAEL) and, where appropriate, the systemic exposures achieved at these levels. A figure for the maximum human starting dose can then be assessed using allometric scaling and the application of safety factors, as considered appropriate by the Sponsor and Investigator. There are currently no international guidelines on the estimation of the safe starting doses for a clinical trial; however, the FDA has issued draft guidance on this subject (FDA, 2002). The guideline describes an algorithm for deriving

the maximum recommended starting dose for first-into-human clinical trials, recommending that a standard procedure is used to select this dose. The algorithm utilises the NOAEL observed in the most sensitive species and converts this to a human equivalent dose, using a conversion factor based on body surface area, or, where more appropriate, using scaling on a mg/kg basis. Safety factors are then applied to obtain the maximum starting dose.

There is no equivalent European regulatory guidance on setting the starting dose; however, according to the ICH GCP guideline (EMEA, 1995) the route of administration, dose levels and dosage regimen proposed by the Sponsor and Investigator should be justified in the protocol. Sometimes the justifications offered in the protocol are brief, but in any case the proposed dose and regimen should be thoroughly examined in the risk–benefit analysis that is included in the Investigational Medicinal Product Dossier that is submitted to the regulatory authorities as part of the clinical trial application in European Member States (European Commission, 2005).

In summary, the risk–benefit analysis examines the proposed clinical trial protocol, together with the main findings of the non-clinical safety studies and assesses whether the risks associated with the trial are acceptable. The European guidance on clinical trial applications (European Commission, 2005) indicates that the risk–benefit analysis should be a brief, integrated summary that critically analyses the non-clinical and clinical data in relation to the proposed trial. The author(s) of the analysis should use the relevant pharmacology, toxicology and kinetic results as the basis of extrapolation to indicate possible risks in humans. Where appropriate, the safety margins should be discussed in terms of relative systemic exposure to the investigational product rather than in terms of applied dose. The analysis should include discussion of the clinical relevance of any findings from non-clinical and clinical studies, together with recommendations for further monitoring of effects and safety in clinical trials.

ADVERSE EVENTS IN CLINICAL TRIALS

The safety monitoring that is designed into clinical trial protocols will include certain routine procedures that are used to monitor health and well-being of

the study subjects, including the vital signs, routine haematology and clinical chemistry. Additional tests and monitoring methods may also be included in the protocol to allow early identification of adverse events that may be attributed to toxicities revealed by the non-clinical studies, for example additional ECG/Holter monitoring and additional assays for specific biomarkers in blood or urine.

In first-into-human and other early phase clinical studies, it may be possible to identify some likely adverse events from the non-clinical results and there are always likely to be adverse events such as colds and headaches that may or may not be related to the investigational product. It remains true, however, that the profile of events for a given investigational product remains uncertain until the safety data have been gathered and analysed. As such, care must be taken to consider all events carefully and to assess causality. In early trials with few subjects, it would be easy to overlook rare or mild effects that may prove to be important signals when larger, more mixed and less healthy populations are exposed to the product.

A review of all adverse events recorded in volunteers during two separate 12-month periods (1993 and 1998) at the Clinical Trials Unit of Charles River Laboratories Clinical Services International Ltd (formerly Inveresk Research) has been conducted. All adverse events reported spontaneously, elicited by staff questioning, or observed were collected. Two doctors performed the allocation of each event to the trial medication independently with a third arbiter in cases of disagreement. The doctors were blinded to the study medication and allocated causality according to the known pre-clinical pharmacology and toxicology of the drug and the timing of the adverse event.

Of a total of 30 studies (32 drugs) available for review in 1998, 10 were single ascending dose tolerability studies and 5 were multiple-dose tolerability studies. The remaining studies were pharmacokinetic studies. Several therapeutic classes of drugs were represented. Drug-related adverse events were those considered possibly, probably or definitely related to the medication. Data were compared with those collected in 1993 involving a total of 23 studies (18 drugs). Comparison of the numbers of studies and exposures is made in Table 7.1 and details of the adverse events are given in Tables 7.2–7.4.

In the 1993 report, the frequency of adverse events reported in volunteer studies was much greater than

Table 7.1. Comparison of number of studies and exposures in 1993 and 1998.

	1998	1993
Studies	30	23
Drugs	32	18
Subjects	704	502
Active exposures	994	627
Placebo exposures	169	120

Table 7.2. Comparison of adverse events in healthy volunteer studies in one clinical unit in 1998 and 1993.

	Active		Placebo	
	1998	1993	1998	1993
Total exposures	994	627	169	120
Exposures resulting in at least one adverse event	354 (36%)	246 (39%)	58 (34%)	45 (38%)
Total adverse events	620	468	106	97
Adverse events per subject experiencing at least one adverse event	1.8	1.9	1.8	2.2

that reported by Orme *et al.* (1989). However, the incidence reported in 1993 was confirmed by the 1998 data. It is also notable that, in 1993, there was a similar frequency of adverse events in volunteers receiving an active drug and those receiving a placebo. This differs from the findings of Sibille *et al.* (1992), who reported a difference in the incidence of adverse events between active drug and placebo treatment, active being significantly higher. Once again, the 1993 results were confirmed in 1998. It is therefore concluded that the incidence of adverse event reporting in healthy volunteer studies is 34%–39% with an almost identical incidence in placebo exposures as in active exposures. Most adverse events were mild and self-limiting, and in both 12-month periods the most common event in both active and placebo exposures was headache (19%–30%).

Table 7.3. All adverse events reported in 1998 compared with 1993

Adverse events	Active		Placebo	
	1998	1993	1998	1993
Total	620 (100%)	468 (100%)	106 (100%)	97 (100%)
Headache	143 (23%)	142 (30%)	21 (20%)	19 (20%)
Rash	56 (9%)	26 (6%)	6 (6%)	13 (13%)
Nausea	41 (7%)	22 (5%)	2 (2%)	0
Dizziness	34 (5%)	24 (5%)	6 (6%)	4 (4%)
Pain (musculoskeletal)	24 (4%)	0	9 (8%)	0
Pain (other)	22 (4%)	0	10 (9%)	0
Rhinitis	21 (3%)	9 (2%)	6 (6%)	6 (6%)
Pharyngitis	20 (3%)	0	4 (4%)	0
Abdominal pain	19 (3%)	0	4 (4%)	0
Hepatic function abnormal	14 (2%)	0	0	0
Diarrhoea	12 (2%)	0	0	0
Somnolence	11 (2%)	12 (3%)	4 (4%)	2 (2%)
Asthenia	11 (2%)	13 (3%)	0	4 (4%)
Sweating	10 (2%)	9 (2%)	0	1 (1%)
Herpes simplex	9 (2%)	0	3 (3%)	0
Cough	9 (2%)	24 (5%)	0	0
Constipation	9 (2%)	0	0	0
Other	155 (25%)	187 (40%)	31 (29%)	48 (49%)

Table 7.4. Drug-related adverse events in 1998

Adverse event	Active	Placebo
Total	323 (100%)	29 (100%)
Headache	93 (29%)	12 (41%)
Rash	37 (11%)	1 (3%)
Nausea	30 (9%)	0
Dizziness	26 (8%)	3 (10%)
Hepatic function abnormal	13 (4%)	0
Abdominal pain	12 (4%)	2 (7%)
Diarrhoea	9 (3%)	0
Constipation	9 (3%)	0
Herpes simplex	8 (2%)	2 (7%)
Somnolence	7 (2%)	2 (7%)
Other	79 (24%)	7 (24%)

The experience of Charles River Laboratories Phase I clinic over a 10-year period from 1996 to 2005 indicates that the incidence of treatment-emergent Serious Adverse Events in Phase I studies in healthy volunteers is low; approximately 1–2/1000 for volunteers exposed to one or more doses of active or placebo drug (See Table 7.5). The majority of these serious adverse events fall into the category of a medically important event. This is similar to the incidence

reported in a survey by The Association of Independent Clinical Research Contractors (AICRC) who reported an incidence of 1 in 509 (0.2%) from a total of 128 in 65 205 subjects (AICRC members' communication, 1999). Only one of the serious adverse events reported by Charles River Laboratories over 10 years, a low grade biochemical hepatitis of probable immunological pathogenesis in an asymptomatic subject, was considered to be probably drug related. This case occurred in a late Phase I study; several thousand patients had received the drug in clinical development, no similar cases had been reported and there was no evidence of hepatotoxicity in non-clinical studies. Two further SAEs were considered possibly related to the IMP.

The incidence of a single 'probably related' and two 'possibly related' serious adverse events in 10 823 subjects (0.03%) indicates that current standards for pre-clinical safety testing of new drugs are successful in ensuring that early drug development studies in humans are safe and that the risks to individuals subjects are relatively low.

The adverse event data gathered in Phase I and other early phase trials are essential to expanding the safety profile of the drug product and may be considered as an extension to the non-clinical data.

Table 7.5. Serious adverse events reported in one Phase I clinical unit from 1996–2005

Year	Number of subjects dosed	Number of SAEs	Nature of SAE (Time since last dose)	Relationship to treatment
2005	818	0		
2004	726	0		
2003	1100 [▲]	1	Severe headache resulting in hospital admission (5 months)	Not Related
2002	1100 [▲]	8*	1. Distal radial fracture of wrist (20 days) 2. Plasmodium vivax malaria (< 1 day) 3. Excision of nodule at base of thumb (41 days) 4. Perforated duodenal ulcer with associated peritonitis (18 days) 5. Fracture of radius and ulna (64 days) 6. Unplanned pregnancy – terminated for social reasons (1 day) 7. Biochemical hepatitis – subject asymptomatic (6 weeks) 8. Chest pain – non cardiac (3 months)	Not Related Possibly Related Not Related Possibly Related Not Related Not Related Probably Related Not Related
2001	1100 [▲]	2	1. Diabetes mellitus – Type 1 (1 day) 2. Atrial fibrillation (1 week)	Unlikely Unlikely
2000	1020	2	1. Infected eczema in groin (10 days) 2. Deliberate paracetamol overdose with associated jaundice (14 days)	Unlikely Not Related
1999	1176	1	Fractured ankle (1 day)	Unlikely
1998	1200 [▲]	1	Perianal abscess (1 week)	Not Related
1997	1246	1	Fracture of 1st metacarpal (6 days)	Not Related
1996	1337	1	Stomach cramps and bloody diarrhoea – several close contacts affected (2 days)	Unlikely
Total SAEs	10823	17		

Note: Only treatment emergent SAEs are reported.

▲ Total subjects dosed for these years have been rounded to the nearest 100.

* In most years only one or two SAEs (if any) were reported. The year 2002 was an exception with eight reported. A possible explanation for this is that there were several studies conducted that year, involving biological and immunological type products with extended follow-up periods of up to 9 months.

Critical assessment of the possible relationship of an adverse event to the product is fundamental to detecting signals of toxicity and to correctly assessing drug safety prior to moving to larger scale trials. When reviewing the causality of adverse events, it is notable that the 1998 data on adverse events that were considered to be drug related (possibly, probably or definitely) reveals that certain adverse events, most notably headache, occurred at higher incidence in subjects receiving placebo than in subjects receiving active (Table 7.4). In contrast, those events which can be measured in animals, for example constipation, diarrhoea and abnormal liver function tests, feature

only in the active group. It may be concluded that these sorts of events are more reliable indicators of drug effect and may differentiate active from placebo.

Attribution of or, conversely, discounting relationship of an event to treatment should, however, be done with caution. It is known that elevations in transaminase concentrations can occur in healthy volunteers for several reasons, including excess caloric intake, relative to normal, due to reduction in physical activity (Kanamaru *et al.*, 1989; Purkins *et al.*, 2004). Similar findings have been noted at approximately equal prevalence in both active- and placebo-treated subjects during periods of residence

of ≥ 7 days in this clinic (Wyld, 1991; Unpublished internal study conducted at Charles River Laboratories, 2003). In the 2003 study, data was collected from nine Phase I, randomised, double-blind, placebo-controlled multiple-dose tolerance studies, in which, doses were administered during at least 7 days of confinement. Over 300 subjects were included. Clinically significant (CS) abnormalities were defined as > 1.5 times the upper limit of normal and were reported as adverse events. The incidence of CS abnormalities for alanine aminotransferase (ALT) was 9% for active- and 8% for placebo-treated subjects. For aspartate aminotransferase (AST) the incidences were 2% and 1% for active- and placebo-treated subjects, respectively. These differences were not statistically significant (ALT $p = 0.850$; AST $p = 0.652$) when analysed using the Chi-squared test.

The liver function test data highlight the need to take all factors into account when assessing the cause of an adverse event. Although increases in liver function tests may be an artefact caused by changes to the diet, exercise and environment of volunteers in clinical studies, the findings must be carefully considered before ruling out adaptive changes or toxicity. Only small numbers of volunteers are used in Phase I clinical trials so it is important to review the data gathered in all the clinical trials performed with a new pharmaceutical, identifying consistencies across the studies. It is notable that hepatic toxicity was, together with hypersensitivity/skin reactions, the human toxicity with the poorest correlation with animal studies in Olson's review (Olson, 2000). These were also the two toxicities that led most often to termination of clinical development.

Further study of mechanisms underlying such toxicities is required, especially in view of the number of drugs that have been withdrawn or have had warnings added to their labels due to hepatotoxicity. In the case of troglitazone (an antidiabetic drug, voluntarily withdrawn from the market by the licence holder in 2000), it was reported that 1.95% of patients treated with troglitazone in clinical trials developed elevations of aminotransferases that were greater than three times the upper limit of normal. A similar finding was noted in 0.6% of placebo-treated patients, so the increase seen in the active-treatment groups seems quite modest (Lin, Chern and Chu, 2003). In the light of subsequent incidences of serious idiosyncratic liver toxicity associated with this product whilst on the

market, it would seem that when there are differences in the incidence of liver enzyme elevation between active- and placebo-treated groups in clinical trials, this should be considered a signal to examine the clinical and non-clinical data very closely before licensing.

This example highlights the danger of missing early signals of toxicity that may, in themselves, appear to be mild and of little or no significance but which may be early signals of a toxicity which will be problematic in some individuals. It is equally clear that the same minor events may well be of no toxicological or clinical significance and should not hinder the clinical development of the product in question. It is important, therefore, to consider the non-clinical and early clinical safety data carefully as it becomes available and relate it to the previous study data in order to identify any trends. If data from an individual study are examined in isolation, it is easy to write off some mild effects that may not have clear statistical significance or may not show a marked dose relationship or related pathology. For example, a minor increase in liver function enzymes in a rodent toxicology study, with no clear dose relationship, may not cause any undue concern if no associated macroscopic or microscopic changes in the liver are observed. If, however, similar minor effects were seen in a second species, it may not be sufficient to stop the transition to humans but it would be appropriate to monitor the liver enzymes carefully in early phase clinical studies. A similar principle applies as the product progresses through clinical trials, increasing the safety database. Minor increases in liver enzymes seen in Phase I trials in volunteers may be related to changes in diet, exercise pattern and environment, as noted above, but the possibility of a drug-induced change should not be ruled out, especially if similar changes have been noted in the non-clinical studies. Careful monitoring and surveillance of the data from subsequent studies will be required to determine the nature and ramifications of this type of effect. In effect, clinical safety studies and, if the product progresses to market, pharmacovigilance form a continuum with the non-clinical safety studies.

CONCLUSIONS

Although there are limitations, non-clinical data is predictive of some human toxicities seen in clinical use. Experience shows that the degree of prediction

is not as good for idiosyncratic toxicities as for those associated with the pharmacology or metabolism of the drug, as would be expected. Pharmacovigilance data will therefore always be required to detect rare and idiosyncratic human toxicities. Thorough and objective review of non-clinical data does, however, detect toxicities that are linked more directly to the actions of the drug and which have the potential to affect humans. For the foreseeable future, therefore, non-clinical data will continuously be used to identify potential human toxicities, to identify safe starting doses and dose regimens and to develop the appropriate safety monitoring procedures for the clinical trial protocol. These aspects should be addressed in the risk–benefit analysis for the trial.

Once humans have been exposed in clinical trials, the data generated should be considered carefully with the non-clinical data until a picture of the human toxicities has been developed. Experience shows that not all toxicities are predictable based on the non-clinical and early clinical trial data; however, literature suggests that the rate of prediction is approximately one half to two thirds. Increasing knowledge of the mechanisms of toxicity and of species differences, together with the judicious use of *in vitro* metabolism and receptor binding methodologies, is allowing better species selection. This, together with the increasing availability of non-clinical disease models gives hope that predictability will increase, or at least not decrease, provided that the data are carefully and objectively assessed.

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Mechanisms of Adverse Drug Reactions

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INTRODUCTION

An *adverse drug reaction* (ADR) may be defined as ‘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’ (Edwards and Aronson, 2000). This has to be contrasted with the term *adverse drug event*, which refers to untoward occurrences following drug exposure but not necessarily caused by the medicine (Asscher, Parr and Whitmarsh, 1995). This chapter focuses on ADRs rather than adverse drug events.

Although the drug discovery process has been revolutionised by new techniques such as combinatorial chemistry and high-throughput screening, drug safety assessment lags well behind and is still reliant on many of same technologies that have been used for several decades. By the time a drug is marketed, only about 1500–3000 patients may have been exposed to the drug (Asscher, Parr and Whitmarsh, 1995; Rawlins, 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 ADRs therefore is likely to represent

an important aspect of drug therapy for many years to come, and indeed, with the development of new biotechnology compounds, it is likely that the pattern of these reactions will change. Furthermore, using gene and protein screening technologies, many new targets will be discovered. 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 the exacerbation of multiple sclerosis, systemic lupus erythematosus (SLE) and blood dyscrasias that have been reported with anti-tumour necrosis factor (anti-TNF) therapies (Furst *et al.*, 2000; Sharief and Hentges, 1991) or cardiovascular events with cyclo-oxygenase-II (COX-II) inhibitors (Fries *et al.*, 2006) may not have been reasonably expected given the *known* pharmacology of these therapies.

IMPORTANCE OF ADVERSE DRUG REACTIONS

Adverse drug reactions are a major clinical problem (Bates *et al.*, 1995a,b, 1997; Classen *et al.*, 1997; Einarson, 1993). A meta-analysis suggested that

Table 8.1. The direct and indirect effects of ADRs.

Cause admission to hospitals or attendance in primary care
Complicate hospital inpatient 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 few patients will preclude use of the drug in most patients
Mimic disease and result in unnecessary investigations and/or delay treatment

ADRs were between the fourth and sixth commonest cause of death in the United States in 1994 (Lazarou, Pomeranz and Corey, 1998). A large prospective study in the United Kingdom has shown that ADRs were responsible for 6.5% of all hospital admissions (Pirmohamed *et al.*, 2004). 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). ADRs can also have many other indirect effects

(Table 8.1), which in total, highlight the overall importance of ADRs in modern medicine.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

There are many different classifications of ADRs. 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 8.2). 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 readily reversible on drug withdrawal or even simply after dose reduction (Table 8.2). By 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.

Table 8.2. Characteristics of types A and B ADRs.

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 uncharacterised) 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 ADRs	80%	20%
First detection	Phases I–III	Usually phase IV, occasionally phase III
Mechanism	Usually because of parent drug or stable metabolite	May be because of parent drug or stable metabolite, but CRMs also implicated
Animal models	Usually reproducible in animals	Very few reproducible animal models

TYPE A ADVERSE DRUG REACTIONS

Pharmacological (type A) ADRs are the most common forms of drug toxicity (Pirmohamed *et al.*, 1998). They can occur because of the primary and secondary pharmacological characteristics of the drug (Figure 8.1). More emphasis is now placed on the secondary pharmacology of new drugs during pre-clinical evaluation, 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 contin-

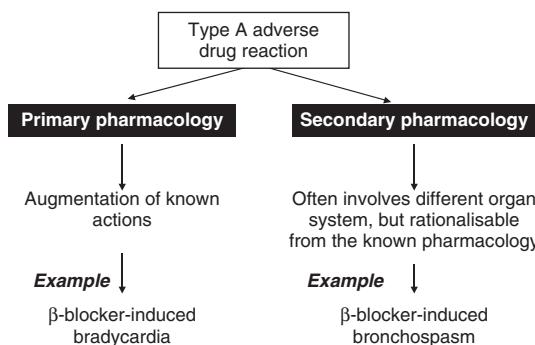


Figure 8.1. Type A ADRs can occur because of the primary and/or secondary pharmacological characteristics of the drug.

Table 8.3. Factors predisposing to pharmacological type A ADRs.

Type	Example	Toxicity	Mechanism
Pharmaceutical	Phenytoin	Phenytoin toxicity (ataxia, nystagmus, etc.)	Increase in bioavailability because 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	Indomethacin	Left ventricular failure	Water and sodium retention
Genetic	Nortriptyline	Confusion	Reduced hepatic elimination because of a deficiency of CYP2D6
Drug–drug interactions (can involve any of the above processes)	Lithium and non-steroidal anti-inflammatory drugs	Lithium toxicity	Inhibition of excretion of lithium

Adapted from Pirmohamed *et al.* (1998).

ued development of appropriate *in vivo* and, bridging, *in vitro* test systems for the prediction of secondary pharmacological adverse effects in humans. In June 1993, during phase II trials, 5 of 15 patients given fialuridine died, whereas 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 wood-chuck. *In vitro* studies in cultured hepatoblasts have shown that the toxicity is because of the inhibition of DNA polymerase γ 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 and drug–drug interactions (Pirmohamed *et al.*, 1998) (Table 8.3). 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

many 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 ADRs, 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 because of the normal process of ageing, disease, concomitant drugs or genetic variation or a combination of these factors (Brodie and Feely, 1991).

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 ADRs, polymorphisms in both pharmacokinetic and pharmacodynamic parameters can act as predisposing factors (Table 8.4).

To date, most attention has focused on genetically mediated deficiencies of the drug-metabolising enzymes (Park, 1986; Pirmohamed and Park, 1996). A drug metabolised 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 United Kingdom (Hart *et al.*, 1998). The number of patients attending anticoagulant clinics has doubled in the last decade or so, largely because of its use in atrial fibrillation. The major risk of warfarin treatment is haemorrhage with an incidence of 8–26 per 100 patient-years (Petty *et al.*, 1999); this is related to the intensity of anticoagulation. Minimisation of the risk of bleeding depends on accurate clinical prediction of dosage requirements during warfarin therapy. However, this is difficult because there is 20-fold interindividual variability in the dose necessary to maintain the international normalised ratio (INR) within a target range.

The S-enantiomer of warfarin, which is predominantly responsible for the anticoagulant effect, is metabolised by CYP2C9 (Rettie *et al.*, 1992). Polymorphisms in the *CYP2C9* gene result in at least two allelic variants, *CYP2C9*2* ($\text{Arg}_{144} \rightarrow \text{Cys}$) and *CYP2C9*3* ($\text{Ile}_{359} \rightarrow \text{Leu}$) (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). The strong and consistent relationship between *CYP2C9* genotype and dose requirement has been confirmed in a systematic review. *CYP2C9* genotype also seems to

Table 8.4. Genetic polymorphisms and dose-dependent ADRs.

Area affected	Polymorphic gene	Example of drug affected	Adverse reaction
Phase I-metabolising enzyme	Cytochrome P450 2D6 (CYP2D6)	Metoprolol	Bradycardia
Phase II-metabolising enzyme	Thiopurine methyl transferase	6-mercaptopurine	Bone marrow suppression
Drug transporter	Pgp (MDR1)	Digoxin	Digoxin toxicity
Target enzyme	Acetylcholinesterase	Pyridostigmine	Neurotoxicity
Receptor	Dopamine D ₃ receptor	Chlorpromazine	Tardive dyskinesia
Ion channel	Delayed rectifier potassium channel (I_{Kr})	Clarithromycin	Prolonged QT interval and torsades de pointes

Adapted from Pirmohamed and Park (2001a).

be important with respect to warfarin-related bleeding, but the association is not as strong as that observed with dose (Sanderson, Emery and Higgins, 2005). More recently, it has also been shown that 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 55% of the variance in warfarin dose requirements (Rieder *et al.*, 2005; Sconce *et al.*, 2005; Wadelius *et al.*, 2005). Sconce *et al.* (2005) have recently gone onto develop a dosing table based on a regression equation combining age, height and *CYP2C9* (*2 and *3) and the *VKORC1* ($-1639G > A$) single-nucleotide polymorphisms (SNPs). Whether such genotype-based dosing, in the absence of other possible factors that might influence dose requirements, including drug interactions, diet, underlying disease, e.g. thyroid disease, and polymorphisms in other genes involved in the mode of action of warfarin, will lead to an improvement in the dosing and safety of warfarin, requires further study (Pirmohamed and Park, 2001a).

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, Berger and Jacobson, 1992). An Australian study showed that 4.4% of all ADRs resulting in hospital admission were because of drug interactions (Stanton *et al.*, 1994), whereas a study in the United Kingdom showed that one in six of all adverse reactions causing hospital admission were because of interactions (Pirmohamed *et al.*, 2004).

Drug interactions due to effects on metabolic pathways may be because of either 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 because of a metabolite rather than the parent drug). Enzyme inhibition on the contrary is more likely to lead to type A ADRs because 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 many instances. An important example was the interaction between the CYP3A4 inhibitors ketoconazole and erythromycin and the non-sedating 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, Gillis and Woosley, 1991), which results in the prolongation of QT 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. Interestingly, such enzyme inhibitory interactions can also occur with foods such as grapefruit juice and cranberry juice.

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 and some are responsible for drug efflux, whereas others can transport in both directions. Most of the focus to date has been on P-glycoprotein (Pgp), which is encoded by the multi-drug resistance 1 (*MDR1*) gene. Overexpression of Pgp is one of the mechanisms responsible for resistance of tumours to chemotherapy (Germann, 1996). However, Pgp is also responsible for the transport of many 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 the 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.

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, Pirmohamed and Kitteringham, 1992) are listed in Table 8.5. The toxic reactions may affect many organ systems either in isolation or in combination (Table 8.6).

Type B ADRs have been characterised as being dose-independent (Table 8.2) or rather there is no simple relationship between dose and the occurrence of toxicity (Park, Pirmohamed and Kitteringham, 1998). Certainly, the evaluation of patients with and without hypersensitivity to a particular compound shows very little difference in doses received, and indeed in the patients with hypersensitivity, the doses may have been lower because the drug had to be

Table 8.5. The mechanisms of type B or idiosyncratic ADRs.

Mechanism	Example
Pharmaceutical variation	Eosinophilia-myalgia syndrome with L-tryptophan
Receptor abnormality	Malignant hyperthermia with general anaesthetics
Abnormal biological system unmasked by drug	Primaquine-induced haemolysis 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
Multi-factorial	Halothane hepatitis

Adapted from Park *et al.* (1992).

Table 8.6. Examples of organs affected by type B or idiosyncratic ADRs.

Organ system	Type of reaction	Drug examples
Generalised reaction	Anaphylaxis	Penicillins
Generalised reaction	Hypersensitivity	Temafloxacin
Skin	Toxic epidermal necrolysis	Non-steroidal anti-inflammatory drugs
Liver	Hepatitis	Halothane
Haematological system	Aplastic anaemia, Agranulocytosis, Haemolysis	Remoxipride, Clozapine, Nomifensine
Central nervous system	Guillain-Barré syndrome	Zimeldine
Kidney	Interstitial nephritis	Penicillins
Lung	Pneumonitis	Dapsone
Heart	Cardiomyopathy	Tacrolimus
Reproductive toxicity	Etretinate	Various foetal abnormalities

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 be some kind of dose-response relationship because if the patient had not received the drug, then they would not have developed the hypersensitivity reaction. Because many type B ADRs are thought to be mediated by the formation of chemically reactive metabolites (CRMs) through metabolism by P450 enzymes (a process termed 'bioactivation') (Park, Pirmohamed and Kitteringham, 1998), perhaps a relationship exists with the 'internal dose', i.e. the concentration of the toxic metabolite formed in the body. However, because these metabolites by definition are unstable, it has not been possible with the 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 patient 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), whereas for acute treatment of PCP, much higher doses (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 as 80% have been reported (Carr and Cooper, 1995; Pirmohamed and Park, 1995).

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-metabolising enzyme that may be a phase I and/or II enzyme (Woolf and Jordan, 1987) (Figure 8.2). A drug may undergo sequential phases I and II metabolism, or alternatively, it may only undergo either phase I or phase II metabolism (Tephly and Burchell, 1990).

In certain circumstances, the drug-metabolising enzymes can convert a drug to a toxic, CRM, a process termed 'bioactivation' (Pirmohamed, Kitteringham and Park, 1994; Pirmohamed, Madden and Park, 1996) (Figure 8.2). Bioactivation may represent less than 1% of the overall metabolism of a drug. The

body is equipped with formidable defence mechanisms, and in most cases, the CRM will be detoxified (a process which 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 phases I and II enzymes can cause drug bioactivation, but in most cases, it is the former, i.e. the cytochrome P450 enzymes, which are responsible (Pirmohamed, Kitteringham and Park, 1994).

Inadequate detoxification of a CRM is often the first step in the initiation of idiosyncratic drug toxicity (Park, Pirmohamed and Kitteringham, 1992; Pirmohamed, Kitteringham and Park, 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 detoxification may lead to a selective imbalance in that tissue resulting in tissue-selective toxicity (Park, Pirmohamed and Kitteringham, 1995). An imbalance may be the consequence of a genetically determined deficiency of an enzyme, or alternatively, it may be acquired because 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, Madden and Park, 1996). Other factors such as tissue repair enzymes, immune responsiveness and the biochemical processes that modulate tissue injury may all serve as factors determining 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, Pirmohamed and Kitteringham, 1995) (Figure 8.2). The binding of a CRM to nucleic acid may result in teratogenicity or carcinogenicity (Figure 8.2).

The binding to cellular macromolecules may result in either direct or immune-mediated toxicity (Pirmohamed, Kitteringham and Park) (Figure 8.2). With direct toxicity, binding of the CRM to a protein will interfere with its normal physiological function

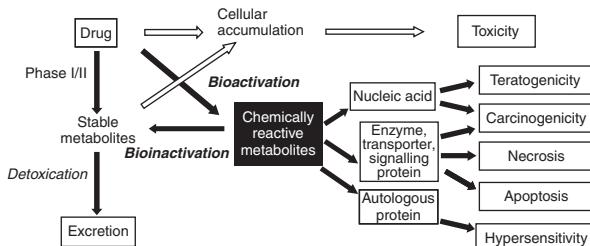


Figure 8.2. The role of metabolism in drug toxicity. Decrease in metabolism can lead to increased drug concentration and dose-dependent toxicity (which may also be because of cellular accumulation). The drug may undergo bioactivation to form CRMs, which if not adequately bioinactivated may bind to various cellular macromolecules and lead to different forms of toxicity.

leading to cellular necrosis. Alternatively, the CRM can act as a hapten and initiate an immune reaction that may be because of a specific humoral (antibody) response, a cellular response (T lymphocytes) or a combination of both (Naisbitt *et al.*, 2000a; Park, Coleman and Kitteringham, 1987; Park *et al.*, 2001; Park, Pirmohamed and Kitteringham, 1998; Pohl *et al.*, 1988). The immune response can be directed against the drug (haptenic epitopes), the carrier protein (auto-antigenic determinants) or the neoantigen created by the combination of the drug and the protein (new antigenic determinants). The factors that determine what type of toxicity is mediated by a CRM are poorly understood but are likely to include (Boelsterli, 1993; Gillette, Lau and Monks, 1984; Park, Coleman and Kitteringham, 1987)

- 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, i.e. 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; e.g. the occurrence of manifestations such as rash, fever, lymphadenopathy and eosinophilia all suggest drug hypersensitivity (Pessaire 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 many drugs that undergo metabolism, CRM will be formed irrespective of the dose of the drug (Pirmohamed, Madden and Park, 1996). When a drug is taken in therapeutic dosage, any toxic metabolite formed will be detoxified by normal enzymatic

or non-enzymatic cellular defence 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 detoxication 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 United Kingdom (Bray, 1993). According to the conventional definition of ADRs, paracetamol hepatotoxicity should not be classified as an ADR, because the hepatic injury occurs when the drug is used inappropriately. However, it is important to note that 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, Kitteringham and Park). Indeed, paracetamol hepatotoxicity has been reported with therapeutic drug use. For example, a recent 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), whereas another 20% had taken between 4 and 6 g/day (which is also regarded as a non-toxic dose) (Zimmerman and Maddrey, 1995).

In therapeutic dosage, paracetamol is largely metabolised by phase II processes (glucuronidation and sulphation) to stable metabolites, but between 5% and 10% also undergoes P450 metabolism to the toxic *N*-acetyl *p*-benzoquinoneimine (NAPQI) metabolite (Nelson, 1990) (Figure 8.3). 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 the 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 the depletion of glutathione (Lauterburg and Velez, 1988) and induction of the P450 isoform CYP2E1 (Raucy *et al.*, 1989). Recent studies in knockout

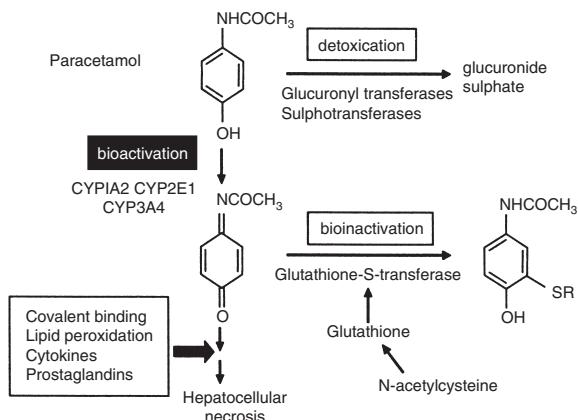


Figure 8.3. The role of metabolism in the hepatotoxicity associated with paracetamol.

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 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 Ca^{2+} pumps (Tsokos-Kuhn, 1989), which can lead to 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). Recently, it has 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 (Hayes *et al.*, 1999; Moinova and Mulcahy, 1998, 1999). If unsuccessful, then 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

that scavenge free radicals, neutralise electrophiles or up-regulate the critical cellular thiol, glutathione. Glutathione depletion caused by a range of chemicals leads to the up-regulation of c-jun and c-fos mRNA and enhances activator protein-1 (AP-1) DNA binding activity (Kitteringham *et al.*, 2000). This response was also accompanied by the induction of γ -glutamyl cysteine synthetase (GCS). 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 defence. Importantly, it has been observed that nuclear translocation occurs at non-toxic 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 defence through the destruction of critical proteins – at least 31 of these critical proteins have been identified (Park *et al.*, 2005).

Paradoxically, studies performed with transgenic mice aimed at clarifying events subsequent to NAPQI formation have only served to confound rather than to clarify. For example, the deletion of components of the glutathione detoxication system such as glutathione peroxidase (Mirochnitchenko *et al.*, 1999) and glutathione transferase-pi (GST-pi) (Henderson *et al.*, 2000) both afforded partial protection against paracetamol hepatotoxicity. The loss of a major hepatic form of GST, which represents over 3% of total soluble protein (Fountoulakis *et al.*, 2000), would have been expected to predispose the animals to hepatotoxicity through a reduction in the glutathione conjugation of NAPQI (Coles *et al.*, 1988). This suggests that GST-pi may be involved in a novel mechanism that determines susceptibility to paracetamol hepatotoxicity. Indeed, a recent study has shown that GST-pi may have a role in cell signalling; it has been shown to be an efficient inhibitor of Jun kinase (also known as stress-activated kinase), the enzyme that activates c-jun and several other transcription factors (Adler *et al.*, 1999). Future studies using other transgenic mouse models will be useful in determining the exact pathway by which paracetamol causes liver damage and may therefore provide novel therapeutic strategies by which to reverse liver damage in patients who present late after paracetamol overdosage.

THE ROLE OF THE IMMUNE SYSTEM IN TYPE B ADVERSE DRUG REACTIONS

Based on clinical criteria, it has been postulated that many idiosyncratic ADRs are immune mediated (Park, Pirmohamed and Kitteringham, 1998; Pirmohamed *et al.*, 1998). Research into this area is now providing some direct evidence to support the clinical impression. The mechanism by which a drug leads to an immune-mediated adverse reaction is explained by the hapten hypothesis (Park, Pirmohamed and Kitteringham, 1998) (Figure 8.2). Central to the hapten hypothesis is the assumption that small molecules such as drugs (<1000 Da) can be recognised 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, Coleman and Kitteringham, 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 immunoglobulin E (IgE) antibodies directed against a drug hapten conjugated to protein (Pirmohamed, Kitteringham and Park; Weiss and Adkinson, 1988). Severe anaphylactic reactions occur in only few 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 immuno-allergic 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 hantenate proteins (Park, Pirmohamed and Kitteringham, 1995). In addition, both humoral and cell-mediated responses directed against drug-induced antigen have been detected in patients, e.g. in halothane hepatitis (Pohl *et al.*, 1990). With some compounds, the immune response seems to be directed predominantly towards an auto-antigen. For

example, in tienilic acid-induced hepatitis, patients have circulating auto-antibodies 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 however recently been challenged by the observation that T-cell clones from patients hypersensitive to many 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 down-regulation in expression of the T-cell receptor upon stimulation are consistent with this mechanism. It is of course possible that both mechanisms may be important in the overall pathogenesis. For example, the hapten-dependent pathway may be more important for primary immune stimulation (sensitization), whereas the metabolism-independent pathway may be all that is necessary for secondary stimulation and elicitation of tissue damage (Pirmohamed, Naisbitt and Park, 2001). Further studies are needed to define the roles of the two pathways of drug (antigen) presentation in the pathogenesis of immune-mediated ADRs.

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+ T cells (Pamer and Cresswell, 1998). MHC class II molecules present longer peptide molecules (13–17 amino acids) to CD4+ cells (Jensen, 1997). Although class I molecules are found on all cell surfaces, class II molecules are only expressed on specialised 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 (INF- γ) (Pichler and Yawalkar, 2000). The nature of the immune response is governed by the differentiation of T cells into T-helper 1

(T_H1), T_H2 , T-cytotoxic 1 (T_C1) or T_C2 subsets. T_H1 and T_C1 cells mediate cytotoxicity and local inflammatory reactions, whereas 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 (Naissitt *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 recognised 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 interleukin-2 (IL-2), TNF- α and IFN- γ that act indirectly on antigen-presenting cells to up-regulate the expression of co-stimulatory molecules. Signal 3 represents polarising cytokines that act directly on T cells. It is known that T_H1 cells produce IL-12 and IFN- γ , 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 recently been proposed in the field of immunology to explain the basis of self-tolerance (Anderson and Matzinger, 2000; Gallucci and Matzinger, 2001; Matzinger, 1994). This can also be applied to the mechanism of drug hypersensitivity (Park, Pirmohamed and Kitteringham, 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 the presentation of an antigen result in an immune response. The nature of the danger signals has not been accurately defined, but pro-inflammatory and polarising 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 hypothesised that the CRM may not only provide signal 1 (by conjugating with a protein) but also provide the co-stimulatory signals 2 and 3 by the activation of signalling 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 *THE ROLE OF VIRUSES IN TYPE B ADVERSE DRUG REACTIONS*).

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 ADRs, 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 herpes virus 6 (HHV6), has recently been implicated in hypersensitivity reactions associated with many drugs including sulphasalazine (Descamps *et al.*, 2001; Suzuki *et al.*, 1998). However, whether this is a true predisposition or merely a co-incidental factor needs further study. Perhaps, the most striking association between viral infection and drug hypersensitivity has been observed in HIV-infected individuals. These patients have a higher frequency of hypersensitivity reactions with numerous anti-infective drugs including co-trimoxazole, sulphadiazine, dapsone, clindamycin, primaquine and thioacetazone (Koopmans *et al.*, 1995; Pirmohamed and Park, 2001b). 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 will develop skin rashes, whereas when used for prophylaxis the figure is 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 has been suggested to be responsible for the increase in susceptibility of HIV-positive patients (Koopmans *et al.*, 1995; van der Ven *et al.*, 1991). A recent study has demonstrated that in the presence of plasma cysteine deficiency, HIV-positive patients have a lower capacity to detoxify the

toxic nitroso metabolite of sulphamethoxazole (Naissib *et al.*, 2000b). However, the fact that prophylactic *N*-acetylcysteine does 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-metabolising capacity (both in bioactivation and in bioinactivation) and immune dysregulation (Pirmohamed and Park, 2001b). In addition, HIV itself may act as a source of a danger signal (Park, Pirmohamed and Kitteringham, 1998; Pirmohamed and Park, 2001b; Sullivan and Shear, 2001; Uetrecht, 1999). Interestingly, the peculiar predisposition of HIV patients to hypersensitivity reactions is now being witnessed with the new antiretrovirals such as abacavir (severe hypersensitivity is seen in 3–8% of patients) and non-nucleoside reverse transcriptase inhibitors such as nevirapine, efavirenz and delavirdine, all of which produce skin rashes at a frequency of between 18% and 40% (Pirmohamed and Park, 2001b). Certainly, liver injury associated with protease inhibitors and nevirapine seems to be more common in HIV patients co-infected with either hepatitis C or hepatitis B (Nunez, 2006).

GENETIC PREDISPOSITION TO TYPE B ADVERSE DRUG REACTIONS

Type B ADRs have typically been defined to be host-dependent (Rawlins and Thompson, 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 ADRs, in most cases, is going to be multi-genic (dependent on a combination of genes) and multi-factorial (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 multi-centre international collaborations (Pirmohamed and Park, 2001a).

The nature of the polygenic predisposition is unclear but in general could be divided into several areas (Figure 8.4) as follows (Park and Pirmohamed,

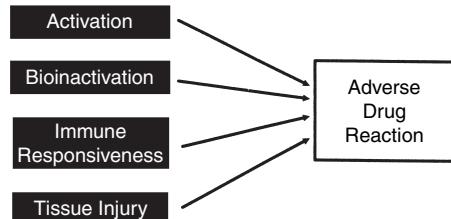


Figure 8.4. Type B or idiosyncratic drug reactions have a multi-factorial aetiology. Variation, which may be genetically determined, in drug *bioactivation* and *bioinactivation*, can lead to persistence of a CRM. If the adverse reaction is immune mediated, then the binding of the CRM will lead to the formation of an antigen, which will be recognised by the body's immune system resulting in an *immune response* and *tissue injury*.

2001; Pirmohamed *et al.*, 1998; Pirmohamed and Park, 2001a):

- **Activation:** Involves the activation of drug to CRMs. The bioactivation of drugs is largely mediated by cytochrome P450 enzymes, many of which have now been shown to be polymorphically expressed (Park, Pirmohamed and Kitteringham, 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, the amplification of a P450 isoform, as seen with CYP2D6 (*CYP2D6*2xN*) (Ingelman-Sundberg, Oscarson and McLellan, 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 characterised 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, Pirmohamed and Kitteringham, 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 GST gene polymorphisms with idiosyncratic drug reactions observed with co-trimoxazole (Pirmohamed *et al.*, 2000), carbamazepine (CBZ) (Leeder, 1998) and tacrine (De Sousa *et al.*, 1998; Green *et al.*, 1995b).

- **Immune-response genes:** The process by which the body's immune system recognises a drug/drug metabolite as being foreign or antigenic and thereby mounts an immune response was conceived to be protective, but, perversely, this may lead to clinical manifestations typical of hypersensitivity. The genes encoding for immune responsiveness include MHC, T-cell receptors and co-stimulatory molecules.
- **Tissue-injury genes:** 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.

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. 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 Sequencing Consortium, 1999).

Abacavir Hypersensitivity

Abacavir, an HIV-1 reverse transcriptase inhibitor, causes hypersensitivity, characterised 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 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 however has not been shown in an African American population presumably because of ethnic differences in linkage disequilibrium patterns in the MHC (Hughes *et al.*, 2004a). The association with the MHC in Caucasians is consistent with the immune nature of the reaction and the identification of drug-specific T cells in abacavir hypersensitive patients (Dodd *et al.*, 2003; Phillips *et al.*, 2005). By contrast, no association has been found with polymorphisms in the genes coding for various abacavir-metabolising enzymes (Hetherington *et al.*, 2002). Mallal *et al.* (2002) have proposed that in Caucasians genotyping for HLA-B*5701 should be performed before the prescription of abacavir, and indeed in their clinic, this has resulted in a reduction in the incidence of abacavir hypersensitivity (Martin *et al.*, 2004). An analysis of the cost effectiveness of prospective *HLA-B*5701* genotyping before abacavir hypersensitivity based on a meta-analysis of three cohorts showed that in Caucasians this would be a cost-effective strategy (Hughes *et al.*, 2004b).

Carbamazepine Hypersensitivity

Carbamazepine, 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 characterised by systemic manifestations such as fever and eosinophilia (Leeder, 1998; Vittorio and Muglia, 1995). Rarely, CBZ can induce blistering skin reactions such as SJS and toxic epidermal necrolysis, two conditions associated with a high fatality rate (Rzany *et al.*, 1999). CBZ hypersensitivity is a T-cell-mediated disease (Mauri-Hellweg *et al.*, 1995; Naisbitt *et al.*, 2003). CBZ is metabolised to CRMs that have been implicated in the pathogenesis of hypersensitivity (Pirmohamed *et al.*, 1992). To date, no polymorphisms in the drug-metabolising enzyme gene polymorphisms have been associated with susceptibility to CBZ hypersensitivity

(Gaedigk, Spielberg and Grant, 1994; Green *et al.*, 1995a). Analysis of the MHC has led to the finding that CBZ hypersensitivity syndrome, but not mild maculopapular eruptions, is associated with the haplotype TNF2-DR3-DQ2 (Pirmohamed *et al.*, 2001). This has also been borne out in more recent studies in an extensive analysis of the heat shock protein (HSP) locus, which has shown that severe but not mild CBZ hypersensitivity reactions are associated with three SNPs in the HSP-70 locus, two in HSP-70-1 and one in HSP-Hom (Alfirevic *et al.*, 2006). These studies suggest that in Caucasians the causal variant for CBZ hypersensitivity resides on the ancestral haplotype 8.1 (Pirmohamed, 2006). In the Han Chinese, however, the susceptibility locus has been suggested to be different following the finding of a strong association between CBZ-induced SJS and *HLA-B*1502* (Chung *et al.*, 2004).

In the future, it may be possible to use a comprehensive, densely spaced, genome-wide SNP map that may screen for pharmacogenetically active genes as whole genome, unbiased searches (Roses, 2000). SNPs are single-base differences in the DNA sequence, observed between individuals, which occur throughout the human genome. The International SNP Map Working Group (2001) has published a map of 1.42 million SNPs throughout the genome, occurring at an average density of one SNP every 1.9 kb; by the end of 2005, almost 10 million have been identified, of which 50 000 code for variants that can lead to amino acid changes. High-density SNP maps derived from this information will provide an opportunity to perform SNP profiling to identify genetic factors predisposing to ADRs. However, before this can become a reality, the cost of genotyping needs to come down. Furthermore, given the need to test for multiple markers simultaneously, an issue that needs to be considered is the sample size and the level of statistical significance required to prevent the detection of false-positive associations. A recent study has reported that for testing 100 000 loci in a genome-wide screen will require a 3-fold greater sample size at a significance level of 2.5×10^{-7} (Cardon *et al.*, 2000). This does suggest that for pharmacogenomic detection of rare adverse events, testing in phases I–III is not likely be practical and will require prospective storage of samples and evaluation in phase IV when a problem has been identified.

CONCLUSION

The importance of ADRs is often underestimated. They are common, can be life threatening and unnecessarily expensive. Because of the wide range of drugs available, the manifestations of toxicity can be variable and affect any organ system. In fact, ADRs 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 the 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 multi-centre 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 SNP 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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9

Micturin and Torsades de Pointes

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RESPONDING TO SIGNALS

MICTURIN AND TORSADES DE POINTES

Micturin® (Mictrol®, terodilane hydrochloride) was withdrawn from sale in 1991 after the discovery of an association with serious cardiac arrhythmias, most notably a rare form of ventricular tachycardia known as torsades de pointes (TP) (Wild, 1992). In most patients, TP occurs in short, self-limiting bursts that lead to temporary interruption of the circulation, causing symptoms of cerebral impairment such as dizziness, acute confusion, syncope or epileptiform fits. Occasionally, it may convert into ventricular fibrillation from which death may result. TP may co-exist with sinoatrial depression, bradycardia and heart block in some patients, which may require temporary or permanent cardiac pace-making. TP is always associated with prior QT interval lengthening in the electrocardiograph (ECG) (Ben-David and Zipes, 1993). Micturin caused prolongation of the QT interval (Stewart *et al.*, 1992; Thomas *et al.*, 1995; Hartigan-Go *et al.*, 1996; Shuba *et al.*, 1999).

Micturin had been licensed in the United Kingdom in 1986, indicated for the management of detrusor instability (urge incontinence). Pharmacologically, it was a tertiary amine with dominant anti-muscarinic

activity, but it also had modest calcium antagonist properties (Husted *et al.*, 1980). Importantly, as will become clear, prior to launch as Micturin, terodilane had been licensed since the mid-1960s in Sweden as an anti-anginal drug (Bicor®). It was side effects on the urinary bladder that led to its re-development as Micturin (Andersson, Ekström and Mattiasson, 1988; Langtry and McTavish, 1990).

Micturin had been successfully marketed for 2 years before the first report of TP. A second report was received almost exactly a year later, quickly followed by a third. A full review of the corporate safety database, and of the pre-clinical data, yielded no information that pointed to a causal relationship. Terodilane's early use as a cardiac drug historically preceded the first published descriptions of TP (Deserterne, 1966), so it is highly likely that any cases of TP were simply not recognised, any emergent arrhythmias being attributed to the disease state. Emphasis had been put on the review because of a serious event that, according to the literature, had virtually no spontaneous incidence; it was usually associated with drugs or metabolic derangement (Stratman and

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Kennedy, 1987). (There is also a rare congenital lengthening of QT interval.) All these early cases (and most of the subsequent cases) were complicated by histories of ischaemic heart disease (IHD) and polypharmacy.

Early in 1991 the fourth report of TP was received (McCleod, Thorogood and Barnett, 1991), and, most significantly, a UK cardiac centre notified the company of an impending publication (Connolly *et al.*, 1991) involving five cases of TP, three of which were the first reports received by the company back in 1988 and 1989. The other two were, until then, not known to the company. Six cases of a very rare disorder, apparently associated with Micturin treatment, could not be ignored. It constituted a potential safety issue and required sharing with the regulators. (Each case had, of course, been reported individually to the regulators according to prevailing serious adverse drug event (ADE) requirements. These had provoked no comments from the Medicines Control Agency (MCA) at the time.)

At this stage, it was far from certain that Micturin might have a direct causal relationship with TP:

- Experts would not entirely rule out an association of the TP with IHD, or its drug treatment, a feature in many of the reported cases.
- Despite the launch of Micturin in other countries, the United Kingdom remained alone in reporting the ADE.
- Index patients had been safely on the drug for a mean of 13 months (the longest was 2 years) before the onset of the symptoms (usually black-outs) associated with TP.

Despite these doubts, the MCA was informed of our concerns. The MCA did not share any prior concern they themselves may have had, and added no more cases to the company database. The MCA saw no need for immediate action on their part, and accepted the company plan of action that included the following:

- Full validation of each case received with on-site due diligence.
- Quantifying the level of risk through sales data.
- Reviewing prescribing experience with key prescribers for unreported cases (none was discovered).

- Re-analysis of the Prescription Event Monitoring database (PEM, Drug Safety Research Unit, University of Southampton), as the original study had not identified an arrhythmia hazard.
- Commissioning a search and case-control study of the GP research database (VAMP).
- Studying the effects of Micturin on QT interval lengthening.

By July 1991, 13 cases of TP (plus three other ventricular tachycardias) had been reported from the United Kingdom, and Micturin was reviewed at a routine meeting of the Committee on Safety of Medicines (CSM). Unexpectedly, CSM decided immediate restriction in the use of the drug was required, despite no new information from any of the research actions the company had agreed with the MCA. A 'Dear Doctor' letter with revised prescribing information was issued on 25 July 1991 (Asscher, 1991). Not unexpectedly, this had immediate effects. Patient and prescriber confidence was immediately lost, and prescriptions dwindled to less than 10% of peak levels in just 6 weeks. Reporting rates for not only TP but also other arrhythmias and sudden, unexplained deaths increased rapidly. Many of these reports were retrospective once the association was recognised. On Friday, 13 September 1991, the company decided, voluntarily, to withdraw the drug worldwide.

At this point of withdrawal, some 69 cases of cardiac arrhythmia and sudden, unexplained death (14 of the 69) had been reported in the United Kingdom. Only three cases had been reported from outside the United Kingdom. Reports included 13 cases of other ventricular arrhythmias and 18 brady-dysrhythmias, in addition to the TP (24 cases). Prior to this point, it was estimated that approximately 450 000 UK patients (and a further 550 000 elsewhere) had been prescribed Micturin. The risk for TP (based only on UK data) was calculated at around 1 in 18 750, but this risk increased to 1 in 6500 for any of the cited events.

Preliminary analysis results became available from the PEM and VAMP databases. In the original PEM study of 1986–87, no case of TP was discovered amongst 12 457 patients. In 1991 these data were revisited (Inman *et al.*, 1993). As it was quite possible that cases of TP could have missed diagnosis (owing to its transient and self-limiting nature in most cases),

re-analysis included all incidents that could have been attributable to cardiac or vascular events. A comparison of the incidence of these events, and deaths, was also made with another drug (nabumetone) that had also undergone a PEM study in a similar age-range of patients. There were no pertinent differences between the two groups of patients.

In the VAMP analysis of 9716 Micturin-treated patients, one case of TP was found (Hall *et al.*, 1993). A subsequent retrospective cohort study, taken from this group of patients, showed no differences in the overall incidence of diagnosed cardiac arrhythmias between Micturin-treated patients and controls matched for age, sex and urinary consultations. Admittedly, the power provided by the VAMP and PEM databases was not high (covering only 22 000+ patients) but, at least, they provided reassurance that there was not a larger, unrecognised problem. Most relevant cases appeared to be being reported.

Studies of QT interval lengthening on ECG have shown an undoubted correlation with Micturin treatment (Stewart *et al.*, 1992; Thomas *et al.*, 1995; Hartigan-Go *et al.*, 1996; Shuba *et al.*, 1999). As QT interval lengthening is prerequisite for TP, it must be accepted that Micturin probably played a role in the development of TP. However, it is not the purpose of this chapter to examine QT interval lengthening and its association with TP. It is important to note that since the withdrawal of Micturin, effects on QT interval have been recorded in a much wider range of drugs than the anti-arrhythmics and psychotropic drugs that dominated the early publications (Stratman and Kennedy, 1987; Yap and Camm, 2000). Perhaps the most notable of the drugs affected have been two humble, and very widely used, over-the-counter (OTC) anti-histamines, astemizole and terfenadine. (Both are available now only on prescription.) Owing to the prevalence of QT interval lengthening with so many classes of drugs now, and the ease with which the effect can be detected and measured, it is important to rule it out early in clinical development.

There are important lessons to be learned from managing the Micturin alert:

1. Never to take false comfort from the fact that a drug has had an apparently long history of safe use. The development for the earlier use will probably

have pre-dated modern standards of development and adverse event reporting.

2. A change of use or indication may be exposing a new profile of the patient, more susceptible to the ADE.
3. Because an event is rare, or even previously undescribed (as TP was until 1966), do not dismiss a possible association. Thalidomide teratogenicity and practolol-associated fibrosing peritonitis caused much morbidity before anyone dared to make the association.
4. We could have reacted more to the early signals. It would have been very easy, and quick, to conduct a case-control study in patients for effects on QT interval lengthening. Unfortunately, thought processes, then, did not immediately encompass the notion that patients without TP might have QT prolongation.

In these sorts of circumstances, it is always easier to find excuses to absolve than reasons to blame.

Would earlier action have actually made any difference to the outcome? This can, perhaps, be answered by examining the reasons that lead to the withdrawal. The drug was not life saving but had potentially lethal side effects. The side effects (taken as a whole) were not all that rare, at about 1 in 6500 patients exposed (between 1 in 10 000 and 1 in 20 000 for TP alone). The risk was probably doubled in the over 75s, a large patient group for the drug (Inman *et al.*, 1993). ECGs were not helpful, as anyone exposed to terodiline will lengthen their QT interval (but, at the time, defining when it became a pathological increase was controversial).

Terodiline had been recognised as being metabolised and excreted more slowly in the elderly during clinical development (Hallén *et al.*, 1989), and appropriate prescribing information resulted. Whilst some patients with TP had been on inappropriately high doses for their age, most were not. Unfortunately, a serum level of terodiline had been measured in only one of the reported cases (Connolly *et al.*, 1991). It is noteworthy that the level in this case was in fact around six times the accepted therapeutic level, and this was from, apparently, recommended dosage. Thus, there was the suspicion that QT prolongation might be related to blood levels (this was subsequently proven) (Thomas *et al.*, 1995).

Why did many of the index patients apparently live happily with their (presumed) prolonged QT for up to 2 years, and then develop TP? Were there co-factors that combined with the QT prolongation and precipitated the TP? Hypokalaemia increases the risk of TP, also through QT lengthening. Co-prescription of other drugs also known to prolong QT interval would have been another risk factor.

Finally, it had to be accepted that there were safer, alternative treatments available. All these reasons left the company with little choice but to withdraw the drug. Some patients thought otherwise, saying they were quite prepared to risk death in order to enjoy the freedom the drug had given back to them. Most patients, and their doctors, however, had already decided the risk was not worth taking.

The irony in this recount will not have escaped the alert reader. Terodilaine had owed its renaissance, as Micturin, to the discovery of side effects on the urinary bladder in cardiac patients. Cardiac side effects in urological patients proved to be its undoing.

POSTSCRIPT

Terodilaine has since been superceded by another molecule, tolterodine. This new molecule does *not* prolong the QT interval. The risk was peculiar to terodilaine and is not a class effect. Oxybutinin, for instance, has been shown not to affect the QT interval (Hussain *et al.*, 1996).

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Withdrawal of Terodilane: A Tale of Two Toxicities

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INTRODUCTION

Apart from drug-induced prolongation of the QT interval, and its subsequent degeneration into torsade de pointes, it is difficult to think of another type A pharmacological adverse drug reaction that has been responsible for the withdrawal of so many drugs from the market over the last two decades. Withdrawal of prenylamine in 1988, followed by that of lidoflazine in 1989 and terodilane in 1991, was to herald a similar misfortune for many other drugs such as terfenadine, astemizole, cisapride, sertindole, grepafloxacin, droperidol, thioridazine and levacetyl-methadol. A number of other drugs, such as pimozide, halofantrine, lumefantrine and mizolastine to name just four, had severe prescribing restrictions placed on their clinical use for similar reason, while others such as moxifloxacin, gatifloxacin and ziprasidone have had their approval greatly delayed in some Member States of the European Union (EU) because their 'QT-liability' was determined to adversely affect their risk–benefit ratio. Not surprisingly, many drugs have recently had their clinical development terminated,

some at a fairly advanced stage, as a result of their potential to prolong the QT interval (Shah, 2002).

Withdrawal of terodilane has a number of important lessons for drug development and pharmacovigilance. Firstly, from a regulatory perspective, terodilane is almost too perfect an example of drugs whose more potent secondary pharmacological effects, observed as adverse drug reactions during their originally intended clinical uses, have led to their clinical re-development for completely different indications. In the case of terodilane, this concerned its potent anticholinergic side effect observed during its approved use as an antianginal agent. Terodilane illustrates how such a strategy can be eclipsed by the virulent appearance of additional secondary pharmacological effects that are not fully explored. With terodilane, this additional activity was its adverse effect on cardiac repolarization and QT interval duration on the surface electrocardiogram (ECG). Indeed, terodilane might therefore be described as a 'pharmaceutical boomerang'. It serves as a reminder of the limitations of drug development programmes in characterizing a relatively rare, but potentially fatal, clinical hazard. Secondly, it emphasizes both the perils

of failing to appreciate the problems associated with other members of the same chemical, pharmacological or therapeutic class of drugs (prenylamine in the case of terodilane), and the necessity of applying all available techniques to characterize a potential class-related safety issue when developing a new drug. This is particularly unfortunate, since drug-induced QT interval prolongation is a concentration-dependent type A adverse drug reaction that can be investigated during preclinical and clinical phases of drug development, and therefore ought to be predictable. Finally, the post-marketing identification of the proarrhythmic risk associated with terodilane through a spontaneous reporting system emphasizes the strengths of systems such as the United Kingdom (UK) Yellow Card Scheme in comparison with formal post-marketing surveillance studies that had continued to assert its cardiac safety.

This chapter will focus on a comparison between terodilane and prenylamine with a view to providing a framework of some of the major issues that need to be considered when preparing the pre-marketing Safety Specification of a new drug, as required by the International Conference on Harmonization (ICH) E2E guideline, and discussing the potential risks that require further evaluation. In this context, it will also discuss the ICH E1A guideline on the clinical safety dataset required to assess the safety of medicines intended for chronic use, and the recently adopted ICH S7B and ICH E14 guidelines on pre-approval investigation of drugs for their potential to prolong QT interval.

DRUG-INDUCED QT INTERVAL PROLONGATION AND PHARMACOVIGILANCE PLANNING (ICH E2E)

The ICH E2E guideline on Pharmacovigilance Planning came into operation in the EU in June 2005, and is intended to assist in planning pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug (Anon, 2004). The guideline includes a section on Safety Specification that should be submitted at the time of marketing authorization application.

In the context of drug-induced proarrhythmias, the guideline recommends that the preclinical elements that should be considered for inclusion in the Safety Specification of a new drug are its potential to prolong the QT interval and for drug interactions.

The Safety Specification also requires a discussion on populations that have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Among the populations to be considered are the elderly, those with relevant co-morbidity (such as hepatic or renal disorders), patients with disease severity different from that studied in clinical trials, those who carry known genetic mutations of relevant drug-metabolizing enzymes and/or pharmacological targets, and patients of different racial and/or ethnic origins.

In addition to providing a detailed account of important information that is missing from the regulatory submission, the Safety Specification requires a summary of the important risks identified to be associated with a drug, any important potential risks and outstanding safety questions which warrant further investigations during the post-approval period to refine an understanding of its risk–benefit profile. With regard to potential risks that require further evaluation, the evidence that led to the conclusion that there were (or might exist) these potential risks should be presented. It is anticipated that for any important potential risk, there will be a further (post-approval) evaluation of the drug to characterize the association.

The ICH E2E also emphasizes that the Safety Specification should identify risks believed to be common to the pharmacological class of the new drug concerned.

RE-BIRTH OF TERODILINE

Terodilane was first marketed in 1965 as an antianginal agent ('Bicor') in Scandinavia, a relatively small market (Wibell, 1968). This period of original marketing of terodilane in the 1960s is worthy of note because it antedates (a) any serious regulatory or clinical interest in drug-induced prolongation of the QT interval and (b) the first description of torsade de pointes as a unique

proarrhythmia associated with prolonged QT interval (Dessertenne, 1966). Moreover, the re-development of terodiline in the early 1980s coincided with increasing number of reports of QT interval prolongation and torsade de pointes in association with two other antianginal drugs, prenylamine (Picard, Auzepy and Chauvin, 1971; Oakley *et al.*, 1980; Abinader and Shahar, 1983) and lidoflazine (Kaden and Kubler, 1977; Hanley and Hampton, 1983). These two drugs ceased to be available for clinical use in the UK – prenylamine in 1988 and lidoflazine in 1989.

Because of the potent anticholinergic properties of terodiline, urinary retention proved to be a frequent and troublesome side effect during its use as an antianginal agent. Terodiline was therefore re-developed in the early 1980s for clinical use in urinary incontinence due to detrusor instability. In isolated airway preparations from rats, terodiline had also been shown to block the bronchoconstrictor effect of acetylcholine. The shift in the acetylcholine dose-response curve induced by terodiline indicated that its anticholinergic property might also explain its observed cilostimulatory effect (Iravani and Melville, 1975). It is therefore not surprising that in the period intervening between these two indications, terodiline was also being investigated for use in chronic obstructive airways disease (Castenfors, Hedenstierna and Glenne, 1975), presumably in an attempt to harness the same, otherwise unwanted, pharmacological property observed during its use as an antianginal agent.

Terodiline was first introduced in the United Kingdom under the brand name of 'Terolin' (later changed to 'Micturin') in July 1986 for use in urinary frequency, urgency and incontinence in patients with detrusor instability and neurogenic bladder disorders. In the EU, it was also approved in Denmark, Ireland, Luxembourg, Belgium, the Netherlands, Spain and West Germany, but not in France, Greece, Italy or Portugal. Overall, the drug was approved in 20 countries worldwide and marketed in a number of these, but the major markets were the UK, Sweden and Japan. The recommended dose in the United Kingdom was 12.5–25 mg twice daily in young adults and otherwise healthy elderly patients, but 12.5 mg twice daily in frail elderly patients. In general, the doses used in Sweden were lower than those used in the United Kingdom, and the dose approved in Japan was half the UK recommended dose.

TERODILINE-INDUCED PROARRHYTHMIAS

One of the earliest suspicions of the proarrhythmic potential of terodiline arose from the sudden unexpected death of a previously healthy 20-year-old man, following an overdose in 1987 (Cattini *et al.*, 1989). Forensic toxicological analysis revealed the presence of a very high blood level of terodiline. His blood and urine levels were greater than 10 µg/mL. No other drugs or metabolites of terodiline were detected. At post-mortem, his organs did not reveal any natural disease. Although the death was suspected to have followed inhalation of vomitus, the probability of a proarrhythmic event preceding aspiration could not be excluded. Although the maximum steady-state serum concentrations of terodiline following 10–15 days of continuous twice-daily dosing with 25 mg are of the order of $0.5 \pm 0.23 \mu\text{g}/\text{mL}$, peak serum concentrations following single oral doses of 12.5 and 25 mg are only 0.066 and 0.105 µg/mL respectively. Based on this kinetics, Boyd (1990) has estimated that this patient might have ingested close to 168 tablets (of 12.5 mg each) as a single dose.

The first proarrhythmic reactions to clinical doses of terodiline were also reported to have occurred in 1987, when there was one case of ventricular tachycardia and one of bradycardia. These reports were followed by an additional one report each of these two reactions in 1988. Following its post-approval routine clinical use, the first three reports of torsade de pointes in association with terodiline were notified to the marketing authorization holder during 1988 and 1989, and the fourth report in 1990 (Wild, 1992). Beginning in early 1991, additional reports of QT interval prolongation and torsade de pointes began to appear (Andrews and Bevan, 1991; Connolly *et al.*, 1991; Davis, Brecker and Stevenson, 1991; McLeod, Thorogood and Barnett, 1991). These events, reported individually to the Medicines Control Agency (MCA, the competent UK authority that preceded the current Medicines and Healthcare products Regulatory Agency), did not raise any immediate concern at first because of the confounding factors associated with some of the reports. By May 1991, however, the marketing authorization holder was aware of 10 cases of torsade de pointes when

the MCA was alerted of the potential hazard signalled collectively by these reports.

Additional reports followed, and by 21 July 1991 there were a total of 21 reports – 14 reports of ventricular tachycardias (including 13 of torsade de pointes) and 7 of bradyarrhythmias. None had a fatal outcome. Therefore, the Chairman of the then UK advisory body, the Committee on Safety of Medicines (CSM), wrote to all the doctors and pharmacists in the United Kingdom warning them of this potentially fatal adverse reaction (Anon, 1991a). On the basis of these reports, the prescribers were advised that the drug should not be used in the presence of risk factors such as age greater than 75 years, ischaemic heart disease, co-prescription with cardioactive drugs, diuretics, antidepressants and antipsychotic agents, hypokalaemia and patients with any cardiac arrhythmias including ECG evidence of (pre-existing) prolongation of QT interval. Age *per se* was not regarded as an absolute contraindication.

After this warning, there followed an avalanche of reports. An additional 48 case reports followed within the next 6 weeks, and by September 1991 there were a total of 69 reports of terodilane-induced serious cardiac arrhythmias. The majority of these 48 additional reports were retrospective cases with the onset of terodilane-associated proarrhythmia antedating the warning letter. Clearly, there were cases of cardiac effects of terodilane, but these were simply not reported because the association might have appeared too implausible to the prescribing community. However, after the alert, the real magnitude of the potential risk started to become apparent.

These 69 reports consisted of 50 reports of tachyarrhythmias and 19 reports of bradyarrhythmias and heart blocks. Amongst these 69 cases were 14 cases of sudden or unexplained deaths (13 in the tachyarrhythmia group). Fifty-one cases had recovered and there was no information on outcome in the remaining 4 reports (but assumed non-fatal). Among the 55 non-fatal reports were 24 cases of torsade de pointes, 5 ventricular fibrillation, 7 unspecified ventricular tachycardia, one of multifocal ventricular ectopics and 18 of bradyarrhythmias.

Patient demography and pattern of drug usage was essentially similar in the tachyarrhythmia and bradycardia groups. Of the 50 patients with tachyarrhythmias, 40 were females and 43 were aged

61 years or more. A dose of 25 mg daily or less was taken by 25 (56%) of the 45 patients with tachyarrhythmias in whom the dose was stated. Information on duration of treatment was available in 40 of these 50 patients. It was less than 1 month in 8 cases, up to 2 months in 10 cases, up to 6 months in 8 cases and more than 6 months in the remaining 14 cases. A dose of 25 mg or less was taken by 11 (65%) of the 17 patients with bradyarrhythmias and heart blocks in whom the information on dose was available.

A further analysis of predisposing factors in these 69 reports of terodilane-induced cardiotoxicity confirmed previous conclusions on potential risk factors: (a) an age greater than 75 years, (b) concurrent use of cardioactive medication ($n = 33$), (c) concurrent use of diuretics ($n = 27$), (d) concurrent use of antidepressants or antipsychotic agents and (e) hypokalaemia ($n = 8$). Ischaemic heart disease was present in 13 patients, and other cardiovascular pathologies were present in 39 patients. In 12 cases (18%), however, there were no clinically identifiable risk factors at all.

While the regulatory action was under consideration, the marketing authorization holder withdrew the drug voluntarily from the market worldwide on 13 September 1991 (Anon, 1991b).

Interestingly enough, at the time of its withdrawal, only 3 reports had come from Sweden (daily doses were 37.5, 50 and 50 mg), 1 from the Netherlands (dose unknown) and none from Japan. There were no reports of cardiac arrhythmias from Denmark, Germany or Ireland. There was no information from Luxembourg. The drug was not marketed in Belgium, France, Greece, Italy, Spain or Portugal. Following its withdrawal, there were isolated reports of terodilane-induced torsade de pointes published from Denmark and Norway, and additional ones from the Netherlands. There was also one report of sudden unexpected death from Germany.

At the time of its withdrawal, about one million patients had been treated with terodilane worldwide, including about 450 000 in the United Kingdom. Even assuming a generous spontaneous reporting rate of 20%, the incidence of the risk was estimated at 1 in 1300 patients exposed. This remarkably high cardiotoxic potential of terodilane, uncovered through a spontaneous reporting system, is in sharp contrast to the generally reassuring safety profile that was being asserted on the basis of observations from

post-marketing surveillance studies (Hall *et al.*, 1993; Inman *et al.*, 1993).

LIMITATIONS OF FORMAL POST-MARKETING SURVEILLANCE STUDIES

A general practice based Prescription Event Monitoring (PEM) study profiled the safety of terodilane in 12 457 patients, treated between November 1986 and September 1987 (Inman *et al.*, 1993). Of these patients, 72.5% were females. The mean age was 65.6 (range 5–98) years in males and 63.3 (range 5–102) years in females. Incontinence (47.8%), frequency (16.9%), bladder irritability (7.7%) and urgency (6.6%) accounted for the majority of the indications for use of terodilane in females. In clinical practice, 62.2% of the patients were receiving a maximum daily dose of 25 mg, 18.2% were receiving 50 mg and a minority had used other regimes, including some up to 100 mg per day. Terodilane was reported to have been effective in 56% of the patients. Cardiovascular events reported during the first 6 months and at any time during and after treatment with terodilane, but *not* considered to be adverse reactions to it, included dizziness ($n = 135$ and 255, respectively), syncope (41 and 105), hypotension (15 and 30), atrial fibrillation (8 and 30), tachycardia (8 and 17), bradycardia (2 and 10), arrhythmias (2 and 8), ventricular fibrillation (0 and 3), heart block (0 and 2) and cardiac arrest (0 and 2). Even in a subsequent survey (initiated in 1990) of co-prescribing of various cardioactive medications, it could not be established whether the excess of syncope, arrhythmias, bradycardia, hypotension and other cardiovascular events was due to drug combinations or the presence of co-existing cardiovascular disease. Of all the events reported in the cohort, only 51 events were suspected to be actual adverse reactions to terodilane and these included 2 cases of dizziness. No case of cardiovascular collapse attributable to torsade de pointes could be found.

Even a retrospective study, undertaken in the aftermath of the powerful signal from the spontaneous reporting system and the withdrawal of terodilane from the market, failed to better quantify the risk of cardiotoxicity of terodilane. In this study using

the VAMP database (Hall *et al.*, 1993), a preliminary open study identified a total of 9176 terodilane-treated patients. A total of 77 (0.8%) of these 9176 patients had an ECG investigation during the study period. There was only one confirmed case of torsade de pointes in a 41-year-old female who had hypokalaemia at the time of the event. Apart from a 50 mg daily dose of terodilane, she was concurrently receiving a tricyclic antidepressant. Altogether, a total of 59 patients were found to have had a cardiac arrhythmia during the follow-up period. This open study estimated the risk of terodilane-induced torsade de pointes to be 1.1 per 10 000 patients. A retrospective but limited inquiry into the nature of arrhythmias in the 59 patients with cardiac arrhythmias elicited information in only 19 patients. These included 6 bradycardia, 4 heart blocks, 3 ventricular tachycardias, 2 ventricular conduction defects, 2 extrasystoles, 1 'tachy-brady syndrome' and 1 cardiac arrest. None had previously been reported to the CSM through the yellow cards and 16 of the 19 practitioners concerned agreed to complete a yellow card.

In another retrospective cohort extension of the above VAMP study, 5705 terodilane-treated patients were compared with 9604 controls. It concluded that there was no significant difference in the risk of developing an arrhythmia in the terodilane-treated patients compared with that in the controls. The relative risk compared with controls was estimated at 1.1 (95% CI: 0.64–1.90). Even the patients reporting symptoms suggestive of cardiac arrhythmias (syncope, collapse, blackouts) were not overly represented in the terodilane-treated cohort. Only dizziness and falls were reported significantly more frequently in the terodilane-treated patients (5.13% vs. 3.35%).

Both these studies had failed spectacularly if it was intended that they would test or strengthen what is frequently, and deprecatingly, termed merely a 'hypothesis' when reports of serious reactions are gathered through a spontaneous reporting system.

The failure of formal post-marketing surveillance studies to detect or quantify the risk of drug-induced QT interval prolongation, with or without torsade de pointes, associated with some potent torsadogens is not unfamiliar (Pratt *et al.*, 1994; Hanrahan *et al.*, 1995; Staffa *et al.*, 1995; de Abajo and Rodriguez, 1999; Layton, Key and Shakir, 2003).

INITIAL REGULATORY DELIBERATIONS

Questions arise, inevitably in retrospect, as to whether terodilane should have been approved at all and whether its proarrhythmic potential could have been anticipated. While it may be easy to answer some of these questions in retrospect, the commentary that follows is not based entirely on the benefit of hindsight, because the nature of the problem had become apparent at the regulatory authority immediately on receipt of the first two to three reports of terodilane-induced proarrhythmias.

There is little doubt that urinary incontinence, although relatively benign in terms of morbidity, is a highly prevalent condition that has a serious adverse effect on the quality of life. At the time of the approval of terodilane in 1986, there was no other drug available with a comparable efficacy and favourable risk–benefit ratio. Clinical trials had shown terodilane to be effective and, by all accounts, relatively safe. The efficacy of terodilane had been demonstrated in a number of studies (Fischer-Rasmussen, 1984; Yoshihara *et al.*, 1992; Anon, 1993a; Norton *et al.*, 1994). The majority of adverse reactions reported were anticholinergic in nature and mild in severity. In one randomized, double-blind, two-periods cross-over (3 weeks duration for each period) study in 89 women with motor urge incontinence without other neurological symptoms, no statistically significant difference in incidence of side effects could be demonstrated between 37.5 mg daily of terodilane and placebo (Peters, 1984). The safety of terodilane at a higher dose of 50 mg daily was also evaluated in a 6-month study in 100 women with urgency/urge incontinence (Fischer-Rasmussen, 1984). Ninety-one patients were evaluated after 3 months and 70 after both 3 and 6 months. Adverse reactions, usually those to be expected from the anticholinergic pharmacological effects of the drug, resulted in 12 patients discontinuing the treatment. No significant changes in heart rate or blood pressure occurred except for a small but statistically significant increase (about 2 mmHg) in resting diastolic blood pressure after 6 months. Mean levels of all clinical chemistry variables were well within the normal range. No significant laboratory changes were seen except for a small increase in platelet, serum creatinine and ESR. Unfortunately, ECGs were not recorded in either of these pre-approval studies.

Given the therapeutic options available at the time, there is no question that approval of terodilane was the most appropriate decision in 1986. Even during the few months immediately following its withdrawal, many patients and physicians continued to write to the Agency, testifying to its efficacy and positive impact in transforming the quality of life of many patients, and complaining about the abrupt loss of a clinically useful drug. An option to make the drug available on a named patient basis was under consideration but never followed through. Equally, the withdrawal of terodilane in September 1991 was not a difficult decision, since its risk–benefit was shown conclusively by then to be unfavourable and another equally effective drug, oxybutynin, had already been approved for use in urinary incontinence in January 1991.

SIMILARITIES BETWEEN TERODILANE AND PRENYLAMINE

In the context of the ICH E2E guideline on Pharmacovigilance Planning, some vital pieces of information that might have presaged the potential proarrhythmic risk from terodilane were already known at the time of its re-development. The analogy between terodilane and prenylamine goes well beyond their therapeutic class, and extends into their chemical structures and stereoselective pharmacological and toxicological profiles (Table 10.1).

First, it was well known that the use of antianginal drugs (prenylamine and lidoflazine) might be associated with QT interval prolongation and torsade de pointes. Prenylamine was introduced in the United Kingdom in the early 1960s and lidoflazine in 1979. Secondly, both prenylamine and terodilane are highly related in their chemical structures. While terodilane is a diphenyl-propyl derivative of butylamine (Figure 10.1), prenylamine is a diphenyl-propyl derivative of phenylethylamine (Figure 10.2).

The presence of a chiral centre in each drug gives rise to a pair of enantiomers. It is acknowledged that even a minor modification in the structure of a molecule can dramatically alter the activity of a drug, and indeed this is the basis of metabolic inactivation of most drugs. However, notwithstanding the minor

Table 10.1. Similarities between terodilane and prenylamine.

Feature	Prenylamine	Terodilane
Chemical structure	Diphenyl-propyl derivative of phenylethylamine	Diphenyl-propyl derivative of butylamine
Pharmacological class	Calcium channel blocker acting intracellularly	Anticholinergic Calcium channel blocker
Therapeutic class	Antiangular	Antiangular followed by re-development for the treatment of urinary incontinence
Metabolism	CYP2D6 probably metabolizes (+)-(S)-prenylamine	CYP2D6 probably metabolizes (+)-(R)-terodilane
Half-life	Long and highly variable between individuals	Long and highly variable between individuals
Stereoselective elimination	Favours (+)-(S)-prenylamine	Favours (+)-(R)-terodilane
Stereoselective pharmacodynamics	Yes	Yes
IKr or hERG (IC_{50}) of the racemic drug	0.597 μM (for hERG)	0.7 μM (for IKr)
Stereoselective cardiotoxicity	Yes with (+)-(S)-prenylamine being torsadogenic	Yes with (+)-(R)-terodilane being torsadogenic

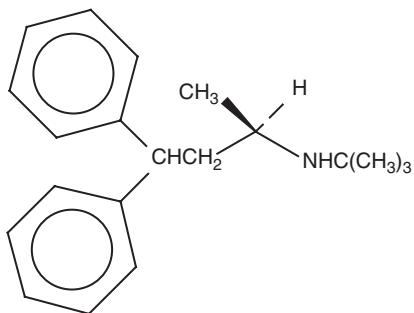


Figure 10.1. (+)-(R)-terodilane.

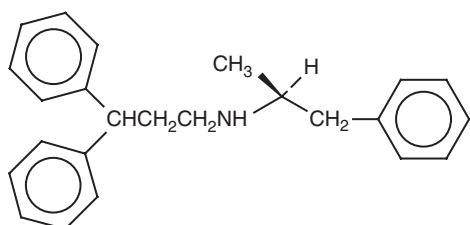


Figure 10.2. (+)-(S)-prenylamine.

structural differences between terodilane and prenylamine, it is intuitive that terodilane must have some cardiac effects since it was marketed originally as a cardioactive antiangular agent. Not surprisingly, both drugs share a very similar complex pharmacological profile that is discussed later. Thirdly, both prenylamine and terodilane are chirally active and there was already evidence of stereoselectivity in the proarrhythmic potential of prenylamine. Fourthly, there was wide inter-individual variability in the metabolism of terodilane, with aberrant pharmacokinetic behaviour of one of the enantiomers. This is also a feature of the pharmacokinetics of prenylamine. Finally, there was evidence of stereoselectivity in the pharmacodynamic activities of the two enantiomers of terodilane, and therefore the unexpectedly high frequency of anticholinergic effect observed during its use as an antiangular agent should have already suggested an unusual behaviour of one of the enantiomers (the enantiomer with predominantly anticholinergic activity).

To illustrate the regulatory deliberations at the time, frequent references will be made to prenylamine in the commentary that follows. This will highlight

in detail the striking similarity between these two drugs, and hence the logic that should have supported the re-development of terodilane. Importantly, this comparison emphasizes the strengths of both a scientific synthesis of all the available information when evaluating the significance of even a handful of spontaneous reports of a unique drug reaction, and of formulating the most appropriate regulatory strategies for risk management.

PRENYLAMINE-INDUCED PROARRHYTHMIAS

Prenylamine was the first drug to be withdrawn from the market worldwide in 1988 because of its high potential to prolong the QT interval and induce torsade de pointes, often with a fatal outcome (Anon, 1988).

Although prenylamine had been marketed since the 1960s, it was not until 1971 that reports (mostly from France and the United Kingdom) linking prenylamine with prolongation of the QT interval, ventricular tachycardia, ventricular fibrillation and torsade de pointes began to appear (Picard, Auzepy and Chauvin, 1971). Despite changes in dose schedules and warnings, prenylamine-induced proarrhythmias continued to be reported, and by 1988, 158 cases of polymorphic ventricular tachycardia were reported in association with prenylamine, and the drug was withdrawn worldwide soon after its removal from the UK market that year. Approximately 80% of these patients were females. The mean age was 68 ± 11 years and 30 of the 109 patients had received prenylamine as the only medication. The vast majority of the patients were taking prenylamine at the usually recommended daily dose of 180 mg. Hypokalaemia was present in 34 of the 82 patients for whom this information was available.

Strikingly, despite being very potent torsadogens, neither prenylamine nor terodilane had shown any evidence of its proarrhythmic potential during its development. Cardiotoxicity following their routine clinical use did not become fully manifest for about 2–3 years after marketing – a disturbing feature also shared by other torsadogenic drugs removed from the market. A number of prospective studies with prenylamine were conducted to investigate its effect on QT interval, but none could demonstrate a significant change after treatment with the

drug. A review of the pre-approval clinical trials data on terodilane proved unhelpful for evaluation of its effect on ECG. However, in one study of 12 asymptomatic patients in sinus rhythm taking stable doses of terodilane (undertaken after its withdrawal from the market), mean QTc interval and QT dispersion were significantly prolonged to 491 and 84 ms during treatment with racemic terodilane compared with measurements of 443 and 42 ms, respectively, made off therapy (Thomas *et al.*, 1995). The mean drug-induced increases were 48 ms for the QTc interval and 42 ms for QT dispersion. In this study, QT interval prolongation was shown to correlate closely with steady-state plasma concentrations of (+)-(R)- and (-)-(S)-terodilane.

Both prenylamine and terodilane further illustrate a more general difficulty in successfully containing a clinical risk by revising the prescribing information. These revisions may include reduced doses, additional contraindications, special warnings and precautions for use, requirements for monitoring patients and details of potentially cardiotoxic drug interactions. Unfortunately, this strategy has proved to be highly disappointing in risk management, as evidenced by the withdrawal of a number of high-profile drugs such as terfenadine, astemizole, cisapride (all associated with proarrhythmias) and troglitazone and bromfenac (both associated with hepatotoxicity) (Shah, 1999). The most recent casualty of inappropriate prescribing (resulting in rhabdomyolysis) was cerivastatin, which continued to be prescribed at high doses at the outset despite a recommendation to start treatment at lower doses, or concurrently with gemfibrozil despite this combination being contraindicated.

POLYMORPHIC CYP2D6-MEDIATED STEREOSELECTIVE METABOLISM

It appears probable that the metabolism of both terodilane and prenylamine may be mediated by the P450 cytochrome CYP2D6, the isoform responsible for debrisoquine hydroxylation. This major drug-metabolizing isozyme is expressed polymorphically in all populations, resulting in two major drug-metabolizing phenotypes – extensive (EM) and poor (PM) metabolizers. The latter are unable to effect the metabolic elimination of CYP2D6 substrates, and

these include antiarrhythmic agents, β -blockers, anti-hypertensive drugs, neuroleptics and antidepressants. Consequently, PM individuals are exposed to higher concentrations of the parent drug for longer duration.

The pharmacokinetics of prenylamine are enantioselective, favouring the elimination of the (+)-(S)-enantiomer (Gietl *et al.*, 1990; Paar *et al.*, 1990). On multiple dosing, the apparent oral clearance of the (+)-(S)-enantiomer was 4.6-fold and the renal clearance 2.4-fold higher than that of the (-)-(R)-enantiomer. The maximum plasma concentration and AUC (area under curve of plasma concentration vs. time) of the (+)-(S)-enantiomer were 4–5 times lower than those of the (-)-(R)-enantiomer. After a single dose, the mean plasma half-lives of (-)-(R)-prenylamine and (+)-(S)-prenylamine were 8.2 and 24 hours, respectively. On chronic dosing, the mean half-lives for (-)-(R)-prenylamine and (+)-(S)-prenylamine were reported to be 13.7 and 17.4 hours, respectively (Gietl *et al.*, 1990). However, the apparently only slightly higher mean value of the half-life of (+)-(S)-enantiomer following a single dose was mainly a consequence of its extremely long plasma half-lives of 82 and 83 hours in 2 of the 8 volunteers. The remaining 6 subjects showed an average half-life of 11 hours. Although none of these subjects had been phenotyped for their CYP2D6 metabolic capacity, prenylamine fulfils all the structural requirements of a CYP2D6 substrate and it is worth speculating whether these two individuals were PMs of CYP2D6 with an impaired ability to eliminate (+)-(S)-prenylamine. Patients with prenylamine-induced proarrhythmias have not been genotyped or phenotyped for their CYP2D6 metabolizing capacity.

Studies with rat liver microsomes suggest that more than one CYP isoform may be involved in the metabolism of terodiline, with different isoforms mediating the metabolism of the two enantiomers (Lindeke *et al.*, 1987). In studies using human liver microsomes, the metabolism of terodiline at high concentrations has been shown to be stereoselective favouring the (+)-(R)-enantiomer (Noren *et al.*, 1989), although the ratio of concentrations of the two enantiomers at steady-state following administration of clinical doses is close to unity (Hallen *et al.*, 1995).

Although much of the data in man are incomplete, puzzling or often difficult to reconcile, there is fairly persuasive evidence to suggest that the major

isozyme involved in the metabolism of (+)-(R)-terodiline is CYP2D6, and therefore the metabolism of (+)-(R)-terodiline is subject to genetic polymorphism. The formation of *p*-hydroxy-terodiline from (+)-(R)-terodiline was found to be impaired in one PM of debrisoquine (Hallen *et al.*, 1993). In this study of the pharmacokinetics of a 25 mg oral dose of (+)-(R)-terodiline in healthy volunteers, the mean half-life of this enantiomer in 4 EMs of debrisoquine was 42 (range 35–50) hours and in the only PM in this study, it was 117 hours. In another study (Thomas and Hartigan-Go, 1996) in healthy volunteers, which included 7 EMs and 2 PMs who were administered a single oral dose of 200 mg racemic terodiline, the maximum plasma concentrations and AUC of (+)-(R)-terodiline were significantly higher compared with (-)-(S)-terodiline, although their half-lives were similar. Even at this high dose (which would be expected to conceal the pharmacokinetic difference between the two genotypes), the PM/EM clearance ratios for (+)-(R)-terodiline and (-)-(S)-terodiline were 45% and 56%, respectively. In common with all drugs subject to polymorphic metabolism, the pharmacokinetic difference between the EMs and the PMs are less evident at higher doses because of increasing saturation of metabolism in EMs at higher doses.

It is worth pointing out that the (+)-(R)-enantiomer of tolterodine (a structural analogue of terodiline) with anticholinergic properties is marketed for the treatment of urinary incontinence. Its oxidative hydroxylation has been confirmed in *in vitro* and *in vivo* studies to be mediated principally by CYP2D6 (Brynné *et al.*, 1998; Postlind *et al.*, 1998). CYP3A4-mediated dealkylation provides a major alternative, albeit less effective, route of elimination in those who are PMs of CYP2D6 (Brynné *et al.*, 1999).

The consequence of this stereoselective and (most probably) polymorphic metabolism is that the calcium antagonistic (-)-(S)-terodiline would accumulate in all patients over time, but in addition there will also be an accumulation of the anticholinergic (+)-(R)-terodiline in the poor and intermediate metabolizers of CYP2D6 substrates. Thus, genetically determined accumulation of (+)-(R)-terodiline could constitute another risk factor. While it is true that the doses used in Sweden and Japan were generally lower, this CYP2D6-mediated metabolism of (+)-(R)-terodiline might also explain the striking inter-ethnic differences

in the incidence of ventricular arrhythmias associated with its use. Whereas 9% of the UK population are PMs, the corresponding figures for Sweden and Japan are only 6.8% and less than 1%, respectively. The higher frequency of PM alleles in the UK population will necessarily result in a higher prevalence of the heterozygous CYP2D6 genotype – a subgroup most at risk of drug–drug interactions – and therefore give rise to a higher potential for drug–drug interactions in the United Kingdom between terodilane and other QT interval-prolonging substrates of CYP2D6, such as neuroleptics, antidepressants and other antiarrhythmic drugs.

Ford, Wood and Daly (2000) investigated the roles of CYP2D6 and CYP2C19 genotypes in eight patients who survived terodilane-induced proarrhythmias (six with torsade de pointes and two with ventricular tachycardia). One of these eight patients had a CYP2D6 PM genotype, and it was observed that CYP2D6 alleles were no more frequent in these eight individuals than in the normal population. This study also found a statistically higher frequency of the mutant CYP2C19*2 allele in this population. As a result, these investigators suggested that whereas CYP2D6 PM status was not a risk factor for terodilane cardiotoxicity, possession of the CYP2C19*2 allele might contribute to adverse cardiac reactions to terodilane. This study, however, has serious limitations that the investigators themselves have acknowledged. Only two mutant alleles of CYP2D6 were looked for and there was no ECG evidence confirming the adverse drug response phenotype (i.e. the presence of QT interval prolongation or torsade de pointes). There was a lack of information on co-medications in 2 patients. In another 2 patients, there was co-administration of diuretics that may predispose to hypokalaemia, and therefore to torsade de pointes.

It may be speculated whether any of the 12 patients with terodilane-induced proarrhythmias reported to the CSM, and in whom there were no obvious risk factors may have had a pharmacogenetic defect in their CYP2D6-mediated drug metabolism of (+)-(R)-terodilane. Connolly *et al.*, (1991) and Andrews and Bevan (1991) have also reported one case each of torsade de pointes in patients without any risk factors and in whom plasma terodilane levels were markedly elevated. Information on the genotypes of such patients would have

been more helpful in elucidating the role of (pharmacokinetic) genetic susceptibility to terodilane-induced proarrhythmias.

In addition, the susceptibility role of CYP2C19*2 suggested by Ford, Wood and Daly (2000) does not explain either the absence of terodilane cardiotoxicity among the Japanese (in whom the frequency of the CYP2C19*2 allele is much higher at 0.29–0.35), or the high frequency of anticholinergic effects mediated by (+)-(R)-terodilane in Scandinavia (where the frequency of the CYP2C19*2 allele is far lower, at no more than 0.08). There is also the evidence showing that the frequency of this allele is not any higher among the elderly (Yamada *et al.*, 1998), who were the target population for the use of terodilane. Neither can the closely related CYP2C9 isoform be implicated. Terodilane 50 mg daily did not influence the plasma levels of warfarin enantiomers, nor the anticoagulant effect, following continuous daily administration of a mean dose of 5.3 mg warfarin (Hoglund, Paulsen and Bogentoft, 1989).

PHARMACOKINETICS AND RECOMMENDED DOSE SCHEDULES

Both terodilane and prenylamine bear an uncanny resemblance in their pharmacokinetics. Therefore, the dose schedules of the two drugs should be scrutinized in the context of wide inter-individual variability, their long elimination half-lives and the potential to accumulate.

Prenylamine is extensively metabolized in man by ring hydroxylation and further methylation of the subsequent phenolic metabolites – its absolute bioavailability is estimated to be 15% (Paar *et al.*, 1990). This metabolism displays wide inter-individual variation, with a terminal elimination half-life of 14.1 ± 6.9 hours. Generally, the steady-state plasma level was reached after 5–7 days, indicating that the terminal half-lives of both the enantiomers of prenylamine were in the region of 24 hours (Gietl *et al.*, 1990). The time to steady-state concentrations may be much longer in those who cannot eliminate the drug effectively (see later). However, when first marketed, the standard recommended dose of prenylamine for the majority of patients was 60 mg three-times daily, which could be increased to 60 mg four- or five-times

daily in those patients who did not respond within 7 days of starting treatment.

Thus, another area of concern in the re-development of terodiline should have been its metabolic disposition and its impact on dosing recommendations. Terodiline is also extensively (85%) metabolized to a phenol, *p*-hydroxy-terodiline, and there is wide inter-individual variation in its metabolism (Karlen *et al.*, 1982; Hallen *et al.*, 1994). Although *p*-hydroxy-terodiline has a profile of pharmacological activity similar to that of racemic terodiline, its potency is low. Even at steady state, this metabolite constitutes only 10%–20% (about 0.05 µg/mL) of the terodiline steady-state plasma level in man. These observations indicate that in man the contribution of this metabolite to the anticholinergic effect observed in clinical studies is minor (Hallen *et al.*, 1990).

Following their studies on the pharmacokinetics of terodiline in nine healthy volunteers who were given (i) 12.5 mg intravenously and orally and (ii) 20 mg intravenously and 25 mg orally, on two different occasions, Karlen *et al.* (1982) had concluded that the long serum half-life of terodiline should permit its once-daily administration. Side effects were often encountered at concentrations exceeding 0.6 µg/mL (Andersson, 1984). The mean half-life of terodiline in the elderly is 131 (range 63–237) hours, in contrast to 57 (range 35–72) hours in young adults (Hallen *et al.*, 1989). Therefore, the corresponding times to steady-state plasma levels would be 7–15 days in young adults but 2–7 weeks in the elderly.

The average steady-state serum concentrations on a 12.5 mg twice-daily dose are 0.238 µg/mL in healthy volunteers, and 0.518 µg/mL in geriatric patients. This concentration in the elderly, the main target population for the use of terodiline, is close to the toxic concentration, and yet the dose recommended for the elderly was 25 mg twice daily.

The similarity to the inappropriate dosing recommendation for prenylamine is self-evident. The dosing recommendations for prenylamine and terodiline have to be seen in the context of their CYP2D6-mediated polymorphic metabolism, and the potential for accumulation in those unable to effectively eliminate the cardiotoxic enantiomers.

When announcing its withdrawal, the marketing authorization holder of terodiline advised prescribers to identify immediately all their patients being treated

with it, and to stop the drug as soon as practicable. They also cautioned prescribers to bear in mind the long half-life of terodiline if alternative anticholinergic treatment was considered, and recommended a washout period that on average would be 2–3 weeks (but in some cases as long as 6 weeks).

PHARMACODYNAMIC SIMILARITY TO PRENYLAMINE

Terodiline also resembles prenylamine in terms of pharmacodynamic activity. Both have complex pharmacodynamic effects that are stereoselective and are active at multiple channels. Some aspects of this similarity had been pointed out as long ago as 1983 (Fleckenstein, 1983).

Although prenylamine has been described as a calcium antagonist, it is not a true calcium channel blocker since it does not act selectively at the membrane-associated, voltage-dependent calcium channels. However, it is a potent inhibitor of calmodulin-dependent enzymes, relaxes smooth muscle and reduces slow inward current. In addition, it depresses peak sodium conductance (Hashimoto *et al.*, 1978; Bayer, Schwarzmaier and Pernice, 1988). Hashimoto *et al.* (1978) have also shown that prenylamine increases action potential duration, indicating that the drug may interfere with the late outward repolarizing current mediated by potassium ions. Thus, in addition to its negative inotropic effect, prenylamine most probably has sodium and potassium channel blocking activities. More recently, prenylamine has been shown conclusively to block the potassium channel that is primarily responsible for cardiac repolarization (Katchman *et al.*, 2006).

With regard to stereoselective pharmacodynamic effects, (+)-(S)-prenylamine has a positive inotropic effect in cat papillary muscle preparations that is particularly evident at low concentrations, and at low stimulation rates (Bayer, Schwartzmaier and Pernice, 1988). The maximum velocity of depolarization is somewhat increased by both (+)-(S)-prenylamine and the racemic mixture at low concentrations. (−)-(R)-prenylamine is associated with a negative inotropic effect and a decrease in the maximum velocity of depolarization. As far as cardiac repolarization is concerned, (+)-(S)-prenylamine prolonged the action

potential duration and induced arrhythmia in 4 of the 12 isolated papillary muscle preparations. In contrast, the (−)-(R)-isomer shortened the action potential duration to a minor extent. This effect was independent of stimulation rates but evident at low concentrations.

Terodilane not only blocks the uptake of calcium, it also blocks the utilization of some intracellular stores of calcium. Pressler *et al.* (1995) have investigated the *in vitro* and *in vivo* electrophysiological effects of terodilane, and have shown that it blocks sodium and calcium channels as well as muscarinic receptors in canine cardiac tissues. Terodilane has been shown to be a non-selective muscarinic receptor antagonist (Noronha-Blob *et al.*, 1991), and therefore its anticholinergic effects on the heart are not altogether surprising. The primary pharmacological activities of terodilane are potent calcium antagonistic and non-selective anticholinergic effects within the same clinical concentration range. Although both activities probably contribute to the therapeutic effect to a variable extent, the anticholinergic effect predominates at low concentrations and the calcium blocking action at high concentrations (Andersson, 1984). In another study in anaesthetized dogs, terodilane (10 mg/kg given intravenously) significantly prolonged the QTc interval by 6%–8%, an effect associated with induction of torsade de pointes (Natsukawa *et al.*, 1998). Like prenylamine, terodilane too has been shown to block the potassium channel responsible for cardiac repolarization (Jones *et al.*, 1998).

The pharmacological activities of terodilane are also enantioselective. The effects of racemic terodilane on isolated detrusor preparations from rabbit and man were compared with those of its (+)-(R)- and (−)-(S)-isomers, and with those of its main metabolite, *p*-hydroxy-terodilane (Andersson, Ekstrom and Mattiasson, 1988). It was concluded that (+)-(R)-terodilane is the main contributor of the detrusor effects of the racemate, and that a component of this activity is anticholinergic in nature. Whereas (+)-(R)-terodilane has been shown to be almost ten times more potent than (−)-(S)-terodilane in its anticholinergic activity, (−)-(S)-terodilane is almost ten times more potent than its antipode as a calcium antagonist (Larsson-Backstrom, Arrhenius and Sagge, 1985; Andersson, Ekstrom and Mattiasson, 1988).

Available data indicate that terodilane in low concentrations has mainly an anticholinergic action

arising from the (+)-(R)-enantiomer, and as the concentration rises, additional calcium antagonistic effects from (−)-(S)-terodilane begin to emerge (Husted *et al.*, 1980). Since *in vitro* data suggest that at high concentrations the metabolism of terodilane is stereoselective favouring the (+)-(R)-enantiomer (Noren *et al.*, 1989), it seems likely that the dominant enantiomer circulating in human plasma at clinical doses of 25 mg is (+)-(R)-terodilane. As discussed below, this has significant implications in terms of the cardiac effects of terodilane.

STEREOSELECTIVITY IN PROARRHYTHMIC POTENTIAL

Stereoselective interactions at receptors and ion channels are well known in the activities of β -blockers and dihydropyridine calcium channel blockers. Similar stereoselective interactions at potassium channels have also been described with enantiomers of drugs such as (+)-(R)-bupivacaine, (+)-(R)-halofantrine and (−)-(4S,6S)-acetylmethadol (levacetylmethadol). As regards their adverse pharmacodynamic effects on the heart, both prenylamine and terodilane display stereoselectivity (Rodenkirchen, Bayer and Mannhold, 1980; Bayer, Schwarzmaier and Pernice, 1988; Hartigan-Go *et al.*, 1996).

Although a number of currents, predominantly mediated by potassium ions, are involved during repolarization, the one almost universally affected by all the drugs (non-cardiovascular and non-antiarrhythmics alike) that prolong the QT interval and induce torsade de pointes is the rapid component of the delayed rectifier potassium channel, known as the I_{Kr} current. At a molecular level, the native I_{Kr} channel is a co-assembly of hERG (human ether-a-go-go related gene) α -subunits and MiRP1 β -subunits. The hERG channel is the target of almost every QT-prolonging drug. Although prenylamine and terodilane have both been shown now to block either the hERG or the I_{Kr} channel (Jones *et al.*, 1998; Katchman *et al.*, 2006), there are no published reports of *in vitro* studies investigating the activity of individual enantiomers of these drugs on either of these targets. Interestingly, however, tolterodine (a structural analogue of terodilane) is marketed as the (+)-(R)-enantiomer, and has

recently been shown in *in vitro* studies to block the hERG cardiac ion channel (Kang *et al.*, 2004).

As discussed earlier, the overall data suggest that the proarrhythmic effect of prenylamine in man is most likely mediated by (+)-(S)-prenylamine, as demonstrated by studies on action potential duration (Bayer, Schawrzmaier and Pernice, 1988). This conclusion must be seen in the context of the observations that although the maximum plasma concentration and AUC of the (+)-(S)-enantiomer are normally 4–5 times lower than those of the (−)-(R)-enantiomer, the reverse may be the case in PMs of CYP2D6, since the data suggest that this CYP isoform most probably mediates the metabolic elimination of (+)-(S)-prenylamine. Due to its longer elimination half-life, (+)-(S)-prenylamine would accumulate in the PMs. Not surprisingly, most patients with prenylamine-induced proarrhythmias were also receiving doses in the lower range of the recommended schedule. A number of drugs such as quinidine only induce torsade de pointes at low concentrations because other electrophysiological effects supervene at higher concentrations. As far as the author is aware, there are no published reports of *in vitro* studies investigating the activity of individual enantiomers of terodiline on action potential duration.

There are no *in vivo* data on stereoselective cardiac effects of prenylamine, or on the concentrations of the two enantiomers in patients during episodes of prenylamine-induced proarrhythmias. However, *in vivo* studies in nine healthy volunteers have shown conclusively that the proarrhythmic potential of terodiline resides exclusively in its (+)-(R)-enantiomer (Hartigan-Go *et al.*, 1996). Peak effects occur 8 hours after dosing, when mean increases in the QTc interval from baseline were −3 ms after the placebo, 23 ms after 200 mg racemic terodiline, 19 ms after 100 mg (+)-(R)-terodiline and 0 ms after 100 mg (−)-(S)-terodiline. Although there were differences in the pharmacokinetics of the two enantiomers, these were not sufficient to account for the differences in ECG effects, and at these high doses, their elimination half-lives were similar. In the two genotypic PMs of CYP2D6, the half-lives of (+)-(R)-terodiline ranked 7th and 8th and those of (−)-(S)-terodiline 4th and 9th in order. It will be recalled, however, that at clinical doses, (+)-(R)-terodiline predominates in the plasma and could accumulate further in PMs of CYP2D6.

LESSONS TO BE LEARNT

The important lessons to be learnt from re-development and withdrawal of terodiline are (a) the benefits of drawing on experiences with other drugs of the same class and (b) the perils of exploiting adverse secondary pharmacological effects to re-target a drug. These lessons are highly relevant to the Safety Specification requirements of ICH E2E, and in addressing important potential risks and outstanding safety questions that warrant further investigations in order to refine an understanding of the risk–benefit profile during the post-approval period. A retrospective analysis of the safety issues associated with other drugs of the same chemical, pharmacological or therapeutic class, and the need to explore these, is the cornerstone of strategic development of other new drugs in the same class. This approach, following clinical experiences with prenylamine and lidoflazine (both antianginal drugs associated with QT interval prolongation and torsade de pointes), would have forewarned of the potential cardiac problems associated with terodiline.

Additionally, there should be a more realistic appreciation of the limitations of clinical trials and the weaknesses of even the more formal studies in identifying post-marketing risks. Since QT interval prolongation and/or torsade de pointes are ECG-based diagnoses, the negative findings from PEM and VAMP studies referred to earlier are not surprising. The databases used for these studies (general practice based) were not appropriate for the identification or quantification of risks that require ECG diagnosis, and not sensitive enough to sample hospital-based diagnoses. It is inconceivable that the risk of QT interval prolongation can be characterized when only 0.8% of the cohort under investigation had an ECG investigation (Hall *et al.*, 1993). Inman *et al.* (1993) acknowledge

In what is likely to be the largest study ever conducted on this drug, we can find no case of cardiovascular collapse which was attributed to the so-called torsade de pointes arrhythmia... It is very unlikely, however, that this abnormality would be encountered in general practice since it would only be identified by ECG.

When torsade de pointes is sustained, its clinical manifestations include dizziness, syncope and convulsions. Following the report by McLeod, Thorogood and Barnett (1991) associating terodilane with torsade de pointes, Veldhuis and Inman (1991) re-examined the PEM database for several possible clinical manifestations of this tachyarrhythmia, and compared their incidences in terodilane-treated patients with corresponding rates in broadly matched nabumetone-treated patients used as controls. Confusion, syncope, cerebrovascular accidents, transient ischaemic attacks and falls and fractures were appreciably more frequent in the terodilane group. Although this *post hoc* analysis was not considered conclusive, these investigators recommended that an ECG should be performed on patients who develop confusion, syncope or cerebrovascular accidents while taking terodilane. Of course, from a regulatory perspective, such *post hoc* analyses of non-specific clinical manifestations of a tachyarrhythmia do not confirm the risk of potentially fatal proarrhythmias, and cannot form the basis of any regulatory actions. This point applies especially in this case, because out of all the events reported in the cohort, only 51 were suspected to be adverse reactions causally related to terodilane, and these included only 2 cases of dizziness (a non-specific symptom that may be associated with torsade de pointes).

The problem with the PEM and the VAMP studies was that neither had included a large enough sample of patients with ECG monitoring. Even when a drug is known to prolong the QT interval, it requires large prospectively designed hospital-based studies to uncover the proarrhythmic risk. A particularly good example of such a study is the SWORD study. Although the drug under investigation was (+)-(S)-sotalol, a known potent torsadogen, it required recruitment of as many as 3121 of the planned 6400 patients before it was terminated prematurely (Waldo *et al.*, 1996). The mortality (presumed to be due to arrhythmias) was 5% in the (+)-(S)-sotalol group and 3.1% in the placebo group – an increase of 65% in mortality following the active treatment. Even in this study, the dose of (+)-(S)-sotalol was carefully titrated against QTc interval, and patients were closely monitored during the first few weeks for excessive (and therefore proarrhythmic) prolongation of the QTc interval, and those with duration greater than 560 ms during this period were excluded. Even if the background

frequency of torsade de pointes is zero, it would require approximately 15 000 patients to identify a risk of an event with a frequency of 0.03% at the 99% confidence level, despite assuming that the database is sensitive enough in terms of the population and the adverse reaction to be studied. In contrast, the strength of spontaneous reporting systems in identifying a serious clinical risk that requires hospital-based resources has been demonstrated repeatedly, and almost all major regulatory actions in managing the clinical safety of drugs, or averting major risks to public health, have followed ‘signals’ from spontaneous reporting systems (Clarke, Deeks and Shakir, 2006; Olivier and Montastruc, 2006).

WHY THE REGULATORY CONCERNS ON DRUG-INDUCED QT INTERVAL PROLONGATION?

The QT interval on the ECG, measured from the beginning of the Q wave to the end of the T wave, represents the interval from the beginning of depolarization to the end of repolarization of the ventricular myocardium. Prolongation of QT interval is most frequently associated with prolonged repolarization following administration of class III antiarrhythmic drugs. This class of antiarrhythmic drugs is intended to act by blocking the repolarizing current mediated by potassium channels and produce their desired therapeutic effect by a moderate and controlled prolongation of ventricular repolarization, and therefore an increase in the myocardial refractory period.

However, excessive prolongation of ventricular repolarization, and therefore of the QT interval, can be proarrhythmic and degenerate into torsade de pointes, a ventricular tachyarrhythmia with a unique twisting morphology on the ECG. It is usually transient and self-terminating, lasting only a few seconds, and therefore is often asymptomatic. When sustained, however, the clinical manifestations of torsade de pointes include palpitation, syncope, blackouts, dizziness and/or seizures. Torsade de pointes can subsequently degenerate into ventricular fibrillation in about 20% of cases (Salle *et al.*, 1985) and, not uncommonly, cardiac arrest and sudden death may be the outcome. The overall mortality associated with torsade de pointes is of the order of 10–17% (Salle

et al., 1985; Fung *et al.*, 2000). Clearly, the balance between the therapeutic antiarrhythmic and the potentially fatal proarrhythmic prolongation of QT interval is a very delicate one, and depends not only on the drug concerned and its plasma concentration, but also on a number of host factors. These include electrolyte imbalance (especially hypokalaemia), bradycardia, cardiac disease and pre-existing prolongation of QT interval. Females are at a greater risk, and the risk is further enhanced during the menstrual period.

Unfortunately, however, a number of non-antiarrhythmic drugs are found to possess this class III electrophysiological activity as part of their secondary (undesirable in this instance) pharmacological properties. The number of drugs with 'QT-liability', and by inference a potential to induce torsade de pointes, continues to increase inexorably (Shah, 2002). The clinical and public health concerns on the potential of non-cardiac drugs to prolong QT interval and induce torsade de pointes have been eloquently summarized in an editorial (Priori, 1998). Concerns have legitimately been expressed that:

Almost every week a new agent is added to the list of drugs associated with acquired long QT syndrome (LQTS) and torsades de pointes (TdP). Despite this impressive number of reports, the awareness of this subject is still limited among medical professionals and . . .

It is likely that prevention of drug-induced TdP will never be fully successful, because it is a moving target. A patient may not be at risk when therapy is initiated, and may become at risk 5 days later because

It is intuitive that when two or more agents sharing potassium-channel-blocking activity are simultaneously administered, the risk of excessive prolongation of repolarisation is substantially increased.

The exclusion of potassium-channel-blocking properties might be considered in the future as a requirement before new molecules are approved for marketing, and more strict warnings in the package insert of drugs with known repolarisation prolonging activity could be enforced.

Apart from the number of drug classes implicated, additional concerns arise from the size of the population at risk. The expression of I_{Kr} and other potassium channels is under the control of genes that are

known to carry mutations responsible for expression of channels with diminished or dysfunctional capacity – the so-called 'diminished cardiac repolarization reserve'. I_{Kr} channels with mutations of the hERG α -subunit (encoded by the *KCNH2* gene located on chromosome 7) or the MiRP1 β -subunit (encoded by the *KCNE2* gene located on chromosome 21) very frequently conduct a repolarizing current of smaller amplitude, and in consequence the repolarization process is delayed in individuals carrying these mutations (giving rise to congenital long QT syndromes of types 2 and 6 respectively). The most familiar clinical phenotypes of patients with potassium channel mutations are the Romano–Ward or Jervell–Lange–Neilsen syndromes, with ECG evidence of QT interval prolongation, and the propensity to develop potentially fatal cardiac arrhythmias including torsade de pointes.

However, there is now abundant evidence that in view of the low penetration of many of the mutations of potassium channel genes, the size of the population carrying these mutations may be substantially larger than that diagnosed by ECG evidence of a prolonged QT interval. Relatively large numbers of individuals who carry these 'silent' mutations of long QT syndrome genes have been identified, and despite a diminished repolarization reserve, they have a normal ECG phenotype (Priori, Napolitano and Schwartz, 1999). Nevertheless, because of the compromised repolarization reserve, they are at a greater risk of cardiac arrhythmias following administration of QT-prolonging drugs, even at doses that are clinically safe in non-carriers (Yang *et al.*, 2002; Paulussen *et al.*, 2004; Shah, 2004). It has been postulated that drug-induced long QT syndrome might represent a 'forme fruste' of the long QT syndrome.

It may be speculated whether some of the 12 patients with terodiline-induced proarrhythmias referred to earlier, and in whom there were no obvious risk factors, might be carriers of potassium channel mutations (clinically silent congenital long QT syndrome with a normal ECG phenotype). Genetic factors may also operate remotely through other mechanisms. For example, cardiac failure is the end result of many genetically (and non-genetically) determined cardiac diseases. Cardiac failure is typically associated with down-regulation of potassium channels (Tomaselli and Zipes, 2004), and this will also increase the susceptibility of these

patients to QT interval prolongation and proarrhythmias. It is interesting to note that despite urinary incontinence, 27 of the 69 patients with terodilane-induced proarrhythmias discussed earlier were receiving diuretics, and 33 were in receipt of other cardioactive medications. Hypokalaemia induced by the diuretics, or electrophysiological activities of the cardioactive medications, further potentiate the pharmacodynamic susceptibility of the patients concerned. In addition, patients with a wide range of non-cardiac diseases have a pre-existing prolongation of QT interval, and therefore have an increased susceptibility to torsade de pointes by QT-prolonging drugs. These conditions include those associated with autonomic failure (as in diabetes or Parkinson's disease), hypoglycaemia, cirrhosis and infection with human immunodeficiency virus.

ELECTROPHYSIOLOGICAL BASIS OF TORSADE DE POINTES

Prolonged ventricular repolarization and subsequent QT interval prolongation result most frequently from a reduction in outward repolarizing potassium current. However, in rare instances, these could also result from enhanced or sustained depolarizing inward sodium or calcium currents (Figure 10.3).

Two hypotheses have been proposed to explain the electrophysiologic mechanisms underlying the induction of torsade de pointes (Surawicz, 1989).

One hypothesis postulates a trigger mechanism, while the other has re-entry as its basis. However, it now appears that the two hypotheses are not mutually exclusive, but may in fact be complementary (Figure 10.4) (Antzelevitch, 2004).

Against a background of prolonged QT interval, the presence of a slow heart rate gives rise to early after-depolarizations (EADs), mediated by slow inward calcium current during the late phase 2 of the action potential. The amplitude of these EADs is cycle length dependent, with a strong correlation between the preceding RR interval and the amplitude of EAD that follows. When these EADs reach a critical threshold, they trigger an ectopic beat that initiates torsade de pointes (Figure 10.4).

A ventricular cell subtype designated the M-cell, which is found in the deep sub-epicardial to mid-myocardial layers, is very sensitive to the effects of I_{Kr} blockers. These cells, also found in human ventricles, have electrophysiological properties that are different from those of epicardial or endocardial ventricular cells, and intermediate between those of the ventricular muscle and the Purkinje fibres. Relative to the epicardial and endocardial myocytes, these M-cells are characterized by (i) the weak presence of the slowly activating component of the repolarizing potassium current (I_{Ks}) and (ii) the presence of the more sustained depolarizing slow sodium (I_{Na}) and calcium (I_{Ca}) currents. Another hallmark of these M-cells is the ability of their action potential to lengthen markedly with decreasing stimulation rate.

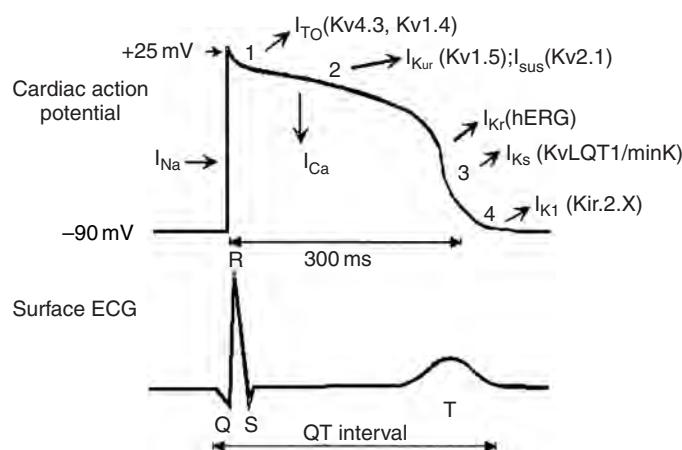


Figure 10.3. Cardiac action potential, ion currents and QT interval on surface ECG.

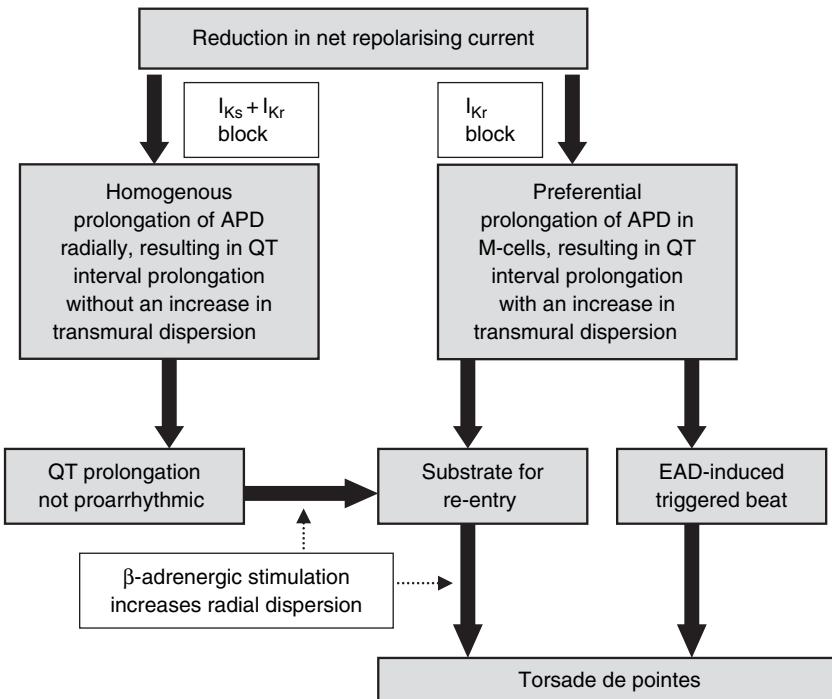


Figure 10.4. Mechanisms involved in torsadogenesis.

Since the repolarizing I_{Ks} is weak, these M-cells rely almost exclusively on the presence of fully functional I_{Kr} for repolarization. All these differences render the M-cells more susceptible to the effects of I_{Kr} block, which thereby respond with a more prolonged action potential and induction of EADs. Not surprisingly, I_{Kr} blockers have profound effect in these cells, giving rise not only to prolongation of the QT interval on the surface ECG, but also to an increase in transmural dispersion of repolarization (radially) across the myocardial wall at tissue level. An increase in transmural dispersion of repolarization creates an electrophysiological environment, or gradient, for the development of re-entry (Figure 10.4). This radial dispersion of repolarization, rather than QT interval prolongation, is now widely regarded as both the proarrhythmic substrate and a more predictive and reliable marker of the proarrhythmic risk (Fenichel *et al.*, 2004; Antzelevitch, 2005).

As a corollary, drugs that block both I_{Kr} and I_{Ks} (and other relevant ion channels and receptors) may be expected to uniformly prolong the action potential across the entire thickness of the ventricular wall

(and therefore, the QT interval), without having any significant effect on transmural dispersion of repolarization. Although these agents (e.g. amiodarone and the recently developed antianginal drug ranolazine) prolong the QT interval, they have not been found to be proarrhythmic.

DRUG-INDUCED QT INTERVAL PROLONGATION AND REGULATORY GUIDANCE

In view of the numerous high-profile, non-antiarrhythmic drugs which attracted considerable regulatory attention during the period 1990–96 due to their potential to prolong the QT interval and induce torsade de pointes, the *Committee for Proprietary Medicinal Products* (CPMP) adopted two significant documents in December 1997. One of these was the CPMP document ‘Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products’ (Anon, 1997a). The recommendations contained therein were

not mandatory, but they represented preclinical and clinical strategies that the EU regulators advocated for the investigation of any new chemical entity (NCE) for its capability to prolong the QT interval and induce proarrhythmia. Following the regulatory concerns and the CPMP document, the European Society of Cardiology organized a Policy Conference on drug-induced QT interval prolongation under the auspices of its Committee for Scientific and Clinical Initiatives. This conference endorsed a more rigorous investigation of the preclinical electrophysiologic and clinical electrocardiographic effects of new drugs (Haverkamp *et al.*, 2000). A similar Expert Meeting in the United States, sponsored by the Duke Clinical Research Institute and American Heart Journal, also advocated a proactive approach to identifying this important risk (Anderson *et al.*, 2002).

A number of drugs such as terfenadine, astemizole, pimozide and cisapride were found to induce torsade de pointes and other proarrhythmias following drug interactions. Therefore, the other strategic document adopted by the CPMP was its 'Note for Guidance on the Investigation of Drug Interactions' (Anon, 1997b).

Such is the regulatory concern on drug-induced QT interval prolongation that there has now evolved two internationally harmonized regulatory guidelines on strategies by which to evaluate new drugs for this liability. In May 2005, the ICH adopted two guidelines that deal with this safety concern – one dealing with preclinical strategy (ICH S7B) and the other dealing with clinical strategy (ICH E14). While the focus of ICH S7B is on detecting delayed ventricular repolarization and QT interval prolongation, ICH E14 focusses on detecting QT/QTc interval prolongation. At the time of writing this chapter, the Committee for Medicinal Products for Human Use (CHMP) of the EU had adopted (Step 5 of ICH) these guidelines (ICH E14 as CHMP/ICH/2/04 and ICH S7B as CHMP/ICH/423/02) during their meeting in May 2005, with an operational implementation date of November 2005 (Anon, 2005a,b). Both the US Food and Drug Administration and the Japanese Ministry of Health, Labour and Welfare will notify later the dates for implementation of these guidelines within their jurisdictions. Both ICH S7B (preclinical) and ICH E14 (clinical) provide state-of-the-art recommendations on strategies for investigating a new drug

for its potential to delay ventricular repolarization and induce QT interval prolongation.

Both the CPMP document 'Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products' and the ICH guideline S7B provide recommendations on preclinical strategies by which to investigate a drug for its QT-liability. The core studies recommended by the ICH S7B guideline are *in vitro* I_{Kr} or hERG channel studies, and *in vivo* investigations in dog or other laboratory animals such as monkey, swine, rabbit, ferret and guinea pig.

Both the CPMP document 'Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-cardiovascular Medicinal Products' and the ICH guideline E14 also provide recommendations on clinical strategies by which to investigate a drug for its potential to prolong the QT interval. Of special current interest is the call by ICH E14 for a single clinical trial, termed the 'thorough QT/QTc study', specifically dedicated to investigating the effect of an NCE on ECG parameters, with a special focus on QT interval (Anon, 2005b). This clinical guideline raises a number of important issues and will present significant challenges during drug development.

The conduct of the 'thorough QT/QTc study', typically in healthy volunteers, requires prior knowledge of the full pharmacology of the drug, as well as its potential therapeutic doses in man. Unfortunately, even today, the CYP isoform(s) responsible for the metabolism of terodilane has not been adequately identified, and the role of CYP2D6-mediated genetic factors remains a matter of informed speculation. It is also obvious that the pharmacokinetics and pharmacodynamics of each individual enantiomer of chirally active drugs should be fully investigated. Despite the known stereoselectivity in primary pharmacodynamics of terodilane enantiomers, little was investigated with respect to their cardiac effects, most particularly their electrophysiological effects at ion channels, and yet the techniques were available at the outset. In the absence of these vital data, it is impossible to predict special patient populations at risk, and the hazards from potential drug interactions. It is ironic that terodilane should have been withdrawn from the market in the year in which the CPMP adopted its guideline on 'Clinical Investigation

of Chiral Active Substances' (Anon, 1993b; Shah, Midgley and Branch, 1998).

PRECLINICAL INVESTIGATIONS OF THE 'QT-LIABILITY' OF A DRUG

Since the discovery of the hERG channel in 1994, sponsors conduct *in vitro* studies (unicellular preparations as well as recombinant hERG channels expressed in heterologous systems) to evaluate all new chemical entities (NCE) for their potential to inhibit the current mediated by the native cardiac I_{Kr} channel. Indeed, early use of hERG channel studies as a screening test is now routine. As long as the results are interpreted carefully with regard to safety margins and other properties of the drug, these studies are valuable in identifying drugs with a potential to prolong the QT interval and hence probably induce torsade de pointes (Shah, 2005a). Drugs known to be torsadogenic in man have always been shown to be positive in these assays. False positive hERG studies are relatively frequent. Rarely, a false negative result may arise if the drug concerned prolongs repolarization not by inhibiting hERG, but by interfering with normal trafficking of this channel protein (e.g. arsenic trioxide or pentamidine) (Ficker *et al.*, 2004; Katchman *et al.*, 2006; Kuryshev *et al.*, 2005).

Unicellular recordings of action potentials from ventricular tissues, myocytes or Purkinje fibres are also used to evaluate the effect of drugs on action potential duration and therefore the QT interval. Arising from the qualitative and quantitative distribution of various ion channels, M-cells seem to have a better predictive value than do other tissues. From one set of *in vitro* investigations, it is possible to obtain a broad range of clinically useful information. The species used for these tissue experiments could be guinea pig, rabbit or dog, depending on laboratory skills and database. The relevance of the selected species and tissue to man is perhaps the most important determinant of how useful the information obtained from these studies will be with regard to the risk posed by the drug to humans.

In addition to the above *in vitro* investigations, studies are also performed *in vivo* using dogs or other suitable species, and a number of proarrhythmic models have been developed over the last few years.

Preclinical investigations of drugs for their potential to delay ventricular repolarization and prolong the QT interval are now very sophisticated, and have a remarkable predictive value with regard to clinical risk of torsade de pointes (Fenichel *et al.*, 2004; Joshi *et al.*, 2004; Shryock *et al.*, 2004; Recanatini *et al.*, 2005; Sanguinetti and Mitcheson, 2005).

More recent focus of preclinical studies is to document the predictive value of transmural dispersion in repolarization and TRiAD (triangulation, reverse use dependency, instability and dispersion), rather than QT interval prolongation alone. HERG blockade still remains the basic mechanism underlying these relatively new markers (Antzelevitch, 2004; Shah and Hondeghem, 2005). Efforts are also underway to evaluate the predictive value of beat-to-beat variations in the morphology and amplitude of T-waves, which may potentially serve as indicators of delayed repolarization and electrophysiological instability.

Of the drugs listed earlier in the Introduction, studies with hERG channels would have successfully predicted the proarrhythmic activities of pimozide, sertindole, astemizole, terfenadine, cisapride, halofantrine, thioridazine, droperidol and levacetylmethadol. Studies using hERG channels have also been used to characterize the relative QT-prolonging potencies of various members of a chemical or pharmacological class, such as quinolone antibacterial agents or gastric prokinetic drugs.

Recent *in vitro* studies have confirmed that terodilane blocks the I_{Kr} current – the molecular substrate for prolongation of the QT interval. Whereas the therapeutic concentrations of terodilane are in the range of $1.5\text{ }\mu\text{M}$, its IC_{50} value for I_{Kr} block was found to be $0.7\text{ }\mu\text{M}$ (Jones *et al.*, 1998). In guinea pig papillary muscles and ventricular myocytes, clinically relevant concentrations of terodilane lengthened the action potential duration by up to 12%, while higher concentrations shortened the duration in a concentration-dependent manner. Further voltage-clamp studies in guinea pig ventricular preparations indicate that terodilane at much higher concentrations also inhibits two other membrane currents that govern repolarization: (i) an L-type calcium current (IC_{50} value of $12\text{ }\mu\text{M}$) and (ii) a slowly activating, delayed rectifier potassium current (I_{Ks}) with an IC_{50} value of $26\text{ }\mu\text{M}$ (Shuba *et al.*, 1999). Fossa *et al.* (2002) tested cisapride and terodilane in conscious

dogs at their clinically relevant free drug concentrations. Using a sophisticated beat-to-beat QT-RR interval assessment, they were able to demonstrate the QT-prolonging effects of both these drugs. The dose-response curve for both was bell-shaped. For terodilane, the greatest mean QT prolongation occurred at a free drug concentration of $0.0329\text{ }\mu\text{M}$, with concentrations higher than this being less active in this regard. This is interesting in view of the stereoselective concentration-dependent pharmacodynamic properties of terodilane discussed earlier. Fossa *et al.* (2002) were also able to show that for drugs that affect repolarization through multiple channels, the effect on the mean QT interval may be more difficult to detect, but individual responses to the QT-RR interval relationship increased the sensitivity for more accurate clinical prediction.

PRE-APPROVAL CLINICAL SAFETY DATASET

The extent of the dataset required in terms of ECG monitoring in subsequent clinical studies will depend on a variety of factors, particularly the results from S7B-compliant preclinical studies and the ‘thorough QT/QTc study’ (Shah, 2005b).

The ICH E1A guideline (‘The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-term Treatment of Non-life Threatening Conditions’) (Anon, 1995) is helpful when considering the clinical safety dataset necessary for regulatory submissions when exploring the potential of an NCE indicated for a long-term treatment of non-life threatening conditions, and for hazards associated with other drugs of the same chemical, pharmacological and/or therapeutic classes. For the most usual case, that is frequent and early onset (these are generally concentration-related) events, this guideline (adopted in 1995) provides for 1500 patients to be studied over 3 months. It is estimated that this database will characterize an adverse event with a cumulative 3-month incidence of about 1% or more. Whereas prolongation of the QT interval may be observed in some patients in the dataset, it is most unlikely that any episodes of torsade de pointes (induced by a non-antiarrhythmic drug) will be identified, since the latter is often transient, requires an ECG machine for diagnosis and

usually has a frequency in the order of 1 in 10 000 or much less.

EXCEPTIONAL CIRCUMSTANCES REQUIRING EXTENDED DATABASE

The ICH E1A guideline recognizes that a larger database and/or a longer period of exposure than usual may also be required in some circumstances. To this end, it provides for exceptional circumstances when the harmonized general standards for clinical safety evaluation may not be applicable and an expanded database may be required. These exceptions cover a diverse range of circumstances, and can best be discussed using drug-induced QT interval prolongation/torsade de pointes as an example. The approach is equally applicable to other rare but serious adverse effects, such as clinical hepatotoxicity, gastro-intestinal haemorrhage, neutropenia and so on. Although there are a number of exceptional circumstances specified in the guideline, six are particularly relevant to most NCEs.

CHEMICAL STRUCTURE

Without doubt, any drug that shares a structural similarity with prenylamine is a candidate for an expanded clinical safety dataset, in order to better assess its potential to prolong the QT interval. Not surprisingly, terodilane, terfenadine, cisapride and pimozide all bear an obvious structural similarity to prenylamine, and would have called for an expanded clinical dataset to characterize their potential for QT interval prolongation and torsade de pointes. With regard to QT interval prolongation, many chemical classes have been implicated (Shah 2002; Aptula and Cronin, 2004; Aronov, 2005; Recanatini *et al.*, 2005), and therefore a wide range of NCEs would require an expanded clinical dataset.

PHARMACODYNAMIC/PHARMACOKINETIC PROPERTIES KNOWN TO BE ASSOCIATED WITH SUCH ADVERSE EVENTS

When an investigational drug is found in preclinical studies to block I_{Kr} or hERG channel and/or prolong the action potential, ICH E14 recommends

that the clinical safety dataset focussing on ECG effects needs to be expanded, regardless of a negative ‘thorough QT/QTc study’ if the preclinical/clinical discrepancy cannot be explained. References have already been made to pharmacodynamic and pharmacokinetic similarities between terodiline and prenylamine. In retrospective preclinical studies conducted post-approval, prenylamine, terodiline, terfenadine, astemizole, pimozide, halofantrine, cisapride and levacetylmethadol have all been found to possess QT-prolonging properties, and would have called for an expanded clinical dataset had these studies been conducted prior to their approval. Focussed clinical studies with terodiline, albeit following its removal from the market, and other drugs confirmed that they had the potential to prolong the QT interval in man.

DATA FROM ANIMAL STUDIES

In compliance of the ICH E14 guideline, the clinical safety dataset needs to be expanded if ICH S7B-compliant *in vivo* studies are strongly positive, regardless of the status of the ‘thorough QT/QTc study’. The requirements for preclinical investigations at the time of developing prenylamine were rudimentary. Information on findings from animal studies with prenylamine is now difficult to obtain. Although original preclinical studies with terodiline showed no effect on the QT interval in conscious dog or rat, ECG effects (including prolongation of the QT interval) were reported in anaesthetized cats. This finding in itself would have warranted further preclinical studies and an extended clinical safety database. Webster *et al.* (2001) have recently shown that terodiline does induce QT prolongation in dogs and emphasized that for compounds known to be clinical torsadogens (terfenadine, terodiline, cisapride), there is little differentiation between the QT-prolonging and the clinically effective free plasma concentrations in man (<10-fold). This is reflective of their limited safety margins.

OTHER AGENTS OF THE SAME PHARMACOLOGICAL CLASS

A range of ICH guidelines (ICH E1A, ICH E2E, ICH S7B and ICH E14) emphasize the need to take

into account the pharmacological activities associated with other members of the same chemical or pharmacological class as the NCE under investigation. Therefore, this particular scenario requires that the safety database be expanded to exclude any class-related risks. Apart from prenylamine and lidoflazine, a number of other antianginal drugs such as bepridil, tedisamil, fendiline and aprindine have all been shown to prolong the QT interval and induce proarrhythmias. Therefore, during their clinical development, terodiline as well as any other antianginal drug would call for an expanded clinical safety database, for routinely evaluating their potential to prolong the QT interval. This is analogous to all non-steroidal anti-inflammatory drugs (NSAIDs) being evaluated for their gastro-intestinal toxicity. With regard to QT interval prolongation, many pharmacological classes have been implicated (Shah, 2002; Aptula and Cronin, 2004; Anson *et al.*, 2005; Aronov, 2005; Recanatini *et al.*, 2005), and therefore, again as stated above, a wide range of NCEs would require an expanded clinical dataset.

When discussing the ‘pharmacological class’ of a drug, the notion of its ‘therapeutic class’ deserves a comment. Following structural modifications of a lead compound or following the approval of a drug, it is often discovered to have more potent activity at a pharmacological target other than that intended originally. Therefore, drugs are often intended for development in one specific therapeutic area but are later developed or used clinically in an entirely different therapeutic area. Thus, drugs frequently cross ‘therapeutic boundaries’ (Shah, 2002). Therefore, lack of a safety concern in drugs of a therapeutic class is not altogether wholly reassuring when developing another drug in the same therapeutic class – what really matters is the chemical or the pharmacological class. Terodiline itself was re-developed for use in a completely different therapeutic area (urinary incontinence) that was not associated with any proarrhythmic risk. Terfenadine is another typical example. It was discovered through a central nervous system programme aimed at synthesizing new antipsychotic agents, but because of its more potent secondary pharmacological effects at the H₁-antihistamine receptor, its development was diverted to market it as the first non-sedating H₁-antihistamine. However, like other antipsychotic agents, it was sooner or later bound to

attract regulatory attention because of the potential of antipsychotics-related chemical structures to have an effect on the QT interval. As an antihistamine, terfenadine remained a highly successful and popular drug until withdrawn, due to reports of torsade de pointes resulting from drug interactions. Sildenafil, originally intended for development as an antianginal drug, was developed instead for male erectile dysfunction, and it is not surprising that at high concentrations, it too has been shown to prolong cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current (Geelen *et al.*, 2000). At clinical doses, however, a significant effect on QT interval is most unlikely (Morganroth *et al.*, 2004), especially since the drug is used intermittently. However, its further development for use in pulmonary hypertension may present interesting dilemmas (Shah, 2005b).

NEED TO QUANTIFY LOW FREQUENCY EVENTS

Depending on whether a drug is a class III antiarrhythmic drug or not, the frequency of QT interval prolongation and/or torsade de pointes can vary widely. For a number of antianginal or non-cardiac drugs, these are low frequency events associated with their use. It is therefore self-evident that an expanded clinical safety database would be required for a new antianginal drug. The size of the database would be determined by the preclinical data and the anticipated frequency of the event to be detected, as well as the confidence with which the risk is to be excluded. Since the risk of torsade de pointes is often as low as 1 in 10 000 or even lower, requirements for very large databases can be counter-productive to the extent that they delay the introduction of otherwise beneficial medicines to the market.

ALERTS/SIGNALS DURING CLINICAL TRIALS

A dataset that is larger and/or of longer exposure may also be appropriate when a specific serious adverse event that represents an alert is observed unexpectedly in early clinical trials. When the potency of an NCE to delay ventricular repolarization is high, signals are often detected during early clinical trials, frequently pharmacology studies in healthy volunteers

or early dose-ranging studies in patients. Pimozide, for example, was found to prolong the QT interval in about 10% of the patients in one study in 1989. Similarly, halofantrine was also found to produce an effect on the QT interval during early clinical trials. This is especially important when an event is a 'moving target' depending on the presence of other risk factors, such as drug interactions or other intercurrent events.

As it was, the clinical trials database on terodilane was comparable with those for other contemporary drugs intended for urinary incontinence. In retrospect, however, it was not large enough for a drug with its chemical and pharmacological pedigree. It had included 8 controlled ($n = 229$) and 6 uncontrolled ($n = 147$) studies with a total population of 376 patients exposed to terodilane. Of these, 241 had received the drug for up to 1 month, and a further 39 for 2–3 months. Seventy-five patients had been treated for 4–12 months. In the aftermath of its withdrawal, a number of studies investigated the ECG effects of terodilane. Apart from the study by Thomas *et al.* (1995) referred to earlier, other studies have shown that adequate ECG monitoring of the patients during clinical trials ought to have identified the proarrhythmic risk. In the study by Yoshihara *et al.* (1992) in 109 Japanese patients receiving 24 mg daily of terodilane for 4 weeks, side effects such as orthostatic hypotension and arrhythmia were observed, and these symptoms disappeared following discontinuation of the treatment. Of note is the prospective study by Stewart *et al.* (1992) in 8 elderly in-patients treated with terodilane for urinary incontinence. They found that after 7 days of treatment with 12.5 mg twice daily, terodilane significantly increased the QT interval by a mean of 29 ms and the QTc interval by 15 ms and decreased the resting heart rate by a mean of 6.7 beats per minute.

As a result of experiences with some of the established as well as newly introduced drugs, clinical trials programmes now usually include ECG monitoring in at least one or two large studies, particularly those investigating high doses or studying the effect of inhibition of drug elimination (e.g. drug interaction studies). Depending on the ECG findings from these 'exploratory' studies, the database may require expansion to address the proarrhythmic risk more fully.

RISK–BENEFIT ASSESSMENT

Despite the fact that QT interval is not a very reliable surrogate of torsade de pointes, it is nevertheless true that drugs that prolong QT interval are considered more likely to cause torsade de pointes in susceptible patients than drugs that do not. Therefore, QT interval prolongation has been used in distinguishing safer drugs from those that are less safe within the same class. Not surprisingly, regulatory authorities are reluctant to approve drugs that prolong the QT interval when the potential benefits are very modest, and especially when alternatives without the QT-liability are already available. For example, ebastine (a non-sedating H₁-antihistamine) has not been approved in the United States because of its ability to prolong the QT interval, although there are no documented reports of torsade de pointes associated with its extensive use elsewhere. The reason is almost certainly the availability of alternatives without such a liability. However, it should not be assumed that just because a drug prolongs the QT interval, it might not be approvable.

A number of factors determine whether drugs that prolong the QT interval can be approved, particularly because the QT-liability of a drug does not necessarily translate into a proarrhythmic activity (Shah, 2002; 2004). In contrast to ebastine, drugs such as ziprasidone or arsenic trioxide that prolong the QT interval to a much greater extent have nevertheless been approved, because they were considered to have an acceptable risk–benefit profile. Arsenic trioxide illustrates particularly well how even a drug with very marked potential to prolong the QT interval, and actually induce torsade de pointes, may be approved with specific guidelines associated with its clinical use, if it is shown to fulfil an unmet need. Arsenic trioxide ('Trisenox') was approved in September 2000 in the United States and in October 2001 in the EU for its remarkable efficacy in induction of remission and consolidation in patients with a specific form of acute promyelocytic leukaemia who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy. Protease inhibitors are another class of drugs that block hERG, prolong the QT interval and induce torsade de pointes (Anson *et al.*, 2005). However, their clinical benefits far outweigh their very small proarrhythmic risk.

With respect to risk–benefit analysis of a drug that actually induces torsade de pointes and other ventricular tachyarrhythmias, the benefit offered by the new drug merits very careful assessment. Furthermore, the risk of torsade de pointes is not an 'all-or-none' effect. Depending on the benefit offered by the drug, an incidence of 1 in 3000 might be unacceptable whereas an incidence of 1 in 500 000 may be considered acceptable with a whole range of risk–benefit in between. As stated earlier, risk–benefit analysis in drug development and the regulatory approval process includes not only the alternatives already available, but also the seriousness of the condition under treatment. For relatively benign indications such as hay fever or gastroparesis, a risk of proarrhythmias even as low as 1 in 100 000 recipients is unlikely to be acceptable.

DEVELOPMENT OF SINGLE ENANTIOMERS OR METABOLITES OF MARKETED RACEMIC DRUGS

The comparison between prenylamine and terodiline described in this chapter shows the strengths of a scientific synthesis of all the available information when evaluating the significance of even a handful of spontaneous reports of an adverse event, and formulating the most appropriate regulatory strategies for risk management. This is especially relevant when another member of the same chemical, pharmacologic or therapeutic class is associated with the same low frequency adverse event.

The marketing authorization holder of terodiline has to be commended for the speed and the willingness with which the drug was withdrawn as soon as it became evident that the risk is unlikely to be immediately manageable. Unfortunately, they did not follow up the recommendation from the regulatory assessor to investigate separately the two enantiomers systematically for their pharmacology, and possibly develop one of these if it can be shown to be devoid of potassium-channel-blocking activity while retaining a beneficial therapeutic effect. In the light of subsequent investigations showing that (−)-(S)-terodiline does not affect the QTc interval (Hartigan-Go *et al.*, 1996) and does indeed have some anticholinergic properties, the possibility that (−)-(S)-terodiline might have

a much superior risk–benefit profile compared to the racemic mixture is a real one. At the time of its withdrawal in 1991, the development of a single enantiomer may have appeared an arduous and potentially unrewarding activity, but paradoxically this has been one of the striking features of new drug development in the period 1994–2002. This trend has resulted in the development of (S)-ketoprofen, (S)-ofloxacin, (S)-omeprazole, (R)-salbutamol, (S)-citalopram and (S)-ketamine among many others that are still in the pipeline (Shah, 2000).

It is interesting that astemizole has two metabolites – desmethylastemizole and norastemizole. Preclinical data show that desmethylastemizole is as cardiotoxic as the parent drug. Since desmethylastemizole has a very long half-life relative to astemizole, plasma levels of desmethylastemizole are generally about 30-fold higher than that of astemizole, and the clinically observed cardiotoxicity appears to be mainly due to desmethylastemizole. In one patient with astemizole-induced torsade de pointes, plasma desmethylastemizole and astemizole concentrations were 7.7–17.3 ng/mL and < 0.5 ng/mL, respectively (Volperian *et al.*, 1996). Not surprisingly, cardiotoxicity of astemizole is the highest following an overdose, or when a high loading dose is administered to quickly achieve the steady-state therapeutic concentrations (Anon, 1987). In both these situations, there is rapid accumulation of desmethylastemizole. Findings such as these not only preclude the development of some metabolites, but also illustrate the strengths of simple observations that should guide the drug development programme and evaluation of post-marketing case reports of adverse drug reactions.

Development of active but safer metabolites which are devoid of the unwanted secondary cardiotoxic pharmacology, or unwanted metabolic profile and drug interaction potential, has been another trend in drug development (Shah, 2005a). Preclinical data have suggested that the risk–benefit ratio might be superior for the metabolite compared to the corresponding parent drug for fexofenadine (a metabolite of terfenadine), norcisapride (a metabolite of cisapride), norastemizole (a metabolite of astemizole), desmethylloratadine (a metabolite of loratadine) or norlevacetylmethadol (a metabolite of levacetylmethadol). These preclinical leads have already been followed up for some of these metabolites, and fexofe-

nadine and desmethylloratadine are now already on the market.

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11

Nomifensine and Haemolytic Anaemia

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INTRODUCTION

Nomifensine was introduced by Hoechst AG into clinical practice in West Germany in 1976 and into the United Kingdom the following year. It was thought to have the advantages over older tricyclic antidepressants of causing less sedative, anti-cholinergic, cardiac and epileptogenic effects. The drug was withdrawn almost a decade later in January 1986 because of the occurrence during treatment of acute immune haemolytic anaemia associated with serious clinical sequelae. In the United Kingdom, these included three fatalities, occurring in 1985.

This chapter discusses the response of the company to a drug alert in the post-marketing phase. With the benefit of hindsight several years later, this might seem a relatively straightforward task; it was a clear-cut case of increased recognition of a potentially life-threatening type B adverse reaction, acute immune haemolytic anaemia. Although reported in small numbers, the unpredictability and speed of onset of the reaction precluded advice to doctors on early diagnosis and treatment. It was this, as much as the distressing condition and the consequences of medical and surgical intervention (including exploratory

laparotomies), that prompted the manufacturer to withdraw the product in the interests of patient safety.

Until the company made its announcement on 22 January 1986 in full consultation with the regulatory authorities, there had been no suggestion in the medical literature, the general or medical press or any other media that the drug should be withdrawn from use. Whilst the product withdrawal was co-ordinated worldwide, this account of the events leading up to the withdrawal relates only to the situation in the United Kingdom (Stonier, 1992).

Over the years since the withdrawal, those with legal, political and consumer interests were able to come to their own conclusions about the product and the activities of prescribers, regulators and the manufacturer, which turned nomifensine into something of an international 'affair' (Schönhöfer, 1991).

BACKGROUND

Nomifensine was first introduced in Germany in 1976 and in the United Kingdom in 1977 and was finally registered in 98 countries. It was a novel chemical entity, a tetrahydroisoquinoline, unrelated chemically

to any other antidepressant. Like tricyclic antidepressants, however, its supposed mode of action was the inhibition of the presynaptic reuptake of biogenic amines in the brain, enhancing their concentration with the aim of combating depression (thought to be mediated by a relative deficiency of these amines). Nomifensine was also a powerful inhibitor of the reuptake of dopamine, with lesser effects on noradrenaline and, through its metabolites, on serotonin (Nicholson and Turner, 1977).

Its preclinical properties, which were confirmed in clinical use, showed the drug to have few anticholinergic and sedative effects. It was therefore a possible safer alternative to tricyclic antidepressants, which could be especially troublesome when taken in overdose. Nomifensine proved to be well tolerated in overdose and was not associated with significant cardiotoxicity or epileptogenic activity. These properties meant that the drug was potentially useful in certain depressive disorders, notably retarded depression, and in certain subgroups, such as those associated with cardiovascular disease and epilepsy. It was also considered to be of value in the treatment of elderly depressed patients and, through its dopaminergic properties, patients with early Parkinson's disease.

Depression is a very common condition with approximately one in seven general practitioner (GP) encounters being a follow-up appointment of a patient with depressive symptoms, and one in 25 encounters a new case. Only 10% of cases seen by GPs are referred to psychiatrists (Beaumont, 1984). The mainstays of pharmacological treatment during the 1980s, the tricyclic antidepressants and monoamine oxidase inhibitors, were associated with a considerable number of adverse reactions in most physiological systems (Edwards, 1981).

Nomifensine joined mianserin as a representative of a new generation of antidepressants that caused fewer side effects. Other drugs of this category introduced into practice at or near this time were maprotiline, viloxazine, tryptophan, zimeldine, trazodone and lofepramine, each with its own subsequent history of benefit and risk.

In the decade up to 1980, the total number of deaths from drug poisoning in England and Wales remained steady at about 3000 per year, two-thirds of which occurred outside hospital. During this time, the proportions due to different groups of drugs changed

considerably, with deaths due to barbiturates falling by half and those due to analgesics and tricyclic antidepressants doubling. In 1980, tricyclic antidepressants were second only to barbiturates in causing death by poisoning (Crome and Chand, 1980). An antidepressant with low toxicity in overdose would thus have life-saving potential if a patient, despite all efforts at prevention, decided to attempt suicide with the medication. Nomifensine proved to be exceptionally well tolerated in overdose in many published reports (Crome and Chand, 1980; Garnier *et al.*, 1982; Ali and Crome, 1984).

HAEMOLYTIC ANAEMIA

Drug-induced haemolytic anaemia results from a type II immune reaction in which antibodies to the drug or its metabolite(s) attack blood cells. Antigens on the cell's surface combine with antibody and complement to stress the cell to the point of destruction. The cell damage causes anaemia. There is an increased production of bilirubin, although a healthy liver can excrete six times the normal load before unconjugated bilirubin accumulates in the plasma; jaundice is therefore mild. Severe haemolysis can result in prerenal uraemia and renal failure.

POST-MARKETING EXPERIENCE 1977–82

Figure 11.1 shows the market data for nomifensine in the United Kingdom. Unit sales are shown in terms of defined daily doses of 100 mg. This terminology was not routinely used in 1979–80 and was only adopted by the World Health Organisation (WHO) in January 1992 as an international standard denominator for calculating incidence. The numbers of prescription were provided by the Committee on Safety of Medicines (CSM) from the Prescription Pricing Authority, and the percentage UK market share achieved by nomifensine is shown; the total represents all antidepressant prescribing including generic compounds.

Figure 11.2 shows the incidence of reports of haemolytic anaemia, hepatic events and fever over time.

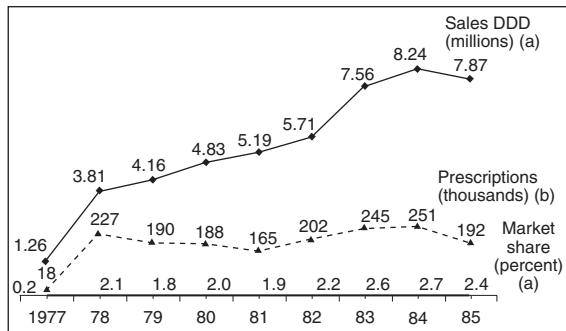


Figure 11.1. Market data for nomifensine in the United Kingdom. DDD, defined daily dose of 100 mg of nomifensine.
(a) Source: UK manufacturer; (b) Source: CSM.

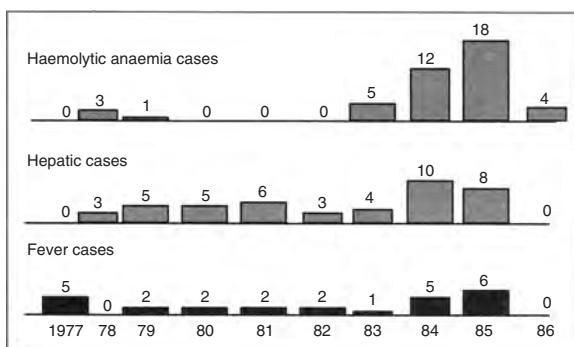


Figure 11.2. Incidences of reports of haemolytic anaemia, hepatic events and fever associated with nomifensine submitted to the UK manufacturer 1977–86.

Nomifensine was first marketed as a 25 mg capsule formulation on 10 October 1977, whereas the 50 mg capsule was made available on 1 January 1979. Between 1978 and 1979, four reports of acute or chronic haemolytic anaemia occurring during treatment with nomifensine were received by the manufacturer (Table 11.1). The patients were females with an age range of 25–64 years. Three of them were taking 150 mg nomifensine daily. Each had a different history of exposure and onset of haemolytic anaemia.

The type of haemolytic anaemia was characterised as chronic or acute, depending on the pattern of symptoms, their severity and the presence or absence of intravascular haemolysis. The symptoms of chronic-onset haemolytic anaemia included lethargy, fatigue and breathlessness, whereas the acute presentation of the condition involved backache, loin pain, jaundice

and haematuria and, in certain cases, fever, renal failure and cardiorespiratory collapse. The Coombs' (anti-globulin) test was positive in all four cases. All of the patients had received concomitant medication, although it was considered to be non-contributory. When nomifensine was stopped, the patients made a full and uneventful recovery.

The first documented report of haemolytic anaemia, published in the *Lancet*, came from France. This was a case of immune haemolytic anaemia and acute renal failure in a 50-year-old woman, who was diagnosed in May 1978 (Bournerias and Habibi, 1979). She had had seven episodes of malaise, chills, pain and fever of 2–4 h duration that were accompanied by dark urine and transient jaundice.

During one of the episodes in July 1978, she had had oliguria. At this time, she had a positive Coombs' test and a haemoglobin level of 10 g/dl. Before the episode, she had been treated for an unrelated illness with levomepromazine, diazepam and nomifensine. She made an uneventful recovery on stopping the medication. The serum of the patient demonstrated an antibody that agglutinated red blood cells only in the presence of nomifensine. The authors called for immunological studies for anti-nomifensine antibodies in patients on long-term treatment.

Another case of acute haemolysis and renal failure (following an overdose of nomifensine) was published the following year (Prescott *et al.*, 1980) (Table 11.1), and three others from outside the United Kingdom were published in 1981–82 (Eckstein *et al.*, 1981; Habibi *et al.*, 1981). One of these cases had intravascular haemolysis during treatment with nomifensine (Lyllof *et al.*, 1982).

Although these reports were of concern, it was not considered at the time that nomifensine was more liable to cause haemolytic anaemia than other marketed drugs. However, heightened vigilance was recommended, and the manufacturer initiated many retrospective and prospective immunological studies. These investigations failed to provide support for a cause-and-effect relationship between nomifensine and haemolytic anaemia. Some patients with haemolytic anaemia had a negative Coombs' test, whereas other patients with a positive Coombs' test did not have haemolysis. Nevertheless, in view of the suspected link between the antidepressant and the blood dyscrasias, haemolytic anaemia was included

Table 11.1. First reports of haemolytic anaemia received by the UK manufacturer 1978–79.

Date notified	Demographic data	Dose	Exposure	Type	Exposure time to provoking dose	Coombs' test	Outcome
29 August 1978	Female aged 43 years	50 mg tds	1	Chronic	4 months	IgG+++	Full recovery
20 November 1978	Female aged 25 years	2 g	2	Overdose		IgG	Full recovery
28 November 1978	Female aged 54 years	50 mg tds	2	Chronic	5 months	IgG+	Full recovery
25 June 1979	Female aged 64 years	50 mg tds	1	Acute	21 days	C ₃ d	Full recovery

among the side effects listed in the January 1981 data sheet.

Between 1981 and 1982, there were three more UK cases of haemolytic anaemia reported to the Department of Health and Social Security (DHSS). They had not been referred to the manufacturer. They occurred among patients who had received a total of 990 000 prescriptions for nomifensine. This suggested an incidence of only about 1 per 150 000 patients, and thus no regulatory action was considered necessary (CSM Update, 1986; Mann, 1988).

These reports did not provide a consistent basis for any general announcement concerning the safety of nomifensine from the company or from a regulatory authority. They placed nomifensine at worst with a group of marketed drugs associated with haemolytic anaemia. This included stibophen, quinidine, paracetamol, penicillin, sulphonamides, tolbutamide, chlorpromazine, tetracycline, cephalosporins, insulin, rifampicin, hydralazine, streptomycin, triamterene and probenecid for immune haemolytic anaemia, and amongst methyldopa, mefenamic acid, flufenamic acid and levodopa for autoimmune haemolytic anaemia.

Nevertheless, the company acted on the reports to institute both retrospective and prospective studies in Germany, France, the United Kingdom and Austria, to determine potential groups at risk. Between January 1979 and June 1980, 312 patients in these studies who had been treated for more than 3 months with nomifensine were given a Coombs' test, and sera from 220 patients were subjected to intensive immunological investigations. Even with these studies, the results did not prove a causative link with nomifensine. The Coombs' test proved to be inappropriate as a

prediction of possible groups at risk amongst nomifensine users. Some patients without haemolysis had a positive Coombs' test, and later several patients with haemolytic anaemia were found to have a negative Coombs' test.

In the course of time, supportable evidence for attributing haemolytic anaemia to nomifensine was produced, and in January 1981, this addition to the UK data sheet was agreed: 'Haemolytic anaemia has also been reported in rare cases as has a rise in body temperature'. This also appeared in the *ABPI Data Sheet Compendium* in October 1981.

Concern over the occurrence of haemolytic anaemia and the other serious reactions led to many additional immunological investigations, and this work in due course provided further evidence for the immunological basis of the haemolytic anaemia reaction (Walti *et al.*, 1983; Miescher, 1985; Salama and Mueller-Eckhardt, 1985).

Salama *et al.* (1984) demonstrated a nomifensine-dependent antibody that reacted exclusively to its *ex vivo* antigen (fresh serum of a volunteer who had taken a therapeutic dose of the drug) but not to nomifensine itself. The investigators later showed an 'extraordinary heterogeneity' of antibody response following the ingestion of the antidepressant. Of 19 samples, only 5 were primarily reactive to nomifensine. The majority reacted in the presence of one or more metabolites and *ex vivo* antigens, indicating specificity for an unidentified early or late metabolite.

All samples belonged to the immunoglobulin G (IgG) or IgM class or both and were capable of activating complement. At least one sample had two nomifensine-dependent red blood cell antibodies,

whereas one had platelet antibodies. The latter explained the occurrence of purpura alongside the haemolysis. It is of interest that 7 of the 19 patients had also signs of transient renal insufficiency, whereas 6 had increased levels of serum transaminase (type not specified; Salama and Mueller-Eckhardt, 1985).

Previously (in September 1978, published April 1979), the data sheet had been amended to draw attention to the association of nomifensine with fever. There had been several reports of this in Germany, and five reports were submitted to the UK manufacturer in 1977. The data sheet stated that there had been 'rare cases of rise in body temperature which returned to normal when the drug was withdrawn'.

The data sheet of 1981 also drew attention to the association of nomifensine with changes in liver enzymes by stating that

In rare cases, increases in liver enzymes (serum transaminases and alkaline phosphatase) have been observed.

Because of receiving four reports of haemolytic anaemia in 1978–79, the manufacturer undertook the following actions:

- Full investigation of each case report. The normal company's operating procedure involved acquiring full information on each case from the prescribing doctor, if necessary visiting the doctor to discuss the case and being accompanied on such visits by medical personnel from the central drug safety department of the company headquarters.
- All cases to be reported to the parent company and the UK DHSS.
- Re-appraisal of all preclinical work and clinical trials to see whether there was any evidence of blood dyscrasias. None was found.
- Retrospective and prospective immunological studies. These produced no consistent results related to the clinical use of the drug.
- Sales representatives to be informed of publications and investigative activities to respond appropriately to enquiries.
- Data sheet changes with international agreement relating to fever, haemolytic anaemia and the liver.

POST-MARKETING EXPERIENCE 1983–86

The increasing incidence of haemolytic anaemia from 1983 might appear to have been related to the launch of the 100 mg single daily dose formulation on 31 January 1983 (Figure 11.1). However, no evidence emerged to support this. It appears that new additional sales were generated by this launch and that the associated promotion may have made doctors more aware of nomifensine. Prescriptions, sales and market share increased in 1983 by 21%, 32% and 18%, respectively. This, together with the data sheet changes and literature reports, may have served to alert doctors to the association of unusual symptoms with the use of nomifensine.

Reports of other severe untoward events that could have had an immunological basis also appeared in the literature in 1984–85: thrombocytopenia (Green *et al.*, 1984), hepatitis (Vaz *et al.*, 1984), alveolitis (Hamm *et al.*, 1985) and a systemic lupus erythematosus (SLE)-like reaction (Garcia-Morteo and Maldonado-Cocco, 1983; Schönhöfer and Groticke, 1985). Those appearing in the British medical literature could possibly have contributed to an increased awareness amongst prescribers of adverse events associated with the drug. The first fatal case of immune haemolysis was published in 1985 (Sokol *et al.*, 1985), and two other cases were reported later the same year (Hamm *et al.*, 1985; Schönhöfer and Groticke, 1985).

In the early to mid-1980s following the withdrawal of ibuprofen and the recognition of problems with other non-steroidal anti-inflammatory drugs, together with promotion of the government's Yellow Card scheme, there was an increasing acceptance amongst doctors of the need to report adverse experiences with commonly prescribed drugs. In September 1983, the antidepressant zimeldine was withdrawn from the market following the identification of a serious neurological disorder, the Guillain–Barré syndrome. The publicity given to this may have affected the reporting of adverse events to drug therapy, including nomifensine.

The purpose of showing the comparative incidences of fever, hepatic reactions and haemolytic anaemia in Figure 11.2 is not to suggest any common underlying pathology to these three conditions; none has ever been substantiated. It is to indicate that, whilst reporting rates of haemolytic anaemia and hepatic problems

(enzyme changes, jaundice or hepatitis) significantly increased with time, this was not the case with reports of febrile reactions. The incidence of these never reached the same levels as in some other countries, e.g. Germany. Cases in the United Kingdom in which fever was associated with haemolysis were catalogued in the haemolytic anaemia group.

Table 11.2 shows the UK manufacturer's total database of 296 events; this is to be compared with the CSM's Yellow Card database of 543 suspected adverse reactions. The company had 45 reports of haemolytic anaemia of which 43 were thought to be associated with the drug. This is to be compared with the CSM's 59 reports of which 49 contained sufficient information to attribute nomifensine as the probable, or a possible, cause. Forty-five of the 49 (92%)

Table 11.2. Nomifensine adverse events reported to the UK manufacturer 1977–86.

Adverse event	Total number of reports
Haematological	
Aplastic anaemia	1
Increased bleeding time	1
Leucopenia	1
Thrombocytopenia	4
Positive Coombs' test	16
Haemolytic anaemia	45
Hepatic disorders	
Jaundice	27
Abnormal liver function tests	12
Hepatitis	6
Hepatic necrosis	1
General	
Pyrexia	13
Influenza-like symptoms	12
Allergic reactions	3
Other	12
Renal	
Interstitial nephritis	1
Other	5
Autonomic	3
Skin	21
Central nervous system	72
Cardiovascular	18
Endocrine	1
Gastrointestinal	17
Musculoskeletal	1
Respiratory	1
Overdoses	2
Total	296

patients were women, although females received only 71% of the prescriptions for the drug. Some of the subjects, who had had a previous course of nomifensine without experiencing unwanted effects, developed acute haemolytic anaemia on recommencing treatment, whereas others developed haemolytic anaemia after months or years of continuous use. In 18 patients, the haemolysis was severe: 11 of them developed renal failure and 4 died. Although haemolytic anaemia was the most frequently reported serious adverse reaction, concern was also expressed over other untoward effects (CSM Update, 1986).

From 1983 onwards, there was a steady rise in the number of reports of haemolytic anaemia to the UK manufacturer, with 5 reports in 1983, 12 in 1984 and 18, including 3 fatalities, in 1985. The first nomifensine-associated fatality in the United Kingdom was reported on 10 February, the second was reported on 31 March and the third on 10 April 1985. The three cases were discussed with the DHSS on 1 May 1985.

The first of these fatal cases was published in the *British Medical Journal* in August 1985 (Sokol *et al.*, 1985). The patient was a 36-year-old female who collapsed 1 h after taking one 100 mg tablet. She had been treated with nomifensine for 1 week but stopped taking it because of dizziness. There was no jaundice or haematuria. On examination, she was conscious but pale, cyanosed and shocked. Her blood pressure was 90/50 mmHg, and her pulse was 90/min. Haematological tests showed spontaneous red cell agglutination, with free haemoglobin in the plasma, and the following results: haemoglobin 5 g/dl, bilirubin 4 µmol/l and lactate dehydrogenase 1071 IU/l. The patient had severe acidosis. Acute intravascular haemolysis was diagnosed. Attempts at resuscitation failed, and the patient died. Immunological investigations showed a positive Coombs' test with antisera to IgG, IgM and Cl. The serum contained cold-reacting auto-antibodies and pan antibodies. In the presence of nomifensine, the antibodies led to the agglutination of red cells.

The proposed mechanism was that drug and antibody combined to form loose immune complexes that attached themselves to the red cells and activated complement. Complement activation led to haemolysis, disseminated intravascular coagulation and the shock-lung syndrome.

Between January 1983 and mid-June 1985, the DHSS was aware of 29 reports of haemolysis in 592,000 prescriptions—approximately one in 1:20,000 prescriptions (CSM Update, 1986).

In July 1985, the CSM's bulletin, *Current Problems*, highlighted the dangers of newer antidepressants and presented a summary of adverse drug reactions to nomifensine. A new data sheet was published with information submitted in October 1984. This stated that

In rare cases, haemolytic anaemia and abnormal liver function tests with or without clinical jaundice have been observed. These reactions subside within a short time of discontinuing Merital (nomifensine) but may recur if it is taken again.

In September 1985, there were joint discussions between the company and the DHSS on a complete revision of the data sheet. On 24 September, the current data sheet was put in abeyance pending the outcome of these discussions and all promotion of nomifensine ceased.

On 30 September 1985, the company issued a 'Dear Doctor' letter warning of the serious adverse reactions reported internationally; this letter was a version of a similar 'Red Hand' letter issued at the same time by the parent company in Germany.

On 7 December 1985, the 'CSM Update' on antidepressants, published in the *British Medical Journal*, summarised the comparative adverse reaction reports on all antidepressants (CSM Update, 1985).

On 16 December 1985, the *Drug and Therapeutics Bulletin* published an article 'Trouble with nomifensine' after several revisions since the first draft in May. This was followed by many newspaper reports on the drug.

Between mid-June and the end of November 1985, the DHSS was aware of 25 reports of haemolysis in 96,000 prescriptions (1:4000; CSM Update, 1986). This was the first time that the incidence had increased to a level above 1:10,000 (the accepted WHO definition of a rare incidence), giving rise to a situation in which the benefits of the drug could no longer be said to outweigh the risks of haemolytic anaemia.

Four further cases of haemolytic anaemia were reported to the company in January 1986. One of these patients subsequently died. The UK data contributed

to the ongoing appraisal of nomifensine being undertaken by the parent company, and this led to the product's withdrawal from worldwide markets on 22 January 1986.

Table 11.3 summarises the events and assessments leading to the withdrawal of nomifensine 10 years after its first market launch.

DISCUSSION

Compared with the pharmacoepidemiological methodologies available today, the measures and methods employed in monitoring the adverse effects of nomifensine were those used in the normal clinical and laboratory assessments of haemolytic anaemia, more specialised immunological investigations into the relationship between the nomifensine and the dyscrasia and epidemiological observations. The last of these was not straightforward in the case of nomifensine because, as discussed, there was a very low rate of reported cases up until the increase in the mid-1980s. This undoubtedly led to the delay in establishing a cause-and-effect relationship between nomifensine and haemolytic anaemia.

It was considered that the rapid escalation of spontaneous reporting could have been because of increased awareness among doctors resulting from reports of haemolytic anaemia in the literature, changes in the data sheets and encouragement to make use of the CSM's Yellow Card system. It could also have been partly because of the increased promotion, sale and market share of nomifensine that occurred at the time. Furthermore, an impetus may have come from the withdrawal from the market of ibuprofen (and increasing recognition of problems associated with other non-steroidal anti-inflammatory agents) during the early to mid-1980s. The neurological problems caused by zimeldine also occurred during the early 1980s and may have contributed to heightened concern over, and increased reporting of, adverse reactions in general (Edwards, 1997a).

Altogether, nomifensine was associated with eight deaths before its withdrawal in the United Kingdom. Three of these were associated with haemolytic anaemia (a fourth haemolytic anaemia-associated fatality occurred after the product was withdrawn),

Table 11.3. Nomifensine: events and assessments leading to withdrawal.

Year	Events/assessments	References
1976	Nomifensine launched on to market in Germany	
1977	Nomifensine launched on to market in the United Kingdom	
1978–79	Four cases of haemolytic anaemia reported to UK manufacturer	Stonier (1992)
1979–81	Published reports of haemolytic anaemia ± renal failure	Bournerias and Habibi (1979) Prescott <i>et al.</i> (1980) Eckstein <i>et al.</i> (1981) Habibi <i>et al.</i> (1981) Salama <i>et al.</i> (1984)
	Demonstration of nomifensine-dependent antibody	
1984–85	Published reports of Thrombocytopenia Hepatitis Alveolitis (fatal) SLE-like reaction (fatal)	Green <i>et al.</i> (1984) Vaz <i>et al.</i> (1984) Hamm <i>et al.</i> (1985) Schönhöfer and Groticke (1985)
1985	Published reports of fatal case of immune haemolysis Promotion of nomifensine discontinued 'Dear Doctor' letter, United Kingdom 'Red Hand' letter, Germany Estimated incidence of haemolytic anaemia June: 1 in 20 000 November: 1 in 4000	Sokol <i>et al.</i> (1985) Stonier (1992) CSM Update (1986)
1986	Nomifensine withdrawn from market	

Source: Adapted from Edwards JG (1997b). Reproduced by permission of John Wiley & Sons Ltd.

and one each with a cardiac arrhythmia, an overdose of nomifensine in conjunction with lithium, the Stevens–Johnson syndrome, hepatic necrosis and a cerebrovascular accident.

The 'CSM Update' in 1986 outlined the basis for the risk–benefit discussion, which took place late in 1985 when for the first time the incidence of haemolytic anaemia in the United Kingdom was greater than 1 in 10,000 prescriptions. However, reports of other adverse events remained modest.

Hoechst UK's total database was only 55% of the CSM's, but it contained 76% of all haemolytic anaemia reports and 88% of evaluable reports. For hepatic events, the company had 46 reports of which 44 (96%) were thought to be associated with the drug. This compared with the CSM's 51 (86%) reports, but for fever the company had only 25 reports compared with the CSM's 48 (52%). Thus, for perceived serious events, it appeared that prescribers

felt more compelled to contact the company directly. For haemolytic anaemia and hepatic events, the manufacturer received over 75% of the reports that formed the CSM's database compared with approximately 50% for all other adverse reactions, including fever. This supports the view that the company was aware of a greater proportion of serious events than the average reporting rate to the company.

Despite some obvious associations such as increased prescribing, increased awareness of nomifensine after the launch of the 100 mg single daily dose tablet, and literature and media reports, the exact reason for an increase in reports of haemolytic anaemia during 1984 and 1985 was never established nor were the reasons for the timespan of around 9 years from the first introduction of nomifensine to the emergence of a drug safety warning signal that could reasonably be acted upon.

It is possible to compare side effect evaluation between 1976–86 and subsequent years. The current system of evaluation with its heightened awareness amongst healthcare professionals (and indeed society at large) of drug safety risks of marketed products has, at least in part, been the result of the lessons learnt first-hand from problems with former products. These include nomifensine.

The evaluation of nomifensine relied wholly on spontaneous reporting systems with their known inadequacies of incompletely reported data, lack of population data to allow for the calculation of incidence rates and estimates of subgroups at risk; poor international co-ordination of drug safety databases; and the need for confidentiality hampering collaboration between the manufacturer and the regulatory authorities at least in the early stages.

Nevertheless, the risk–benefit appraisal of nomifensine was made through a continuing dialogue between the company and the regulatory authority, taking into account time-honoured but rudimentary indicators of risk and benefit. For the company, these included the general properties of nomifensine in relation to older and newer antidepressants, overdose data, market uptake of the single daily dose, crude adverse drug reaction incidence calculations from prescriptions and sales volume, publications in the medical literature and media reports and comparisons with other drug classes. Specific aspects of nomifensine that were of special concern included the rising incidence of reports of acute immune haemolytic anaemia and the incidence of fatalities.

Of some interest today is what might have been the true effect of a consideration of overdose data on the risk–benefit appraisal of nomifensine, had the successful appeal against the threatened suspension of mianserin using such data been heard earlier (Brahams, 1990). Concern was expressed with mianserin over the number of reports to the CSM of granulocytopenia and agranulocytosis occurring during treatment with this antidepressant, and it was at risk of being suspended. However, it was given a reprieve because of a comparative Prescription Event Monitoring study that was unable to detect any drug-attributable blood dyscrasias and concluded that if mianserin did cause them, then the incidence would probably be in the range of one per 10,000 to one per 100,000 patients. It was also shown that the risks

of overdose of mianserin were considerably less than that of amitriptyline (Inman, 1988, 1991).

Between 1977 and 1984, 74 patients taking an overdose of nomifensine, 28 of them nomifensine alone, were reported to the London Centre of the National Poisons Information Service, Guys Hospital (Ali and Crome, 1984). The most common symptom, either with nomifensine alone or in combinations with other drugs (benzodiazepines, alcohol and/or tricyclic antidepressants), was drowsiness. There were no reports of convulsions or cardiac arrhythmias in those who took nomifensine alone, and all cases made satisfactory recoveries. It was concluded that nomifensine overdose had few clinical sequelae and that there was a notable absence of the complications seen with tricyclic antidepressants.

The nomifensine appraisal might have benefited in a small way, too, from today's pharmacoepidemiological databases and case–control studies. These would have added strength at an earlier stage to incidence calculations and allowed the incidence to be compared with the background incidence in the community. However, even today, there is no rare disease registry that provides the background incidence of haemolytic anaemia in the general population.

Since the mid-1980s, the computerisation of data in the international pharmaceutical industry and the regulatory agencies has greatly facilitated the establishment of drug safety databases and the speed and extent of international reporting, accrual and comparison of pharmacovigilance data. Pharmacoepidemiological databases, such as the Prescription Event Monitoring of the Drug Safety Research Unit (DSRU), the General Practice Research Database (GPRD), the Medicines Evaluation and Monitoring Organisation (MEMO) and Record Linkage, are now available to study, contemporaneously and retrospectively, the cause-and-effect relationship of apparently drug-linked events (Mann, 2001).

There has been a concomitant increase in regulation and legislation concerning the formal recording and reporting of suspected adverse events. The application of Good Clinical Practices (GCP), through the International Conference on Harmonisation (ICH), today formalises all aspects of clinical trials of medicines both before and after licensing. It remains hypothetical, however, whether these would have aided the assessment of nomifensine between 1977 and 1986.

A further area of development has been the increased awareness within companies of the need to develop issues management strategies and teams to co-ordinate the response to matters such as specific drug safety alerts. These bring together all the relevant company resources from medical, regulatory, manufacturing, quality assurance, legal and commercial departments at a local and an international level to address matters raised by, e.g., the increased reporting of a rare side effect. This enables a much more co-operative and proactive relationship to develop between the company, the regulatory authorities and the media to resolve the issues in a timely and diligent manner. Whilst such an approach was taken in the case of nomifensine, it was perhaps more reactive than might be the case today. It remains speculative whether a more formal and rehearsed international issue and relationship management strategy would have helped to shorten the timescale from first alert to the final withdrawal of the drug.

Nomifensine was associated with a rising incidence of a serious life-threatening type B reaction, namely acute immune haemolytic anaemia. The reasons for the rising incidence are not known, although greater doctor recognition and willingness to report, possibly stimulated by literature reports and the media, were undoubtedly factors involved. The immunology was uncertain throughout because of the variety of case presentations, severity and outcomes and conflicting laboratory findings.

Because of difficulties in predicting the haemolytic reaction, distinguishing its initial symptoms from those of other disorders and the variable serological findings, it was impossible to offer firm advice on early diagnosis and treatment.

The drug was withdrawn from sale in the interests of patient safety, even though nomifensine was a well-established antidepressant in many countries, in some of which the problems were thought to be an 'acceptable' risk when seen in relation to the drug's benefits. The decision to withdraw nomifensine was made by physicians employed by the company when, despite the uncertainty, the severity and clinical sequelae of the haemolytic reaction were fully appreciated. It is arguable whether the science of pharmacoepidemiology or the procedures of pharmacovigilance as practised today would have impacted on that decision either in January 1986 or indeed in 2001.

Whilst the professionals who make judgements about risk and benefit of a medicine must be aware of both population statistics and individual patient concerns, the decisions on action to ensure the continued safety for some patients without denying the benefits of an established medicine for others will always be demanding. In this context, the decisions of a company to withdraw its product from the market or of a regulatory authority to revoke the marketing authorisation will remain the most difficult of all.

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Part II

SIGNAL GENERATION

12

WHO Programme – Global Monitoring

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HISTORY

The Programme was established in 1968 as a pilot project with the participation of 10 countries that had organised national pharmacovigilance systems at that time. The intent was to develop international collaboration to make it easier to detect rare adverse drug reactions (ADRs) not revealed during clinical trials. The international drug monitoring centre was moved from the World Health Organisation (WHO) headquarters in Geneva, Switzerland, to a WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, in 1978. This was the result of an agreement between WHO and the government of Sweden by which Sweden assumed the operational responsibility for the Programme. WHO headquarters, Geneva, retained the responsibility for policy matters. The WHO Collaborating Centre is often referred to as the Uppsala Monitoring Centre (UMC).

It is easiest to record the history of pharmacovigilance as a series of milestones that led to the introduction of new concepts or the re-thinking of old concepts within the discipline. A chronological list of these milestones is listed in Table 12.1. It is interesting to note that up to and including the benoxaprofen ('Opron') incident in 1989, changes in drug safety procedures were implemented as a result of drug disasters that had a high media profile. The responses to these disasters constituted

a major re-thinking of drug safety issues. Since the benoxaprofen incident, there have been many drug withdrawals related to safety issues, but these have been managed much more effectively and expeditiously. It may seem that we now have safety systems in place that enable effective action to be taken globally before disturbing numbers of patients are affected. However, it is ironic that the pill scare in the United Kingdom may have caused more distress because of a rapid regulatory response to a safety issue. Since the benoxaprofen incident, the main changes made in pharmacovigilance have been proactive improvements involving fine-tuning of regulatory systems and the adoption of better epidemiological techniques often associated with improvements in information technology (IT). Recently, the withdrawal of the COX2 receptor inhibitor rofecoxib (Vioxx) has led to more criticism of both the regulatory authorities as well as industry. Chief amongst these is the slow action taken over the suspicion of an increase in cardiovascular events. Because this problem is thought to be due to the COX inhibition, it is very complex because of the variable amounts of COX selectivity of older NSAIDS as well as many other new drugs with the attribute of COX2 receptor selectivity. Moreover, there is concern that the COX2 drugs may not produce the wanted reduction in gastrointestinal bleeding thought to result from selectivity (Edwards, 2005a).

Table 12.1. Some important milestones in pharmacovigilance.

Milestone	Issue	Linked development	Other development
Elixir of sulphanilimide (1937)	Formulation defect results in poisoning	Improvements in pharmaceutical regulation National and international collections of ADR reports	Yellow card system, United Kingdom, 1964
Thalidomide (1961)	Phocomelia in children of mothers who took this apparently safe drug		WHO Programme on International Drug Monitoring, 1968 – attempt to create automatic signal generation ('black box')
Clioquinol (1969)	New clinical syndrome reported from Japan (SMONs)	Ethnic susceptibility and drug use issues raised	More realisation of complexity in drug safety Early work on pharmacogenetics
Oral contraceptives (1970s)	Venous thromboembolism	Controversy over epidemiological findings and acceptance, finally, of their importance Realisation that spontaneous reporting will not pick up 'events', not easily recognised as caused by drugs	Prescription event monitoring introduced – Intensive Medicines Monitoring Programme in New Zealand and Prescription Event Monitoring in the United Kingdom
Practolol (1975)	New clinical syndrome, recognised by UK expert (oculomucocutaneous)		Causality algorithms developed National collaboration enhanced under WHO Programme
WHO Collaborating Centre for Drug Monitoring, Uppsala (1978) founded	No 'black box' signal detection solution found	Enhanced 'clinically useful outputs' – critical terms, WHO-ART, WHO-DD, quarterly summaries	
Non-steroidal anti-inflammatory drugs (NSAIDs) (1980–)	Blood dyscrasias, GI bleeding a serious public health problem; high background incidence a problem Unusual photosensitivity	Development of pharmacoepidemiology	Bayesian methods introduced
Benoxaprofen (1982)		United States saw the need to have international industry ADR information – CIOMS ^a I	CIOMS II at risk groups WHO Programme invites more expert help
		Need to have rapid alert system between agencies necessity for regular reporting	WHO Programme begins to work towards greater openness
	Liver necrosis in the elderly		France introduces regionalisation and a causality algorithm
			Start of thinking towards ICH
			United Kingdom takes action to remove drug from the market without United States knowing

Fenoterol – beta agonists (1989) (previous sympathomimetic deaths in 1970s) EU and ICH (1990–)	Linked to death in asthma in case–control studies	Signals from case–control studies debated strongly	Use of databases/nested studies becomes more accepted
Common European policies on pharmacovigilance promoted US, EU and Japan work on harmonised drug regulation	Rapid alert and common international decisions on signals	Development of harmonised methods (ICH) and projects, for example European Pharmacovigilance Research Group (EPRG)	Increasing use of clinical databases
ADR Signal Analysis Project (ASAP) (1994)	International spontaneous report rates available from IMS and used in international signal analysis in WHO Programme	Drug use data more widely used in drug safety	Proportional reporting ratios (United Kingdom and Netherlands)
Bayesian Neural Network (1997)	An automated signal detection method with statistical information to aid expert opinion, in WHO Programme		
Other statistical methods (United States of America and Australia)	A small absolute increase in risk of death causes 'pill scare', followed by abortions and unwanted pregnancies	Focus on the need for good communications practice and consequence evaluation	Re-opens debate on evidence in pharmacovigilance
Third generation oral contraceptives (1997)	Proposes a global effort to reduce medical errors as a cause for patient harm	Increased interest in safety during medical care	
WHO World Alliance for Patient Safety (2004)	Calls for more rapid assessment of drug risks, with several proposals for the use of patient clinical management databases as the source of drug and event information	Data mining seems the most useful tool proposed	
Vioxx withdrawal (2004)			

^a A council for International Organisations of Medical Sciences

PRESENT PROGRAMME STRUCTURE

The number of national centres which are active members of the WHO Programme has increased with about three per year during the last few years to the present 78 countries, and the database grows with almost 200 000 reports per year to now over 3.5 million.

As pharmacovigilance is developing in many countries in the world, additional countries continuously formally apply for membership, and they are considered associate members while the issue of technical compatibility of their reports with the WHO requirements is established. Member countries and associate member countries are listed in the Table 12.2.

Table 12.2. WHO member and associate member countries.

Country	Year of entry
Argentina	1994
Armenia	2001
Australia	1968
Austria	1991
Belarus	2006
Belgium	1977
Brazil	2001
Bulgaria	1975
Canada	1968
Chile	1996
China, PR	1998
Costa Rica	1991
Croatia	1992
Cuba	1994
Cyprus	2000
Czech Republic	1992
Denmark	1968
Egypt	2001
Estonia	1998
Fiji Islands	1999
Finland	1974
France	1986
Germany	1968
Ghana	2001
Greece	1990
Guatemala	2002
Hungary	1990
Iceland	1990
India	1998
Indonesia	1990
Iran	1998
Ireland	1968
Israel	1973
Italy	1975
Japan	1972
Jordan	2002
Korea, Rep of	1992
Kyrgyzstan	2003
Macedonia	2000
Malaysia	1990
Malta	2004
Mexico	1998
Moldova	2003
Morocco	1992
Netherlands	1968
New Zealand	1968
Nigeria	2004
Norway	1971
Oman	1995
Peru	2002
Philippines	1995
Poland	1972
Portugal	1993
Romania	1976
Russia	1998
Serbia and Montenegro	2000
Singapore	1993
Slovak Republic	1993
South Africa	1992
Spain	1984
Sri Lanka	2000
Sweden	1968
Switzerland	1991
Tanzania	1993
Thailand	1984
Tunisia	1993
Turkey	1987
Ukraine	2002
United Kingdom	1968
United States	1968
Venezuela	1995
Vietnam	1999
Zimbabwe	1998
Associated member countries	
Bahrain	
Bhutan	
Congo DR	
Eritrea	
Ethiopia	
Georgia	
Mongolia	
Nepal	
Netherlands Antilles	
Panama	
Pakistan	
Sierra Leone	
Uganda	
Uzbekistan	
Zambia	

In each country, a national centre, designated by the competent health authority, is responsible for the collection, processing and evaluation of adverse reaction case reports submitted by health professionals. Information obtained from these reports is passed back to the professionals on a national basis but is also submitted to the UMC for inclusion in the WHO international database. Collectively, the centres annually provide almost 200 000 individual reports to the WHO of reactions suspected of being drug induced.

Case reports submitted to the WHO centre according to an agreed format are checked for technical correctness and then incorporated in the international database in a weekly routine. The material is screened four times a year, using Bayesian Confidence Propagation Neural Network (BCPNN) knowledge detection technique for new and serious reactions. Many additional examinations of the data are made on an *ad hoc* basis.

The WHO Programme global database for ADRs meets or exceeds the ICH E2B agreed format (<http://www.ich.org>) and is fully searchable online by the participating national centres. There is also a web-based software available for reporting adverse reactions according to the E2B format, called VigiFlow. This software is used by many for reporting to and between databases independent of WHO.

CURRENT WORK

- The database of the WHO Programme is a unique reference source used in many different situations. When a national centre receives the first report of an unfamiliar drug-reaction association, on-line search facilities to Vigibase are at the disposal of national centres to find out whether a similar observation has been made elsewhere in the world. If so, the initial signal may be strengthened. For more complicated studies, the UMC staff can make customised searches in the database.

From the database, cohorts of patients affected by similar kinds of drug-associated reactions may be retrieved. By looking for common features in these

reports, risk factors and hypotheses for underlying mechanisms may be revealed.

- The methodology developed at the UMC using a BCPNN technique in analysing the database was put into routine use already in 1998. The concept of data mining, or knowledge detection as it also may be called, is now operating to support all countries in their work. It is based on artificial intelligence using a Bayesian logic system. It has been fully validated and is under continuous development and has been presented in a doctoral thesis by Andrew Bate in 2003. (Bate *et al.*, 1998a,b, 2000; Lindquist *et al.*, 1999; Bate, 2000; Lindquist, 2000; Orre *et al.*, 2000; Ståhl *et al.*, 2004.)

A combination of automatic signalling devices and scanning by experienced medical personnel is considered most advantageous to fulfil successfully the original aim of the programme, that is the early identification of new ADRs. This method provides a quantitative measure of the strength of association of a drug-reaction combination in the database. Combinations that occur more frequently than expected as compared with the generality of the database are highlighted.

When the new data has been processed and entered into the ADR database, a BCPNN scan is run to generate statistical measurements for each drug-ADR combination. The resulting data are presented in two steps:

- The resulting Combinations database (Combination: *ADR data elements occurring together in ADR reports*) is made available to national centres and to pharmaceutical companies, in the latter case including only information on the company's own patented products. The database is presented in a computerised form which facilitates searching and sorting of the information.
- An Associations database (Association: *Combinations selected from a database on a quantitative basis*) is generated by selecting those combinations that pass a preset threshold. Based on the results of the test runs of the BCPNN, the threshold level for associations is that of the lower 95% confidence limit of the information component (IC)

value crossing zero when a new batch of reports is added.

All associations are followed automatically for 2 years, the data being checked at 6-month intervals. After the final listing, an association may be reintroduced for another 2-year follow-up. The associations are also copied to a cumulative log file (history file), which will serve as a filter to exclude combinations that have in previous quarters passed the threshold level. This will prevent drug-ADR combinations with a confidence limit fluctuating around zero from being fed into the review process repetitiously.

A panel of experts has been established to analyse reactions pertaining to particular body systems. The Associations database is sent to the expert review panel for evaluation. Before distributing the database, associations are checked against standard reference sources [e.g. Physician's Desk Reference (PDR), Martindale] and the published literature (using, e.g., *Medline* and *Reactions Weekly*). This facilitates the review and identifies those associations that are, if not generally known, at least identified previously.

Searching and sorting of the associations data can be done not only on drug, ADR and the various statistical measurements but also on system organ class (SOC) and on therapeutic drug groups using the anatomical-therapeutic-chemical (ATC) classification. To ensure that there are at least two reviewers per SOC, we intend to extend the panel of reviewers from today's 30 experts to around double. Recently, a special panel of experts to review reactions to herbal preparations was set up.

To the Associations stage, the process is purely quantitative, but clinical knowledge and judgement is necessary for the evaluation of associations and is provided by the national centres and expert reviewers. Short summaries of their findings are circulated to participating national centres in a memorandum called 'Signal'. An investigation has demonstrated that the WHO Programme is successful in finding new drug-adverse reaction associations at an early stage and in providing useful information about them to national centres (Ståhl *et al.*, 2003)

Individualised sections of the Signal document are provided to companies on their patented products for their comment.

To aid the expert reviewers, and also to facilitate interpretation of the information presented in the Signal document, a set of guidelines is being used. As with the associations, signals will be reassessed after 2 years, with a possibility of re-introduction for follow-up and also copied to a history file for easy tracking. With the new follow-up procedures that are being introduced, a mechanism by which signals can be re-evaluated following new information will be in place. This enables, for example, renewed consideration of associations for which there initially was not enough information to merit signalling. Signals that are later supported by new evidence can also be highlighted. The nature of the signal will determine what measures need be taken in terms of follow-up.

A larger number of variables than the routine drug-ADR combinations can also be considered using the Bayesian approach, as described above. One of the advantages of a neural network, as used in the BCPNN, is that it can search for patterns of associations between fields that are not determined *a priori*: it can find novel complex relationships. One of the outcomes of these analyses may be to identify patient subgroups that may be at particularly high risk of getting a specific adverse reaction when they have taken a specific drug. Another possibility is to establish that a drug safety problem is related to a particular country, or region, or a certain time period. By further developing the BCPNN methodology for the analysis of the large amount of data in the WHO database, it is expected that not yet revealed risk factors for the development of drug-related ailments may be detected. The UMC develops and uses unsupervised pattern recognition methods to avoid too many preconceptions influencing investigations, which are then largely driven by the data itself. The approach also picks up, and allows analysis of, data and methodological issues such as duplications in reports which may not be obvious (Norén, Orre and Bate, 2005).

- The UMC has an important role to play as a communication centre – a clearing house for information on drug safety at the service of drug regulatory agencies, pharmaceutical industry, researchers

and other groups in need of drug safety information. Requests for special database searches and investigations are received from these parties at a rate of around 225 per year. In addition, flexible on-line retrieval programmes are made available by which the database users may perform a variety of standardised searches by themselves. Access for non-member parties is subjected to some confidentiality restrictions agreed by Programme members. Use of the information released is subject to a caveat document to explain its proper use. Detailed manuals for the on-line service and the customised retrievals on request are available from the Uppsala centre.

The UMC co-operates with WHO to provide drug safety information in the *WHO Pharmaceuticals Newsletter*, distributed by the Health Technology and Pharmaceuticals department of WHO headquarters, leading to a wider distribution of the information to all member countries of WHO. The UMC is responsible for compiling information from national pharmacovigilance centres, including their adverse reaction bulletins, on warnings, recommendations and advice provided to health professionals in relation to the safe use of medicines.

The UMC co-operates with Adis International in the journal *Reactions Weekly* to provide additional information in the section 'Adverse Reaction Case Reports' in the journal. Any claim to a first report in 'Reactions' is supplemented, where possible, by supporting information from the WHO adverse reactions database.

Uppsala Reports is the name of a bulletin which is made freely available to all interested parties by the UMC. It provides an easy-to-read account of news about pharmacovigilance, the WHO Programme, its members and services.

Communications within the WHO Programme have improved with the increasing use of electronic communications media. The UMC is maintaining an e-mail discussion group called 'Vigimed', which allows for rapid exchange of information around the world on drug safety matters. Membership is restricted to persons connected to national pharmacovigilance centres, which means that confidential information before a issue is fully evaluated can be circulated.

The internet home page of the WHO Programme (<http://www.who-umc.org>) is a dynamic tool for communications with all clients of the UMC. Recently, the Products & Services division of UMC, dealing mainly with commercial customers, set up a new website presenting all of their services (<http://www.umc-products.com>).

- International comparisons of drug safety reporting have been made (Lindquist, 1990, 2003; Lindquist and Edwards, 1993). These comparisons have shown important differences in country profiles of reporting. The differences between countries may be due to a variety of factors. Some of the differences may be purely technical but others may relate to differences in medical practice, the use of medical terms and societal influences such as media interest (Mills and Edwards, 1999). Sometimes, the difference in indications, doses of medicines and/or the routes of administration may be significant (Lindquist *et al.*, 1996). It is sometimes alleged that these findings are not signals, but this is to take a narrow view of a 'signal' as simply a previously unreported medicine/ADR association, rather than to consider that any significant new evidence on a medicine-related risk is a signal (see WHO definition – Edwards, 1997).
- Definitions for a variety of pharmacovigilance terms have been proposed and accepted widely (Edwards, 1997). Within the WHO Programme, many definitions of commonly used terms, such as adverse reaction, side effect, adverse event and signal, have been worked out. These definitions contribute to a harmonised way of communicating both inside and outside the Programme (Edwards and Biriell, 1994).
- Guidelines for signal finding have been proposed and widely accepted (Edwards *et al.*, 1990). It is an important concept that a medicine-related signal from spontaneous reports should be considered starting with the seriousness of the apparent signal and then appraising both the quantity of reports as well as the strength/quality of the information in those reports. Because the quality of information on a report is limited does not necessarily mean that the observation underlying it is less valid: but it does mean that objective assessment may be difficult or impossible. Assessing the

weight of reported evidence is a complex clinical decision, which has further been aided by definitions of ‘certain’, ‘probable’, ‘possible’ and so on (Edwards, 1997).

- The idea of the possibility of an exhaustive dataset being stored was initiated, and has become the ICH E2B project. A new WHO database, called Vigibase, containing all the fields was completed in 2002 (see paragraph below) (Lindquist, 1998). First with the Council of International Organisations of Medical Sciences (CIOMS, 1995) and then with ICH, the UMC has developed a comprehensive set of data fields, which have been included in the new database, which is fully operational. In this data model, much more detailed information on each case may be stored.

The new UMC database has great complexity, and it seems unlikely that many of the available fields will be completed until a ‘paperless’ system comes into operation in several countries. The new database is fully compatible with the old one, so that reports both in the old WHO format and the new E2B format can still be accepted. To provide flexibility for users with varying requirements and sophistication is a great challenge, but we are hopeful that the new database will pave the way for the international availability of much more useful case data, without the need to go back to the original provider for more details.

Along with the provision of the new database, the UMC gives more active support to national centres over their IT development by offering VigiFlow, a web-based reporting software solution. The system accesses Vigibase over the internet, so no local installations are required. Reports can be entered and accessed through password-protected, secure internet connection by the reporting doctor, regional centres or the national centre, and will automatically be transferred to the international database. Many delays in the transmission of reports to the WHO are secondary to a variety of technical issues, which can now be minimised.

- The UMC organises training courses to foster education and communication in pharmacovigilance with the main aim of supporting the development of national programmes for spontaneous ADR reporting.

Since 1993, the UMC offers every second year a 2-week training course in adverse reactions and adverse reaction monitoring to which 25 healthcare professionals are accepted from all over the world. The course is for 2 weeks and is divided into three consecutive modules. The first is focused on spontaneous monitoring and the practicalities of managing a drug monitoring centre. This section also offers hands-on experience in using the database of the WHO Programme. The second module is an introduction to wider issues in pharmacoepidemiology. As it is more and more recognised that being able to communicate, often difficult issue in drug safety, is important, a third module on effective communication in pharmacovigilance has been added to the course.

There is an increasing trend towards local and regional meetings and courses in pharmacovigilance. The WHO Programme often takes part in such meetings, particularly those organised in developing countries, to provide support and technical advice. UMC’s expertise is sought in the important WHO Public Health Programmes against HIV/AIDS and malaria, where new drugs causing new problems are used. UMC staff are commonly invited all over the world to speak at professional meetings.

- Every year, representatives of national centres are invited to a meeting arranged jointly by WHO and one of the participating countries. At these meetings, technical issues are discussed, both in relation to how to improve global drug monitoring in general and concerning individual drug safety problems. Because the meetings have very high attendance rates, they are important for the establishment and maintenance of personal relationships subsequently contributing to good communications.

The WHO Programme has developed a standardised adverse reaction terminology (WHOART) and a comprehensive index of reported drugs (WHO-DD), both of which have a utility beyond their importance to the monitoring system. These tools are used in the pre-marketing safety area, as well as for post-marketing studies by many pharmaceutical companies. The WHO Drug Dictionary is unique in its coverage of drugs marketed throughout the world. It is available as computer files for inclusion in users’

own software. The UMC has in conjunction with the introduction of the new database developed it further to incorporate more detailed information and make it compatible with the pre-standard proposed by the European Committee for Standardisation (CEN). A cooperation with IMS Health has started which will further improve the dictionary by making it more comprehensive and more up to date.

More recently, WHO has invited the UMC to be a partner in the WHO Family of Classifications (WHO-FIC). This includes all of the WHO classifications, notably the International Classification of Diseases. The plan is to link all of the WHO classifications, which will include the WHO-DD and WHOART being linked to ICD to harmonise drug-induced disease with other illness classification.

- There is a general need to quantify adverse reaction information. The WHO centre is working jointly with IMS International to analyse adverse reaction reports together with drug use data from different countries, and results of pilot studies have been published (Lindquist and Edwards, 1997; Lindquist *et al.*, 1994, 1996, 1997). These analyses allow national differences in reporting rates to be further analysed for reasons that may be due to differences in indications for use, medical practice and demographics. It is hoped that this type of analysis of international data will serve as a guide to the need for more precise pharmaco-epidemiological investigations and will be taken into regular use.
 - The UMC has been active in refining the concept of benefit–harm analysis for drug safety (Edwards, Wiholm and Martinez, 1996). The previous common pairing of benefit and risk does not provide a logical or helpful contrast: we need to know what are the benefits and their chance of occurring (benefit and effectiveness); and what is the harm and its chance of occurring (harm and risk). Effectiveness–risk analysis, often referred to as ‘benefit–risk assessment’ and also ‘risk management’ should be more than the subjective opinion of a group of experts and is in its infancy an objective way of considering drug therapy. The needs of managed care and the adoption of guidelines for therapy in all therapeutic areas mean that there needs to be satisfactory methods for measuring effectiveness–risk in clinical practice for all major therapeutic interventions, so that those interventions may be compared. Safety must be seen as relative: there is no absolute safety. There is relativity in the risk or harm that one drug causes compared with another and in the risk or harm caused by a drug in relation to its effectiveness or benefits. Risk, above a certain incidence ($>1/1000$), is measurable in clinical trials, but we have much less information on safety than we need, because clinical trials are not well designed to elicit information about adverse effects. Additional information on lower incidences comes from individual case reports of varying quality and quantity and from observational studies, which are not consistently performed with all drugs and all ADRs. The observational material, reports or studies, is susceptible to various biases to different degrees. Most studies actually measure effectiveness (the frequency of a defined beneficial effect) and risk (the frequency of various defined aspects of harm). They do not measure benefit (the degree to which an individual feels improved by a therapy) or harm (the degree to which a person feels damaged by a therapy)
 - The concept and needs for benefit–risk communication have been explored and developed. One of the widely quoted outcomes is the ‘Erice Declaration’, which proposes principles for such communication (Bowdler, 1997; Edwards, 1999; Edwards and Hugman, 1997; Edwards *et al.*, 2000). With the aim of improving communications in pharmacovigilance, initiatives have been taken to call together representatives of all major groups involved in the provision of drug safety information. The Erice report on communicating drug safety information sets out the basis for further development in this area (UMC, 1998).
- It is important that everyone should have a basic understanding of how science and medicine affect their lives and of the basis on which they should make decisions which will influence their health and welfare. Drug safety issues are high on the list of priorities in everyday life. The UMC has been actively committed for some years to the development of open, ethical communication and effective, modern communications practice.

The publication of the two parts of 'Viewpoint' (see <http://www.who-umc.org> – Publications – Viewpoints 1 and 2) is an example of this commitment. 'Viewpoint' provides a comprehensive picture of the complex and vital issues and questions surrounding drug safety and the part played by the UMC, the WHO Programme and its members in improving public health and reducing the potential hazards to patients.

'Viewpoint' has been written and designed to be accessible to the widest possible audience: among the first of its kind in the world. Part 1 explains the basic concepts and issues in drug safety and risk management while Part 2 offers a more detailed and technical account of the science of international pharmacovigilance, but still in relatively simple language and concepts. Both are in full colour and extensively illustrated with pictures, graphs and diagrams.

A recognition of the importance of good communication skills has led to many initiatives, UMC personnel have been involved in the training of journalists in drug safety in various countries, and a new module on 'Effective communications in pharmacovigilance' has been added to the UMC training course on ADRs

- A great number of publications are produced annually from the UMC, both technical which are intended for national centres in the WHO programme directly working with drug safety issues and publications for a wider audience with an interest in the field.

Some of the publications, as *The Importance of Pharmacovigilance* (WHO and UMC, 2002) and *Safety Monitoring of Medicinal Products: Guidelines for Setting up and Running a Pharmacovigilance Centre* (WHO and UMC, 2000) have been published jointly with WHO. The scientific work at UMC has led to the publication of two doctoral theses [Bate 2003; The use of Bayesian confidence propagation neural network in pharmacovigilance (Bate, 2003), and Lindquist, 2003, Seeing and observing in international pharmacovigilance – achievements and prospects in worldwide drug safety (Lindquist, 2003)].

Over the last 10 years, there have been 66 publications in scientific journals actively involving UMC staff.

- It has become increasingly clear that adverse reaction monitoring must be extended to herbal

remedies, not least because of the cultural change in developed countries where more and more people are turning to natural products. In response to this challenge, the UMC has taken initiatives to improve the classification systems for such medicines. In a joint project with institutions in the United Kingdom and the Netherlands, a system compatible with the ATC system used for modern, synthetic medicines has been developed. Input from experts from all parts of the world, representing different therapeutic traditions, is indispensable for this project. The work has been done in collaboration with experts in South Africa, the United States and Germany.

- The UMC database is far enough advanced to be finding some herbal signals and an expert panel to analyse these herbals signals has recently been set up (Farah, 1998, 2000a, Farah *et al.*, 2000b; Lindquist, Farah and Edwards, 2000).
- The need for new pharmacovigilance approaches to deal with the aggressive global marketing of drugs has been identified (Edwards, 2000).

WHAT IS STILL MISSING – WHAT WE MUST DO IN THE FUTURE

The pharmaceutical industry is poised on the edge of new opportunities and challenges in the new millennium (Edwards, 2000). Better and faster ways to develop new medicines clearly give one opportunity, but the real excitement is in the area of genetic knowledge and manipulation, which allows unprecedented interference with disease processes. The industry is faced with challenges to become ever more profitable, and this has resulted in what might be called management experiments of re-structuring, merging, outsourcing, virtual companies and so on. There is an aim to market medicinal products globally and fast. Even recreational drugs are a possible legitimate consideration for the pharmaceutical industry in the future. All of this has implications for the safety of medicines, and the most obvious issue is that the rapid exposure of large numbers of people to novel products, which might have profound effects for ill as well as good.

Many publications attest to the high proportion of hospital admissions that are related to

drug injury (Lazarou, Pomeranz and Corey, 1998; Pirmohamed *et al.*, 2004). Most other disease incidences do not come close to drug injury as a cause for morbidity. Moreover, it seems likely that about half of these events are avoidable. A chronological examination of the literature on drug-related morbidity makes it clear that this public health problem is not decreasing. Why is this?

More drugs become available on the market all the time, and this may itself be a factor in keeping the incidence of drug-related morbidity high. In addition, there can be a higher reporting rate for adverse effects associated with new drugs (the Weber effect). This comes about because of clinical interest in the new drug, the possibility of a novel ADR profile, as well as effects which may have come about because of lack of clinical experience with the agent (e.g. first dose hypotension with calcium antagonists, dependence and withdrawal with selective serotonin reuptake inhibitors).

Multiple drug use may result in adverse interactions, causing ADRs or lack of efficacy (Meyboom *et al.*, 2000a,b). Not only does polypharmacy occur when a single physician is treating compound disease processes but with increasing specialisation, more than one doctor may be prescribing without another's knowledge. In addition, the patient may be taking over-the-counter medications and herbal preparations. Treating compound disease also requires consideration of the interaction of concomitant disease on drugs used for the target illness. More patients are treated for multiple serious illnesses: elderly patients need specific consideration in this respect, and a larger part of the population of most countries is in the geriatric age group.

Fraudulent drugs may cause problems of lack of efficacy (Meyboom *et al.*, 2000a,b) and issues relating to adverse effects resulting from excipients. This growing problem, which affects developed and developing countries, needs a different approach to pharmacovigilance. Certainly, there are many countries which still need to develop effective drug regulation.

Misdiagnosis, bad prescribing, bad dispensing and other poor practice leads to drug injury, but there may be correctable reasons for this poor performance. It is clear that the pressure is mounting on doctors and other health professionals. The technical and professional complexity of their work is increasing

and to this we must add an increasing administrative and bureaucratic load. Undergraduate medical training does not devote sufficient time to drug safety, and post-graduate education is too frequently concerned with the latest therapy and the importance of being up to date in the scholarly rather than practical sense. There is unending pressure on doctors, including the threat of litigation for even the most genuine of errors by the most careful of doctors. Patients are increasingly informed on medical matters and are encouraged, quite rightly, to understand and be active partners in their therapy instead of passive subjects. Unfortunately, the reliability of information sources is very variable, including a huge amount of information accessible to patients on the internet. Increasingly, therefore, doctors are required to justify their advice on therapy and even to undo confusion because of conflicting information.

There may be more reasons why drug-induced injury continues to be a public health problem, but it seems clear that much of it relates to fundamental issues of health professional education and working circumstances. The rest has to do with more drugs, more technical innovation and increasing information overload.

The relationship between clinical practice and patient harm has recently been given a much higher profile. The developments spearheaded in Australia, the United Kingdom and the United States of America have been recognised by a global effort to tackle the problem: the WHO World Alliance for Patient Safety. A central theme in the work will be to understand patient safety and medical error in a systems sense and to avoid a 'blame culture' (Edwards, 2005b). Pharmacovigilance must be a part of this effort and some of the steps below need to be considered in this context.

There are five broad activities that are essential to pharmacovigilance. These are

- suspected ADR signal detection and formation of hypotheses,
- analysis of all issues around the signal, particularly confirmation (or refutation) of hypotheses, estimation of the size of the risk and whether particularly susceptible patients exist,
- consideration of possible changed effectiveness-to-risk issues in therapy,

- communication of information to health professionals and patients in a useful way and possible regulatory action and
- consequence evaluation.

Each of the above steps will be considered below in relationship to some change, critical to make more progress. A basic assumption is that, since drug therapy very rarely constitutes epidemic risks, public health is very much concerned with securing the best benefit-risk for minority groups as well.

DRUG SAFETY SIGNALS

Suspected ADR signals may be related to a new drug or to the way in which any drug is used in the community. Because many hospital admissions are caused by avoidable ADRs, we should take much more notice of reports of known ADRs to older drugs and generally regard any ADR report as something that has concerned a reporter enough to send it! This means not just concentrating on adverse reactions to new drugs (serious and unexpected) but to encourage health professionals and consumers to report any significant adverse effect relating to drug therapy. We need to provide the right climate for health professionals to be observant and critical in their diagnoses and therapy, so that they do not miss any piece of new information that may make therapy safer. IT and data mining can improve the transfer and analysis of the additional reports, respectively. In addition, it will be necessary to widen the scope of reporting to include adverse reactions to herbal and other traditional remedies, drug misuse, abuse, poisoning and overdose and unexpected lack of effect if we really wish to tackle the public health issues surrounding drug therapy comprehensively.

Multipurpose health databases should be used to monitor drug safety signals much more than they are at present. Such databases should be planned so that appropriate data can be captured. Reports from consumers should be acted upon, both with a response to the individual and to the general public where appropriate. The UMC has recently worked with IMS Health on data mining the latter's disease analyser data. This has started with a successful pilot project using approximately two million patients' fully anonymised health care records. The potential

to find unknown patterns of links between prescribed drugs and outcomes, even in sub-groups, is great, including some of the challenges raised in the next sections.

SIGNAL ANALYSIS AND IMPACT – HYPOTHESIS TESTING

Very many signals are produced, and our ability to analyse them is limited. Currently, there seems to be little consistency over what signals will be considered further. Serious signals that appear new, and relate to new drugs, usually elicit regulatory action. Less serious signals that may none the less have an important impact on morbidity, and compliance may not be investigated so rigorously even when the numbers build up. Epidemiological studies may take months to years to perform during which time thousands of patients may be exposed to the signalled risk.

This period of new signal analysis is rarely made transparent, and controversies tend to linger. Almost the whole effort of this vast collection machinery for clinical case report information is directed towards finding new ADR signals. Little use is made of the data for other signal work, such as

- finding at-risk groups (e.g. do some ADRs occur disproportionately with age?);
- interactions (do known reactions occur more frequently with certain medicine combinations?) and
- ADRs related to usage (e.g. do certain reactions occur more frequently in certain countries? At higher doses? Are there systematic errors in use?)

This is not surprising, because the quantity of data is so large and most national centres have few resources. Several needs are apparent if we are to meet the challenges of the future. Amongst the most important are

- to encourage clinicians to report clinically relevant experience, including better details of what happened;
- to do root cause analysis on cases;
- to give advice about the diagnosis and management of ADRs;
- to improve the rapid transmission of quality information to national centres and industry, and thence to the WHO database;

- to find ways of supporting the examination of large amounts of disparate information and
- to be able to bridge the gap between a tentative signal from raw ADR data and observational studies that use specific protocols.

BENEFIT TO RISK ANALYSIS

Much of the debate about comparative benefit and risk is bedevilled by failures of logic and definition (e.g. clearly differentiating between ‘harm’ and ‘risk’) and the use of different criteria in different situations. It is very important that these issues are identified in any critical review of information. The UMC developments in this area involve

- promotion of the principle that responsible safety information must involve an element of benefit-risk analysis, that is what the patients actually feel about responses to therapy. Newer quality of life measurements will aid this process, as will a broader view of the information through consumer and health professional spontaneous reports. They should be seen as consumer concern reports, not as part of epidemiology. Bad quality (having little information) reports should still raise concerns, even though they may not be of much use in determining actual causality between drug and effect. They still expose situations of public perceptions of risk which need to be addressed;
- the further development of definitions that are acceptable to the WHO collaborating national centres;
- to develop much further on the CIOMS IV guidelines on the ‘Principles of benefit-risk comparison’ and
- the development or promotion of methods that will enhance more rigorous benefit-risk analysis, for example
 - comparing like with like;
 - the use of best-case and worst-case analysis for uncertain safety information;
 - international analysis to highlight and to determine reasons for differences in reporting of ADRs and
 - analysis of ADR reports for comparator medical products when important safety signals are raised.

COMMUNICATION OF BENEFIT-RISK INFORMATION

Currently, the emphasis of communication is on deciding whether a drug should be available or not and communicating that information and the provision of official information in summaries of product characteristics (SPCs) and their equivalents or in formulares. Decisions are made by regulators and the industry and their professional advisers as a result of a debate that is not transparent to consumers in most countries. Medicines are somewhat different from most other consumer products, in so far as patients generally do not have the ability, either because of lack of knowledge or insight to make good choices about their own treatment unaided by information presented in a way useful to them and without professional advice. The question then arises as to whether health professionals, as learned intermediaries, have the correct or sufficient information on the benefits and risks of drugs from information that is readily available during clinical practice, for example reference books and SPCs.

Patient information leaflets are now promoted by some authorities, such as the EU and industry. These moves seem reasonable, but there must be a review of their effectiveness.

Communication to health professionals on adverse reactions needs to give some idea of their likelihood, severity and possible outcome to be useful to a clinician and, of course, their patients. Little of this information is made available nor is the level of certainty made clear on the evidence for most reactions.

CONSEQUENCE ANALYSIS

As far as possible, the likely consequences of a response to a safety concern should be considered before the action is undertaken. Input should be sought from experts in communication science, patient groups, practising health professionals and others when trying to predict consequences. This knowledge should guide choices between the options for action available. For example, a consequence analysis should be planned before a warning about a drug is given out or the drug is taken off the market. This analysis should be in two parts: an early investigation designed to ensure that the expected effect was achieved, so that a correction or reinforcement can be applied as

necessary, and a later evaluation to ensure that a positive response is maintained. The UMC has previously looked at the way in which the signals it produces have been used in national centres (Edwards and Fucik, 1996, Ståhl *et al.*, 2003).

JOINING THE WHO PROGRAMME

Considering the sensitive nature of the data being collected within the Programme, countries contributing such data to the scheme have agreed on certain requirements that should be complied with by countries wishing to join. Collaborating with WHO, being an organisation for co-operation between member states, also requires a certain administrative structure of the drug monitoring activity. The basic requirements are

- general acquaintance with the methodology of spontaneous monitoring. A country joining the WHO Programme must have a programme for collection of spontaneous adverse reaction reports in place;
- a national centre for pharmacovigilance must be designated and recognised by the Ministry of Health (or equivalent) and
- technical competence to fulfil reporting requirements to WHO. Case reports collected in the national drug monitoring programme must be submitted regularly to the WHO Programme in a defined format.

The UMC has published *Safety Monitoring of Medicinal Products: Guidelines for Setting-up and Running a Pharmacovigilance Centre* (WHO and Uppsala Monitoring Centre, 2000) and argues the case for good pharmacovigilance practice (Meyboom, 2000).

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CONCLUSIONS

The discipline of pharmacovigilance has developed and improved over the years. Much information on drug safety is now collected and subject to expert analysis and review. However, drug-induced morbidity remains a leading cause of hospital admission in several countries. Many improvements have been mentioned, but the primary immediate need is for effective and efficient communication to health professionals.

This will need a paradigm shift from a gaze focused only on finding novel ADRs to new drugs, to a concentration on finding the problems associated with drug use in the community and how to improve it. Feedback on the results of efforts to improve the therapy of patients in regular clinical practice is essential for the future.

Health professions are criticised for many deficiencies, one of which is drug-related injury, but in our view, society does not equip the health professions with the right resources to improve their performance. On the contrary, health professionals work under increasingly difficult circumstances in many countries. As far as drug safety is concerned, the provision of much better information for health professionals and the time for them to analyse and use the information is the main challenge for the near future. Only then can patients feel that they have the best chance of rational, individually tailored treatment, the best chance of not experiencing ADRs, the best chance of having unavoidable ADRs diagnosed and the best chance of important clinical experiences of ADRs being reported and used for future improvements.

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13

Medical Dictionary for Regulatory Activities (MedDRA®)

ELLIOT BROWN

Elliot Brown Consulting, Barnet, UK

MedDRA is a registered trademark belonging to the International Federation of Pharmaceutical Manufacturers Associations.

INTRODUCTION

MedDRA is a structured vocabulary of medical and other terms relevant to the development and use of medicines in man. It was designed for use in the pharmaceutical industry/regulatory environment, ostensibly to support all stages of the regulatory process concerning human medicines. It began life in the early 1990s as a refinement of the, then new, dictionary developed for the UK regulatory agency's ADROIT (Adverse Drug Reaction On-line Information Tracking) post-marketing safety database. Developed by an international committee of regulators and industry staff, the new terminology had its first incarnation as MEDDRA (Medical Dictionary for Drug Regulatory Affairs) in 1993, then being nurtured and transformed by the International Conference on Harmonization (ICH) M1 Expert Working Group into the subtly renamed MedDRA (Medical Dictionary for Regulatory Activities) (Brown, Wood and Wood, 1999).

Its release to an expectant public 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 Associations (IFPMA), with oversight by a Management Board answerable to ICH. However, the interface with users, who purchase access rights through a system of licensing, is via the MedDRA Maintenance and Support Services Organisation (MSSO) and the corresponding, but distinct, Japanese Maintenance Organisation (JMO). The work of these bodies is undertaken on a commercial basis – currently by Northrop Grumman Mission Systems (for MSSO) and the Japanese Pharmacopoeia (for JMO). The MSSO and JMO release to subscribers updated versions of MedDRA (currently) every 6 months on a CD or by Internet download (MedDRA Maintenance and Support Services, 2005).

Guidance for the use of MedDRA has been developed by the MSSO: this comprises an Introductory Guide that is provided with MedDRA to subscribers, as well as guidance on some specific contentious issues, including version control and use of MedDRA in labelling. In addition, ICH-endorsed guidelines on term selection (MedDRA® Term Selection, 2004)

have been issued by a joint industry-regulators working group ('Points to Consider' guidelines), and this body has also published draft guidance on database searches and presentation (MedDRA® Data Retrieval and Presentation, 2004). Another working group, under the aegis of CIOMS, is developing standardised pharmacovigilance search strategies (SMQs, 2005).

MedDRA SUBSCRIPTIONS

MedDRA is available only on payment of a subscription to the MSSO or JMO, although this is free for regulatory authorities. The usual type of subscription involves the 'core service' (MedDRA Maintenance and Support Services, 2005); this provides for use throughout a company and its wholly owned subsidiaries. The core service supplies the subscribing company with two updated versions of MedDRA each year, together with the facility to request up to 100 changes per month to MedDRA. Changes that are accepted by the MSSO are posted on their website and are available in the next version of the terminology.

The Core Service subscriptions are based on the annual revenue of the company, as published in the annual report. The annual subscription charges in 2005 range from \$3825 for a company with revenue under \$1 million to \$92 292 for a company with more than \$5 billion annual revenue. It does not take a mathematical expert to appreciate that there is some significant disproportion at play here!

MedDRA CONTENTS

The MedDRA terminology contains more than 60 000 terms for medical conditions, syndromes, diagnoses, clinical signs, symptoms, laboratory and clinical investigations and social circumstances. It thus differs from dictionaries such as COSTART, HARTS and WHO-ART, which are more than an order of magnitude smaller and principally composed of adverse reaction terms. However, MedDRA does contain most (if not all) of the terms from these adverse reaction dictionaries, as well as most terms from the International Classification of Diseases ICD9 and its clinical modification, ICD9-CM. The intention was that the terms from these other dictionaries and classifications are retained in MedDRA 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'. It should be appreciated that, although these terms from other dictionaries are present in MedDRA, they do not retain their original relationships and hierarchical locations.

Thus, for example, in WHO-ART, the Preferred Term (PT) *Cholesterol crystal emboli* is located in the *Platelet, bleeding and clotting disorders* System Organ Class (SOC). In MedDRA, *Cholesterol crystal emboli* is a LLT under the PT *Fat embolism*, located in the *Injury, poisoning and procedural complications* SOC.

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 hence perhaps does not strictly comply with the dictionary definition of a dictionary!). It does not include demographic terms, such as those describing gender, age or race – unless these are a component of a discrete medical condition, such as *Infantile spasms* or *Breast cancer male*. MedDRA also does not include numerical expressions, 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 demographics 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.

USES OF MedDRA

From its inception, MedDRA was intended for use throughout the regulatory process of the development of medicines in humans and also during their subsequent clinical 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

or Development Core Safety Information, in annual safety reports and in the safety sections of interim and final study reports. In the European Union (EU), its use is required for the electronic reporting of Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) to the Clinical Trial Module of the Eudravigilance regulatory safety database. The ICH E4M guideline (ICH Harmonised Tripartite Guideline, 2005) 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 (SPC). In the EU, some regulators have requested the use of MedDRA for describing adverse reactions in the SPC, although at the time of writing this is not required by regulations.

The use of MedDRA for recording and for the expedited reporting of adverse reactions for marketed products is required by regulation in the EU and Japan. The mandatory use of MedDRA for this purpose in the United States is anticipated with the (presently delayed) implementation of the FDA's Proposed Rule on Safety Reporting Requirements for Human Drug and Biological Products (FDA, 2003). The use of MedDRA is recommended for expedited reporting to

Health Canada and a requirement for its use for expedited reporting is also described in Australian regulatory guidelines.

The scope of MedDRA for use in individual case safety reports is summarised in the ICH E2B(M) guidelines (ICH Guideline on Clinical Safety Data Management, 2005), 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; sender's diagnosis. An additional use would be in the recording of findings of investigations of the adverse event. MedDRA is also appropriate for use in the Periodic Safety Update Report (PSUR) in line-listings and summary event tabulations, although it is not explicitly required by regulation.

MedDRA STRUCTURE

MedDRA is supplied as flat ASCII files. These files are linked and arranged in a hierarchical matrix. Each MedDRA term is presented as words and also comprises a non-logical 8-number code. The terms are organised within 5 hierarchical levels: Lowest Level Terms (LLT); Preferred Terms (PT); High Level Terms (HLT); High Level Group Terms (HLGT); and System Organ Class (SOC) (Figure 13.1). Conceptually, it can also be considered that the terms are

Number of terms	Level of Term	Example
26	System Organ Class	Respiratory, thoracic and mediastinal disorders
332	High Level Group Terms	Lower respiratory tract disorders excl obstruction and infection
1683	High Level Terms	Lower respiratory tract inflammatory and immunologic conditions
16751	Preferred Terms	Alveolitis allergic
62348	Lowest level Terms	Pneumonitis allergic

Figure 13.1. MedDRA hierarchy (version 8.0).

arranged into 26 vertical axes, each represented by an SOC.

Lowest Level Terms – around 60 000 in number at the time of writing – 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 – for example, a doctor reporting an adverse reaction (the verbatim or ‘reported’ term) – 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 mis-spelt 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 coding new data. MedDRA terms are never deleted from the terminology, although terms may be demoted to the lowest level and made non-current.

Similar LLTs are linked to the same PT, of which there are of the order of 16 000. An example is shown in Table 13.1. Each PT is also duplicated as an LLT. The PT level is that favoured for use in case retrieval and data presentation, each PT ostensibly representing a unique medical concept (although in reality there may be overlap). PTs associated with similar medical conditions are in turn grouped under some 1 600 HLTs (approximately). Examples of PTs grouped under an HLT are shown in Table 13.2. HLTs are grouped as clusters under some 300 or so HLGTs, an example of which is shown in Table 13.3. HLGTs in turn are distributed among 26 SOCs, as shown in Tables 13.4 and 13.5 respectively.

These hierarchical groupings help bring together similar medical conditions for purposes of case-finding and presentation. Thus the HLTs and HLGTs may help to subdivide large tables of aggregate data, as shown in Table 13.6.

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. In this case, MedDRA designates one SOC as being ‘primary’, for purposes of data presentation. The other locations (up to 4) of the PT are referred to as ‘secondary’ locations.

An example of the multiaxial structure of MedDRA is shown in Table 13.7. A problem arises for some

Table 13.1. Lowest level terms under a preferred term.

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

Table 13.2. Preferred terms under a high level term.

Lower respiratory tract inflammatory and immunologic conditions
Allergic granulomatous angiitis
Alveolitis
Alveolitis allergic
Alveolitis fibrosing
Alveolitis necrotising
etc.
Pulmonary sarcoidosis
Pulmonary vasculitis
Rheumatoid lung
Systemic sclerosis pulmonary
Wegener’s granulomatosis

Table 13.3. High level terms under a high level group term.

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

Table 13.4. High level group terms under a system organ class.

Respiratory, thoracic and mediastinal disorders

Bronchial disorders (excl neoplasms)
Congenital respiratory tract disorders
Lower respiratory tract disorders (excl obstruction and infection)
etc.
Respiratory tract infections
Respiratory tract neoplasms
Thoracic disorders (excl lung and pleura)
Upper respiratory tract disorders (excl infections)

users of MedDRA because their database systems do not adequately handle the MedDRA data model. Hence, they may be unable to utilise 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 finding all reports of ventricular arrhythmias, it is helpful that cases of *Sudden death* (primary location of the PT is in the *General disorders* SOC) would be retrieved in a search of the *Cardiac disorders* SOC under the HLT *Ventricular arrhythmias and cardiac arrest*, as the term has a secondary location there – if the database system functions adequately. This will be considered further under Database Searches below.

MedDRA RULES AND CONVENTIONS

There are several MedDRA rules or conventions, some of which will be presented here. First, there are some linguistic/lexical conventions. Thus, for example, abbreviations are permitted if these are in common usage and unambiguous. For example, *ALT*

Table 13.5. System organ classes.

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

Increased is an abbreviation of *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 – thus, for example, *Pneumonia salmonella; Pneumonia staphylococcal; Pneumonia streptococcal*, and so on. A personally rather pleasing convention is that PTs in English use the British spelling (*Oedema; Anaemia; Oesophagitis*). American English is relegated to the LLT level. It is important to remember this, otherwise when looking at tables of data that are arranged alphabetically as PTs under SOC, for example, it is possible to miss terms due to the spelling convention.

Another convention concerns the anatomical location of terms under primary and secondary SOC. The convention is that the pathological process takes precedence over the anatomical location. Thus, congenital conditions have their primary location in

Table 13.6. Display of data using primary SOCs.

SOC: Blood and lymphatic system disorders	HLT	PT
HLGT: Anaemias nonhaemolytic and marrow depression		
HLT: Anaemias NEC	5	
PT Anaemia		3
PT Hypochromic anaemia		2
HLT: Marrow depression and hypoplastic anaemias	2	
PT Aplastic anaemia		2
HLGT: Haemolyses and related conditions		
HLT: Anaemias haemolytic immune	2	
PT Coombs positive haemolytic anaemia		2
HLT: Anaemias haemolytic NEC	1	
PT Haemolytic anaemia		1
HLGT: Platelet disorders		
HLT: Thrombocytopenias	2	
PT Thrombocytopenia		1
PT Thrombocytopaenic purpura		1
HLGT: White blood cell disorders		
HLT: Neutropenias	5	
PT Agranulocytosis		2
PT Neutropenia		3
SOC: Cardiac disorders		
HLGT: Cardiac arrhythmias		
HLT: Cardiac conduction disorders	3	
PT Adams-Stokes syndrome		1
PT Atrioventricular block complete		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	7	
PT Cardiac arrest		2
PT Torsade de pointes		3
PT Ventricular arrhythmia		2

the *Congenital, familial and genetic disorders* SOC. Hence, for example, the PT *Heart disease congenital* has its primary location there, with a secondary location under the *Cardiac disorders* SOC. In the same way, *Pharyngitis streptococcal* has its primary location in the *Infections and infestations SOC*, with a secondary location under *Respiratory, thoracic and mediastinal disorders* SOC. The convention applies equally to neoplasms.

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

A rule regarding the structure of MedDRA is worthy of mention here. Whilst a term may be represented in more than one SOC – multiaxiality – it cannot be present under more than one grouping term within a SOC. Thus, a PT is only associated with one HLT and one HLGT within its primary SOC. It may be associated with a different (single) HLT and (single) HLGT in each of its secondary SOCs. Hence, for example, the PT *Peptic ulcer haemorrhage* is associated with the HLT *Gastrointestinal haemorrhages* in the *Gastrointestinal disorders* SOC. It cannot therefore also be associated with the HLT *Peptic ulcers and perforation* 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.

Table 13.7. Multiaxial linkages for the PT Purpura

	Primary SOC	Secondary SOC	Secondary SOC
SOC	Skin and subcutaneous tissue disorders	Blood and lymphatic system disorders	Vascular disorders
HLGT	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

USING MedDRA FOR DATA ENTRY

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 browser may be downloaded from the MSSO website. 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. 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, then drilling down through the HLT, HLT and PT until appropriate LLTs can be viewed and selected. An illustration of the appearance of MedDRA using a browser is shown in Figures 13.2 and 13.3.

Autoencoders may have the additional capability of scanning narrative texts and presenting expressions likely to need coding. They will often store selections of LLTs that closely match verbatim terms coded historically, in order to improve consistency of term selection. They can code long lists 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.

Guidelines on the selection of terms used to code adverse events have been published by the MSSO (MedDRA® Term Selection, 2004), with the endorsement of ICH. These ‘Points to Consider’ guidelines cover the topics shown in Table 13.8. It is important that each MedDRA subscriber has its own written

procedures that are consistent with these guidelines, in order to make coding as consistent as possible across the organisation concerned.

The general principles presented in the ICH-endorsed guidelines are as follows:

1. Try to clarify ambiguous, confusing or unintelligible data.
2. Promote quality through form design and by training those involved in collection and follow-up.
3. Select the LLT that most accurately reflects the reporter’s words.
4. Use current LLTs only (unless for legacy data conversion).
5. Use medical judgement if there is no exact match for a verbatim term, if there is an existing adequate representation in MedDRA.
6. It is not appropriate to address deficiencies in MedDRA by developing organisation-specific solutions.
7. If there is no adequate representation of a concept in MedDRA, submit a change request to the MSSO.
8. If a specific medical concept (e.g. metastatic colon cancer) has no single MedDRA term, request a new term, and in the interim, use one or more existing terms (e.g. *Colon cancer*, or *Metastases* or use the two terms *Colon cancer* and *Metastases*)
9. Do not subtract or add information: no medical concepts should be excluded from coding; code regardless of causality assessment.
10. Do not invent diagnoses or mechanisms: use the information as provided by the reporter.

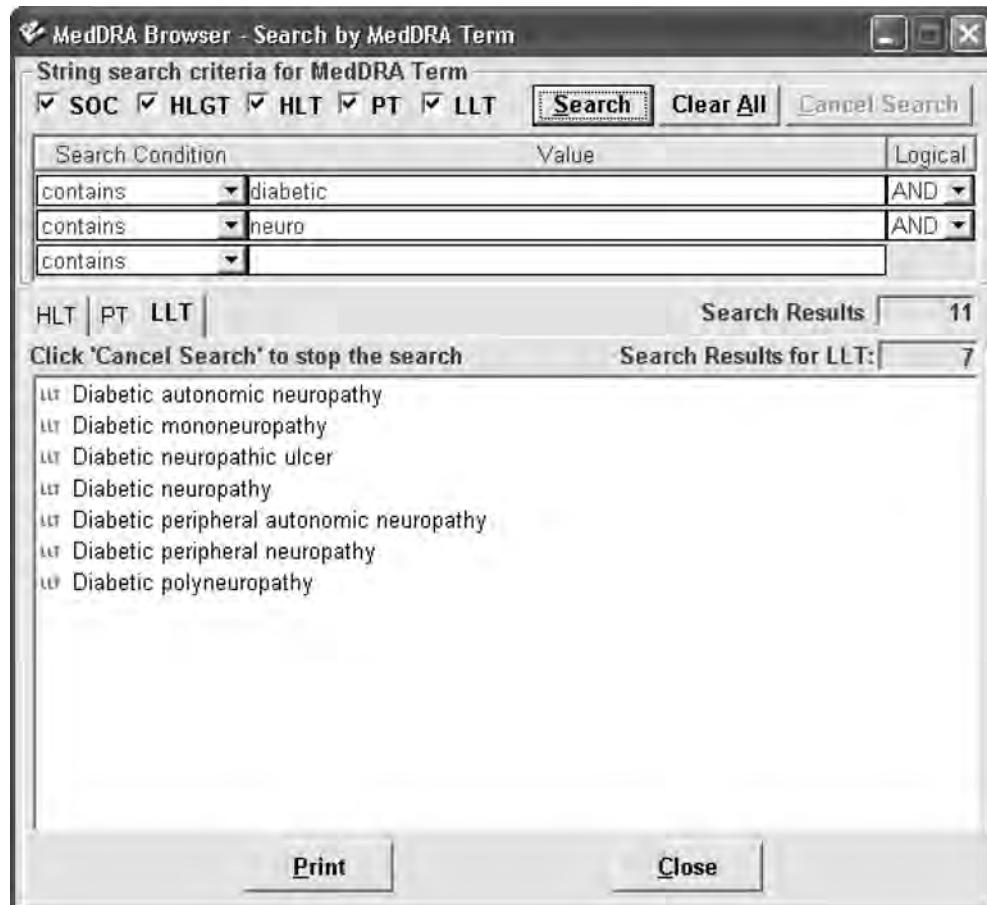


Figure 13.2. Bottom-up search using a browser. Acknowledgements: Northrop Grumman Corporation Browser v2.0.

11. Documentation of selection strategies and Quality Assurance procedures are encouraged.
12. Human intervention is essential to ensure that the end result reflects the original information and makes medical sense.
13. Do not make *ad hoc* structural changes to MedDRA: the assignment of SOCs is pre-determined and should not be altered by users, although a change request may be made if terms are incorrectly placed.

The guidelines also suggest that if a report of an adverse event includes a diagnosis and its symptomatology, it is sufficient to select a term for the diagnosis and not for the signs and symptoms. It remains an

option to code the signs and symptoms in addition. If there are signs and symptoms that are not usually part of the diagnosis, these should be coded as well as the diagnosis.

The guidelines make the following important point: 'The MedDRA terminology is multiaxial and more complex than common terminologies previously used. Therefore, term selection should be reviewed by a qualified individual, a person with medical background and/or training and who is also trained in the use of MedDRA'.

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.

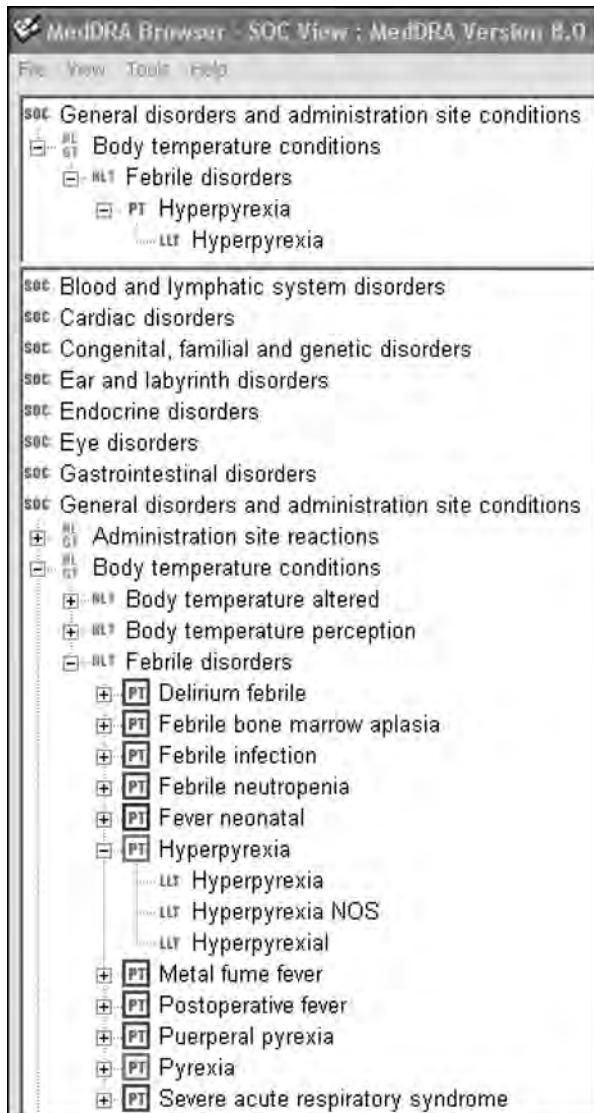


Figure 13.3. Top-Down search using a browser. Acknowledgements: Northrop Grumman Corporation Browser v2.0.

DATABASE SEARCHES AND DATA RETRIEVAL

Here we are concerned particularly with 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 safety

Table 13.8. Points to consider in term selection: ICH-endorsed guidelines on term selection.

- Provisional diagnoses
- Death and other patient outcomes
- Conflicting/ambiguous/vague information
- Combination terms
- Body site vs. Event specificity
- Location vs. Infectious agent
- Pre-existing medical conditions
- Congenital terms
- Medical/surgical procedures
- Investigations
- Medication/administration errors and accidental exposures
- Overdose/toxicity/poisonings
- Drug interactions
- No adverse effect
- Unexpected therapeutic effect
- Modification of effect
- Social circumstances
- Medical and/or social history
- Indication for product use

data such as at the end of a clinical trial, evaluation 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 Preferred Term that is the focus of searches of safety databases. However, the categorisation of these within MedDRA under primary SOC and then under HLT and LLT assists in finding 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 the *Cardiac disorders* SOC. If a multiaxial search is performed, this would additionally find PTs for various dyspnoeas under the HLT *Dyspnoeas* and HLT *Cardiac disorders signs and symptoms* even though their primary location is in the *Respiratory*

disorders SOC. Likewise, PTs for *Oedema* and *Peripheral oedema* are found in their secondary location in the *Cardiac disorders* SOC as well as in their primary location under *General disorders and administration site conditions* SOC.

However, it is essential to remember that terms in the *Investigations* SOC (and also those in the *Social circumstances and Surgical and medical procedures* SOCs) do not (at present) have secondary locations in other SOCs. It is therefore necessary to look under 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 may not be 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 print-out 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 *Investigations* SOC.

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. An example is shown in Table 13.6. However, care still needs to be taken not to miss relevant terms. As an example, in searching for cases relevant to depression, looking in the *Psychiatric disorders* SOC, 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 under the HLGT *Chemical injury, overdose and poisoning* in the *Injury, poisoning and procedural complications* SOC.

The type of search referred to above is illustrated in Figure 13.4. It is based on identifying relevant 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 13.5. 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). There is available a limited number of such searches within MedDRA itself – the Special Search Categories (SSCs). At the time of writing, there are just 13 of these, comprising lists of PTs relating to medical conditions and each spanning several SOCs. Examples are lists of PTs for Haemorrhage, Hypersensitivity reactions and Cardiac ischaemia. In an initiative that the author was instrumental in establishing, a CIOMS working group is preparing a series

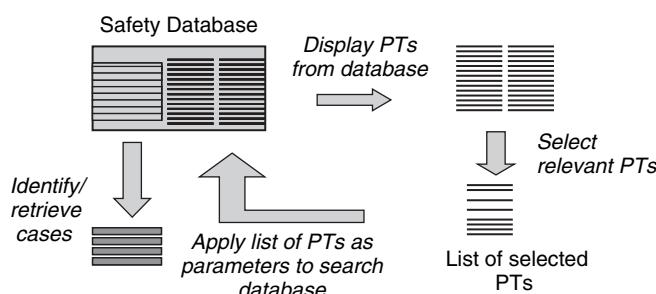


Figure 13.4. Searching a safety database for cases based on Preferred Terms in the database.

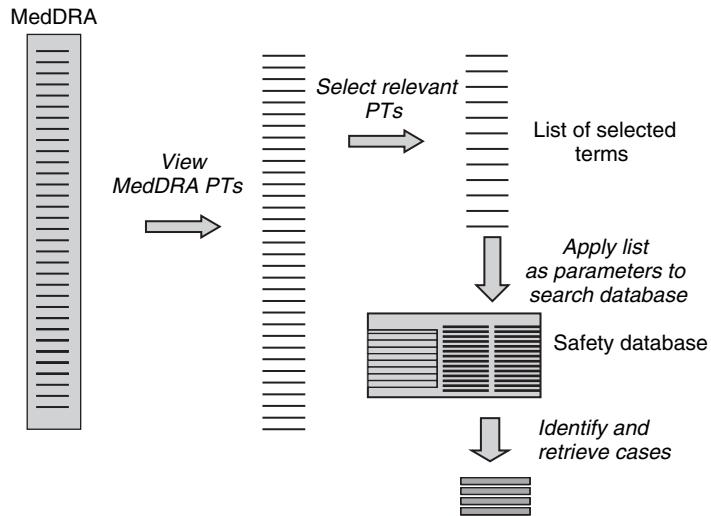


Figure 13.5. Searching a safety database for cases based on Preferred Terms in MedDRA.

of such searches – Standardised MedDRA Queries (SMQs) – which will eventually span the most important topics for pharmacovigilance. Thus, for example, at the time of writing, there are SMQs for Rhabdomyolysis/myopathy; Torsades de pointes/QT prolongation; Hepatic disorders; Haemolytic disorders; Acute renal failure; and Severe cutaneous adverse reactions and approximately another 70 are planned. The SMQ searches are made available to MedDRA subscribers only.

Standardised MedDRA Queries differ from Special Search Categories in that they may include more than one level of MedDRA, for example a list of PTs and a list of HLTs (with all their subordinate PTs). They include searches of differing degrees of specificity and sensitivity – thus, broad searches and associated narrow searches comprising subsets of these (SMQs, 2005). An example of an SMQ is shown in Figure 13.6.

Guidelines on data retrieval and presentation (presently draft, but endorsed by ICH) have been produced by a group including representatives from Industry, Regulatory authorities and the MSSO. The key elements concerning data retrieval are outlined below.

- The way that legacy data have been converted to MedDRA might have an impact on subsequent

searches of the database. (This will be discussed in the next section).

- Careful documentation of data retrieval methods is essential for the interpretation of results.
- Retrieval strategies should be reviewed by a person with a medical background who is trained in the use of MedDRA.
- When basing searches on group terms – HLTs and HLTs – users should review the terms within these groups to ensure that they are all suited to the search under consideration.
- Clinically related PTs might be overlooked or not recognised as belonging together as they might exist in different locations within a single SOC. For example, if searching for terms relating to gastric haemorrhage, these might be expected to be present under the HLT *Gastrointestinal haemorrhages NEC*, under the HLT *Gastric and oesophageal haemorrhages*. However, the PTs *Haematemesis* and *Melaena* are found under the HLT *Non-site specific gastrointestinal haemorrhages*, under the same HLT, whilst the PT *Gastric ulcer haemorrhage* is present under the HLT *Gastric ulcers and perforation* under the HLT *Gastrointestinal ulceration and perforation*. Failure to look under this HLT might lead to underestimation of the number of relevant reports.

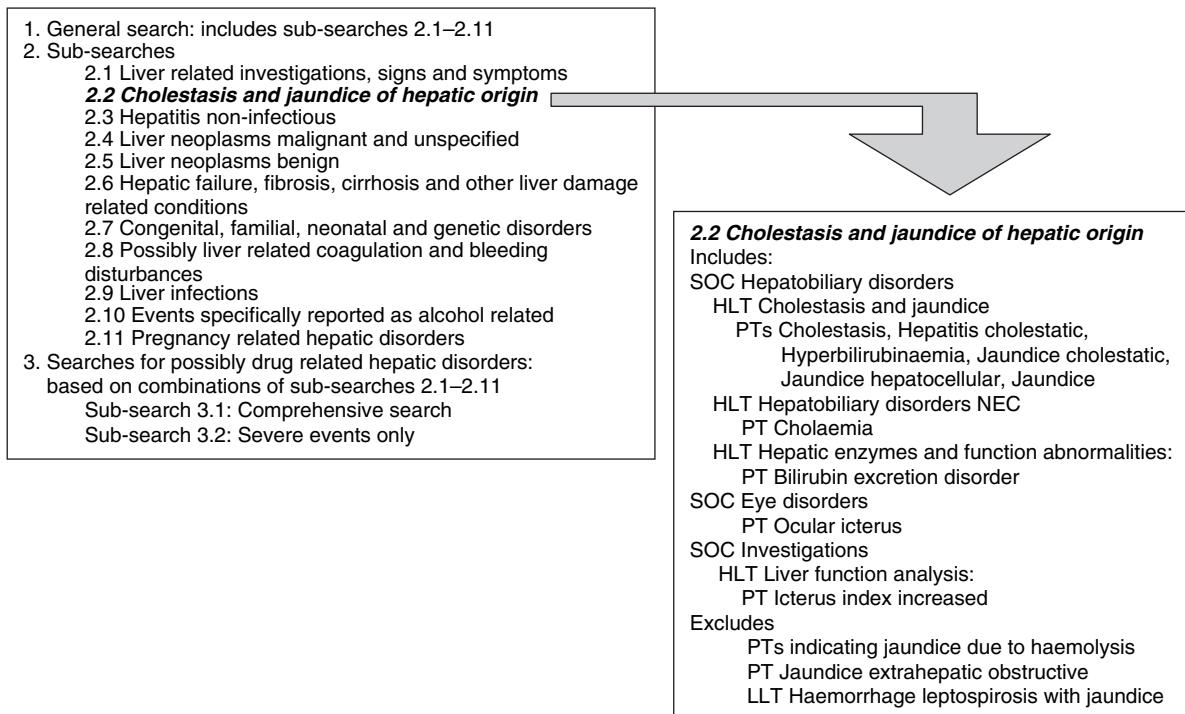


Figure 13.6. Standardised MedDRA query: Hepatic disorders SMQ.

- Users should be aware of primary SOC assignment rules that will affect the way data are distributed across the terminology. For example, terms that refer to congenital conditions are located primarily in the *Congenital disorders* SOC and the secondary location is the body site. For example, the PT *Heart disease congenital* has *Congenital disorders* as the primary and *Cardiac disorders* as the secondary SOC location. Similar rules apply for neoplasms and for infections: the location of the disease is assigned the secondary SOC location.
- Clinically related PTs in MedDRA might be overlooked or not recognised as belonging together because they can be distributed among two or more SOCs. The most important instances are probably those concerning investigation findings and associated medical conditions. For example, *Blood glucose decreased* is assigned to the *Investigations* SOC. *Hypoglycaemia* on the other hand is present in the *Metabolism and nutrition disorders* SOC.
- Data may also reside in SOCs that are not anticipated intuitively by the user and, as with the *Investigations* SOC, multiaxiality may not apply. For example, in reviewing cases of life-threatening ventricular arrhythmias, the *Cardiac disorders* SOC would be the main candidate for a search for relevant terms. In addition, terms for sudden death have a primary location in the *General disorders* SOC, with a secondary location under *Cardiac disorders* SOC. There could also be relevant terms for cardiac surgery and other interventions in the *Surgical and medical procedures* SOC, and ECG abnormalities in the *Investigations* SOC. It is important that these last two SOCs and the *Social circumstances* SOC should not be forgotten in searches, in view of the absence of multiaxial linkages.
- It is acknowledged that all possible secondary SOC assignments for a given concept may not be present in MedDRA, but it is possible to request new linkages from the MSSO.

The Guidelines refer to the SSCs and SMQs as options for searching safety databases. They also highlight the possible effects of changes in version of MedDRA on search strategies. The version used in the search should be documented and users should acquaint themselves with the changes that have been made between versions. The terms used for constructing the searches should be in the same MedDRA version as the data being queried. It is possible that a search based on an old version of MedDRA might not include all the relevant terms in a database that is based on a more recent version. Any queries that are stored for future use should be updated to the appropriate version of MedDRA prior to use on new data.

DATA ANALYSIS AND PRESENTATION

Here we are concerned with the analysis—including quantifying—and presentation of adverse event (and other medical) data that has been coded using MedDRA, as distinct from searching the database and finding the relevant cases. The principal issues are the large number of terms in MedDRA; the most appropriate levels and groupings for the required purpose; multiaxiality; and version changes.

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 paraesthesia 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 paraesthesia 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 13.9.

By contrast, if analysis had been carried out using the respective HLT, *Paraesthesia* and *dysesthesia*, the 10% versus 2% difference would have been maintained. The use of group terms in analyses might also prove problematic, however. Thus, some HLTs – especially in the Investigations SOC – include PTs that represent opposing concepts. For example, the HLT *Platelet analyses* includes PTs *Platelet count decreased*, *Platelet count increased*, *Platelet count*

Table 13.9. Clinical trial adverse events

Parallel group clinical trial: 100 patients in each treatment arm		
<u>Results using legacy dictionary PTs</u>		
Adverse event	Treatment A	Treatment B
Paraesthesia	10	2

Parallel group clinical trial: 100 patients in each treatment arm		
<u>Results using MedDRA PTs</u>		
Adverse event	Treatment A	Treatment B
Burning sensation	2	0
Formation	1	0
Paraesthesia	3	2
Paraesthesia circumoral	1	0
Paraesthesia ear	1	0
Skin burning sensation	2	0

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, ten reports of an adverse event represented by the HLT *Ventricular arrhythmias and cardiac arrest* might relate to ten cases of *Torsade de Pointes* (a particularly serious type of arrhythmia) or ten cases of *Ventricular extrasystole* (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).

Presentation of adverse event data using MedDRA is also the subject of ‘Points to Consider’ Guidelines (MedDRA® Data Retrieval and Presentation, 2004). Many of the points are identical to those concerning data retrieval, or have been described above. However, the Guidelines describe a number

of approaches to presenting data for various purposes and discuss the advantages and disadvantages of these.

Thus, an overall presentation of the safety profile highlights the distribution of ADR/AEs across SOCs and helps identify areas where more in-depth analysis should be conducted. The Guidelines recommend that data should be presented in a way that allows ready recognition of patterns of terms potentially associated with relevant medical conditions. They point out that the conventional display of data as PTs under the respective SOCs alone may not optimally represent the frequency of events and can be misleading. For example, if a number of reports describe a similar medical condition, they could be represented under various specific PTs, so that it may not be apparent that they are associated.

As a first look, one should display all data as an overview according to primary SOC, including HLGTs, HLTs and PTs (as in Table 13.6). This applies to standard tables for clinical trial and post-marketing adverse reaction data and post-marketing cumulative

Table 13.10. Display of data using primary and secondary SOCs.

SOC: Blood and lymphatic system disorders	HLT	PT
HLGT: Anaemias nonhaemolytic and marrow depression		
HLT: Anaemias NEC	5	
PT Anaemia		3
PT Hypochromic anaemia		2
HLT: Marrow depression and hypoplastic anaemias	2	
PT Aplastic anaemia		2
HLGT: Haemolyses and related conditions		
HLT: Anaemias haemolytic immune	2	
PT Coombs positive haemolytic anaemia		2
HLT: Anaemias haemolytic NEC	1	
PT Haemolytic anaemia		1
HLGT: Platelet disorders		
HLT: Thrombocytopenias	5	
PT HELLP syndrome ^b		1
PT Heparin-induced thrombocytopenia ^a		2
PT Thrombocytopenia		1
PT Thrombocytopaenic purpura		1

HLGT: White blood cell disorders

HLT: Neutropenias	5
PT Agranulocytosis	2
PT Neutropenia	3

SOC: Cardiac disorders

HLGT: Cardiac arrhythmias	
HLT: Cardiac conduction disorders	3
PT Adams-Stokes syndrome	1
PT Atrioventricular block complete	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	9
PT Cardiac arrest	2
PT Sudden death ^c	2
PT Torsade de pointes	3
PT Ventricular arrhythmia	2

Note: ^{a,c} Primary SOC: General disorders and administration site conditions

^b Primary SOC: Pregnancy, puerperium and perinatal conditions

summaries. It assures that all events will be seen and the overview might be useful in identifying clusters, perhaps in an HLT or HLGt. For a small data set, this might be all that is required. This overview can be used as the basis for planning more in-depth analyses.

Line listings (both clinical and post-marketing data) can also be displayed by primary SOC and PT. While it might be sufficient to use these for small data sets, the Guidelines indicate that it might be preferable to display data by HLGts and HLTs as well as showing SOC and PTs for more complex data. Graphical display such as histograms, bar charts and pie charts showing event terms might facilitate understanding by the viewer.

In some situations, the Guidelines suggest that a more focused presentation of data may be required, in addition to the Overview by Primary SOC. For example, when reviewing in more depth any clusters seen in Primary SOC output, or for looking at previously identified safety concerns, monitoring events of

special interest or responding to regulatory and other queries, it may be appropriate to expand the presentation by showing additionally terms in their secondary (multiaxial) SOC locations. The Guidelines recommend display of the SOC or the HLGT/HLT relevant to the search, showing all the primary and secondary terms. An example of such a presentation is shown in Table 13.10. It must be remembered that, using this method, displaying more than one SOC may lead to double (or a higher multiple) counting of terms. The Guidelines also suggest, if appropriate, the linking of relevant PTs from the three non-multiaxial SOCs (i.e., SOC *Investigations*, SOC *Surgical and medical procedures* and SOC *Social circumstances*). However, for medical conditions that are likely to involve terms in more than one SOC, it is proposed that users should consider using an SMQ.

MedDRA AND LABELLING

'Best practices' guidelines on the use of MedDRA for labelling have been published by the MSSO (MedDRA Maintenance and Support Services Organization, 2005). They propose three tiers of product labelling: the Company Core Data Sheet (CCDS) for use by the manufacturer and for interacting with regulatory agencies; information for the prescriber; and information for the patient. The MSSO states that it does not foresee a role for MedDRA in any form of patient-oriented product information.

For the CCDS, it is proposed in the MSSO document that MedDRA should be used in narrative and tabular presentations of information, but that flexibility is required, as MedDRA may not be applicable in some sections, such as for indications or dosage. In the adverse reaction section of the CCDS, the MSSO proposes the use of MedDRA, generally at the PT level, but with LLTs, HLGTs and/or SMQs or similar groupings to represent particular conditions, if needed.

The guidelines suggest that, in the CCDS, it might be possible to supplement PTs with lists of corresponding LLTs, to assist in judging listedness and to facilitate automated expectedness determination. However, it is made clear that such lists are no substitute for medical judgement, and that it may be necessary to review additional case-level information in

order to provide context in deciding upon listedness or expectedness.

For product information directed at the health professional, the MSSO recommends the use of familiar medical words and logical groupings, supplemented by specific MedDRA terms or groupings. They point out that the specificity of MedDRA may be problematic when summarising data in a clinically meaningful way and that prescribers may not be familiar with MedDRA conventions. Hence, it may be necessary to translate MedDRA terms into more familiar and understandable medical terms. Again, it may be appropriate to use MedDRA group terms, or SMQs, or *ad hoc* groupings may be needed. One example of such a grouping would be the use of a single term for thrombocytopenia to include PTs for the medical condition (e.g., *PT Thrombocytopenia*) with those for the corresponding laboratory findings (e.g., *Platelet count decreased*).

Existing regulatory guidance on the use of MedDRA in the Summary of Product Characteristics in the EU can be found in Volume 2 of the Notice to Applicants, published by the European Commission (European Commission Enterprise Directorate General, 1999). Draft amendments to these guidelines have been issued and are awaiting the outcomes of consultation at the time of writing (Proposal for Revision of a Guideline on Summary of Product Characteristics Committee for Medicinal Products for Human Use, 2005). Despite the possibility that these may change in due course, it is worth summarising the proposed SPC guidelines as an indication of current EU regulatory thought on the use of MedDRA.

The present and proposed SPC Guidelines propose the use of MedDRA in Section 4.8, Undesirable effects, with a table of ADRs according to MedDRA SOC, listed in accordance with the International SOC Order. ADR descriptions should be based on the most suitable representation within MedDRA, usually PTs, but sometimes the use of LLTs or exceptionally group terms may be appropriate. Within each SOC, ADRs should be ranked under headings of frequency. In addition, the proposed guidance states that, as a general rule, any ADR in the SPC should be assigned to the most relevant SOC related to the target organ. For example, the PT *Liver function test abnormal* should be assigned to the SOC *Hepatobiliary disorder* rather than to the SOC *Investigations*.

The proposed SPC Guidelines include an Annex devoted to the use of MedDRA. This states that a pragmatic approach to the location of terms should be taken in order to make the identification of ADRs simpler and clinically appropriate for the reader. Thus, it may be helpful on some occasions to use secondary SOC locations of some MedDRA PTs, or to use locations that do not accord with MedDRA architecture. The example is given for the terms *Liver function test abnormal*, *Hepatitis* and *Hepatic encephalopathy* – it would be acceptable to include them all under the ‘Hepato-biliary disorders’ SOC, instead of distributing the reactions among ‘Hepato-biliary disorders’, ‘Nervous system disorders’ and ‘Investigations’ SOCs as dictated by their primary location in MedDRA.

The Annex then suggests that it is acceptable to adapt names of group terms if this makes their meaning more transparent, for example HLT *Genitourinary tract disorders NEC* could be presented without ‘NEC’ (not elsewhere classified). ADR terms should be expressed in natural word order, such as ‘Interstitial pneumonia’ not ‘Pneumonia interstitial’. Also, the most widely recognised term for a particular condition should be used, for example the LLT ‘Churg Strauss syndrome’ might be more appropriate than the PT ‘Allergic granulomatous angiitis’.

With regard to estimating frequency of occurrence of adverse events from studies, the proposed guidelines state that appropriate levels of MedDRA should be used in order to group together clinically related conditions in a meaningful way. For example if ‘postural dizziness’, ‘exertional dizziness’ and ‘unspecified dizziness’ were each reported by 2% of patients, this might be represented in the SPC as ‘Dizziness’ occurring in 6% of patients (assuming that only one report of dizziness applied to each patient). It may also be appropriate to use *ad hoc* groupings, or to adapt MedDRA group terms, for example reports of ADRs represented as PTs ‘Diarrhoea’, ‘Diarrhoea aggravated’, ‘Loose stools’, ‘Stools watery’, ‘Intestinal hypermotility’ could not really be represented as standard MedDRA groupings, which comprise three separate HLTs – ‘Diarrhoea (excl infective)’, ‘Gastrointestinal spastic and hypermotility disorders’ and ‘Faeces abnormal’. To make the SPC relevant and comprehensible to clinicians, the condition might simply be represented as ‘Diarrhoea’.

IN SUMMARY

The Medical Dictionary for Regulatory Activities (MedDRA) is a large, hierarchical, multiaxial medical terminology. As the M1 international standard under ICH, its use is increasing within the post-marketing pharmacovigilance environment but also for recording clinical trial safety data. Guidance on its use is increasingly becoming available, and new tools such as SMQs will help users overcome some of MedDRA’s complexities. There remains uncertainty in some areas, such as in the best way of using MedDRA to analyse and present quantitative safety information, but knowledge is growing with experience.

The terminology provides distinct advantages over some other coding systems in facilitating the capture of specific information about the experience of exposure to medicines in patients and in having a scope that extends far beyond the coding of adverse reactions. It remains to be seen how this will translate into benefits in the identification of possible signals of new adverse reactions to medication or to the presentation and evaluation of safety data on new and established drugs.

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14

Regulatory Pharmacovigilance in the EU*

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INTRODUCTION AND HISTORICAL PERSPECTIVE

Modern drug regulation in Europe began in the 1960s in the wake of the occurrence of several thousand cases (most of them in Europe) 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 drug reaction (ADR) 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, authorisation, pharmacovigilance and inspection. In the European Union (EU), the first Community Directive on medicines was enacted in 1965 (Council Directive 65/65/EEC) 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 authorisation.

Despite the extensive requirements for evidence on quality, safety and efficacy which are necessary to gain a marketing authorisation, pharmacovigilance remains 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 authorisation, conclusions on the adverse effect profiles of medicines from clinical trials are limited by the numbers and selectivity of patients included in such trials, their duration and the relatively controlled conditions under which they are conducted. Safety in practice can only be assessed after marketing, and it is well recognised 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, Coulson and Wood, 1996) are summarised in Table 14.1.

Spontaneous reporting schemes continue to underpin such monitoring throughout the EU and have proved successful in identifying many important safety issues. However, both false positives and false negatives have

* Disclaimer: The views expressed in this chapter are those of the authors and not necessarily those of their employers.

Table 14.1. Objectives of regulatory pharmacovigilance.

1. Long-term monitoring of drug safety in clinical practice to identify previously unrecognised safety hazards or changes in the adverse effect profiles
2. Assessment of the risks and benefits of authorised medicines to take action to improve drug safety
3. Provision of information to users to optimise safe and effective use of their medicines
4. Monitoring the impact of any action taken

occurred, one of the most striking examples of the latter being the failure to identify the oculomucocutaneous syndrome induced by practolol at an early stage (Felix, Ive and Dahl, 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 Member States such as the UK General Practice Research Database (Walley and Mantgani, 1997, see Chapter 27) and the Dutch PHARMO system (Herings, 1993) to evaluate the safety of marketed medicines.

During the early 1990s, closer co-operation between 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, and to a new regulatory system that includes procedures for a centralised authorisation and multiple identical authorisations through a decentralised procedure and a mutual recognition procedure. These procedures have had a considerable impact on the operation of pharmacovigilance in the EU. Although pharmacovigilance continues to be based on national systems, particularly in terms of data collection and expertise, there is central co-ordination through the EMEA and 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, which are described further below.

LEGAL BASIS, PRINCIPLES AND ORGANISATION OF THE EU PHARMACOVIGILANCE SYSTEM

The concept of pharmacovigilance was introduced into the legislation at EU level in 1993 through a Council Directive (Council Directive 93/39/EEC amending Council Directive 75/319/EEC). EU medicines legislation has since been codified into a single Directive (2001/83/EC) in which pharmacovigilance is covered in Title IX (Articles 101–108). Directives of the European Parliament and the Council have the objective of harmonising the national legislation of the EU Member States, and Member States 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 process in 2004. These systems vary according to differences in historical development and the organisation of healthcare at national level. Table 14.2 summarises the organisational features of the national pharmacovigilance systems. All are an integral part of the respective national drug regulatory authority (except in Luxembourg for which spontaneous reports are submitted to one of the French regional centres located in Nancy). Through the EU legislation, their activities are specified with regard to medicinal products authorised for use on their territory as follows:

- to collect information about suspected ADRs that occur under normal conditions of use;
- to obtain information on consumption data;
- to collate information on misuse and abuse;
- to evaluate this information scientifically; and
- to ensure the adoption of appropriate regulatory decisions.

Practice has shown that pharmacovigilance needs to be conducted with a view to how the product is used in ordinary clinical practice. This includes use outside the terms of the marketing authorisation. Experience gained during the post-authorisation phase may also provide valuable input into the evaluation of medicinal products at the stage of application for marketing authorisation, if there are chemical or pharmacological similarities with authorised products.

Table 14.2. National pharmacovigilance systems in the European Union.

Member State and Year of Joining the European Union	Year of establishing the national pharmacovigilance centre	Status of spontaneous reporting of adverse drug reaction cases by health professionals	Procedure for compilation of adverse drug reaction cases occurring in this Member State	Procedure for assessment of ADR cases and other data and decision-making for nationally authorised medicinal products	Main tool of communication of safety information to health professionals/public
Austria (1995)	1979	Mandatory	Nationwide reporting to national centre	Case assessment by single expert of national centre and advisory committee, recommendations on regulatory action by advisory committee (meets four times a year)	Press releases routinely published in professional journals, e-mail and fax-based cascade system for provision of information to health professionals through regional health authorities
Belgium (1951)	1976	Voluntary	Nationwide reporting to national centre	Case assessment and recommendations by advisory committee (meets twice a month) to medicines commission which proposes regulatory action	Press releases, monthly bulletin for health professionals
Cyprus (2004)	1996	Voluntary	Nationwide reporting to national centre	Preliminary case assessment by national centre and transmission to pharmacovigilance committee for further evaluation and recommendations to the drug council at the regulatory authority	Press releases
Czech Republic (2004)	1968	Mandatory	Nationwide reporting to national centre	Case assessment by single medical doctor, signal detection meetings at pharmacovigilance unit, signal evaluation by medical assessors, decision-making on the basis of their assessment reports by head of unit/branch/agency depending on public health impact	Press releases, monthly drug bulletin, website, letters to health professionals

Table 14.2. Continued.

Member State and Year of Joining the European Union	Year of establishing the national pharmacovigilance centre	Status of spontaneous reporting of adverse drug reaction cases by health professionals	Procedure for compilation of adverse drug reaction cases occurring in this Member State	Procedure for assessment of ADR cases and other data and decision-making for nationally authorised medicinal products	Main tool of communication of safety information to health professionals/public
Denmark (1973)	1968	Mandatory	Nationwide reporting to national centre	Signal identification process once a month for evaluation by staff at national centre, advice on drug surveillance and patient safety by ADR council	Press releases on website, quarterly publications in scientific journals
Estonia (2004)	1994	Mandatory	Nationwide reporting to national centre	Case assessment and recommendations by advisory committee (meets once a month) to medicines committee which proposes regulatory action as necessary	Press releases on website, quarterly drug bulletin for health professionals
Finland (1995)	1966	Voluntary	Nationwide reporting to national centre, major hospitals operate additional ADR monitoring systems and submit them to the national centre	Case assessment by expert group (meets once a week) and minor regulatory action by national centre, recommendations on major regulatory action by committee on safety and efficacy	Press releases, bimonthly drug bulletin for health professionals
France (1951)	1973	Mandatory	Reporting by health professionals to regional centre (31 regional hospital-based centres), compiled at national centre, reporting by marketing authorisation holders to national centre	Case assessment by single expert at regional centre, signal identification and further assessment by national centre, signal evaluation on causal relationship by technical committee (meets once a month), recommendations on regulatory action by national commission (meets twice a month),	Press releases, vigilance bulletin for health professionals every second month
Germany (1951)	1978	Voluntary	Reporting by health professionals to the drug commission of health professionals for transmission to the national centre, reporting by marketing authorisation holders to national centre	Case assessment by single expert at national centre, sometimes by advisory committee, recommendations on regulatory action by advisory committee (meets at least every second month)	Press releases routinely published in professional journals

Greece (1981)	1986	Mandatory	Nationwide reporting to national centre	Case assessment by single expert at national centre, further assessment and recommendations on regulatory action by pharmacovigilance committee (meets one to two times a month)	Press releases, publications in scientific journals
Hungary (2004)	1985	Mandatory	Nationwide reporting to national centre	Case assessment by single expert at national centre, recommendations made by internal advisory group (involving head of biomedical division, head of pharmacovigilance, two senior medical advisors), decision-making by head of agency	Press releases, publications for health professionals in drug bulletin and scientific journals, post-graduate training
Ireland (1973)	1969	Voluntary	Nationwide reporting to national centre	Case assessment and review by national centre, further assessment and recommendations on regulatory action by internal groups, the advisory committee (meets once for 3 months) and, as necessary, relevant expert sub-committees	Press releases and information update on website, monthly contribution to national prescribing guidance, drug bulletin for health professionals
Italy (1951)	1980	Mandatory	Nationwide reporting to national centre	Case assessment by single experts at national centre, further assessment and recommendation on regulatory action by national drug committee (meets once a month) and higher health council (meets once a month)	Press releases and newsletter on agency website, drug bulletin for health professionals, free telephone information line for the general public
Latvia (2004)	2001	Mandatory	Nationwide reporting to national centre	Case assessment by single expert at national centre and advisory committee (meets six times a year). Recommendations by the committee on regulatory action	Press releases on agency website, drug bulletin for health professionals every second month
Lithuania (2004)	1999	Mandatory	Nationwide reporting to national centre	Case assessment by single expert at national centre, further assessment and recommendation on regulatory action by medicinal products authorisation board (meets once a month)	Press releases, monthly drug bulletin

Table 14.2. Continued.

Member State and Year of Joining the European Union	Status of spontaneous reporting of adverse drug reaction cases by health professionals	Year of establishing the national pharmacovigilance centre	Procedure for compilation of adverse drug reaction cases occurring in this Member State	Procedure for assessment of ADR cases and other data and decision-making for nationally authorised medicinal products	Main tool of communication of safety information to health professionals/public
Luxembourg (1951)	See text	2004	Mandatory	Nationwide reporting to national centre	Case assessment by single expert at national centre and further assessment, if necessary, by scientific committee (meets once a month) which proposes regulatory action
Malta (2004)					Case assessment and (statistical) signal evaluation at national centre, further assessment in consultation with scientific advisory board for transmission of recommendations to medicines evaluation board
The Netherlands (1951)	Voluntary	1963		Nationwide reporting to national centre, five hospital-based regional centres support the national centre in its activities	Case assessment by single expert at national centre and, if necessary, by external experts, minor regulatory actions taken by national centre, recommendations on major regulatory actions are transmitted by the national centre, after consultation with external experts, to the ministry
Poland (2004)	Mandatory	1972		Nationwide reporting to national centre, establishment of regional centres planned (there are currently four independent regional offices at medical schools which cooperate with the national centre on a voluntary basis)	Statements on website, quarterly drug bulletin available on website

Portugal (1986)	1992	Mandatory	Reporting to national centre or to the four regional centres working under the co-ordination of the national centre	Case assessment and signal evaluation by the national centre and, as necessary, submission of safety issues to advisory committee (meets on demand) for further evaluation, recommendation on regulatory action by national centre with participation of pharmacovigilance committee as needed	Press releases, information on website, quarterly pharmacovigilance bulletin for health professionals, monthly publication on regulatory issues, direct mailing
Slovak Republic (2004)	1986	Mandatory	Nationwide reporting to national centre	Case assessment by two experts at national centre and fatal and some other serious reactions by advisory committee (meets three to four times a year)	Drug bulletin
Slovenia (2004)	1983	Mandatory	Nationwide reporting to national centre	Case assessment at national centre, further assessment and recommendation for regulatory action by committee for medicinal products	Press releases, drug bulletin for health professionals
Spain (1986)	1983	Mandatory	Reporting to 17 regional centres co-ordinated by the national centre (common database)	Case assessment and signal identification at the level of the regional centres, recommendations on regulatory action by advisory board (meets six to nine times a year)	Press releases, half-yearly to quarterly drug bulletin for health professionals
Sweden (1995)	1965	Mandatory	Reporting to national centre and regional centres under control of national centre	Case assessment by single expert or advisory committee, recommendation on regulatory action by advisory board and implementation by national centre, recommendation on withdrawal of marketing authorisation by drugs advisory board	Press releases, information on website, bimonthly drug bulletin for health professionals
United Kingdom (1973)	1964	Voluntary	Reporting to five regional centres or national centre as applicable	Case and further assessment at national centre, advice from pharmacovigilance advisory subcommittee (meets five times a year), recommendation on regulatory action by safety advisory committee (meets twice a month)	Press releases, periodic drug bulletin to health professionals, e-mail-based cascade system for messages to health professionals

Source: Adapted from Olson S. (1999) and personal communication with Member State Representatives.

The national pharmacovigilance systems of the Member States together form the pharmacovigilance system in the EU, co-operating in a network structure under the co-ordination of the EMEA and in liaison with the European Commission. Also included are Norway, Iceland and Liechtenstein, which are not members of the EU but are part of the European Economic Area (EEA) (EEA Joint Committee, 1999). 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 authorisation of the product in the EU and are defined in Directive 2001/83/EC, as amended in 2004 as a result of an intensive legislative review process, and Council Regulation (EEC) No. 2309/93, replaced, likewise through the review process, as of 20 November 2005 by Regulation (EC) No. 726/2004. They are further described in guidance documents which were developed at EU level during the 1990s for the competent authorities and marketing authorisation holders in consultation with Member States and interested parties (Table 14.3). These guidelines are in

Table 14.3. Guidance developed by the regulatory pharmacovigilance system of EU at Community level.

- Guidelines for marketing authorisation holders (pharmacovigilance systems, inspections, risk management systems, expedited and periodic reporting, post-authorisation safety studies, evaluation and regulatory action)
- Procedures for competent authorities on the undertaking of pharmacovigilance activities
- Conduct of pharmacovigilance and Crisis management plan for centrally authorised products
- Conduct of pharmacovigilance for medicinal products authorised through the decentralised or mutual recognition procedures.
- Rapid alert and non-urgent information system in pharmacovigilance
- Principles of Collaboration with the World Health Organization in matters of international pharmacovigilance
- Guidelines on electronic exchange of pharmacovigilance information
- Guidelines on pharmacovigilance communication to the public
- Guidelines on product- and population-specific pharmacovigilance

Explanatory note: This constitutes an updated list as of time of going to press. These guidance documents are subject to continuous review and revised documents are announced for publication by the European Commission.

accordance with recommendations agreed at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). They have been amended in the light of experience and are available in a compiled format (European Commission, 2006).

The EMEA is a Community agency, that is a public authority of the EU, set up by a Community act of secondary legislation (Council Regulation (EEC) No. 2309/93) with its own legal personality (European Union institutions and other bodies, 2005). The objective of the EMEA 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 co-ordination of the scientific evaluation of quality, safety and efficacy of medicinal products that have been applied for a central marketing authorisation with the aim of facilitating the access to effective and safe innovative medicinal products throughout the EU; and
- the co-ordination of post-authorisation safety of medicinal products through the pharmacovigilance network.
- The EMEA pools scientific expertise from the Member States for the evaluation of medicinal products, and to provide advice on drug research and development programmes (European Medicines Agency, 2005). More specific to pharmacovigilance, the tasks of the EMEA include the following:
 - co-ordination of the supervision (including pharmacovigilance activities) of medicinal products authorised in the EU;
 - provision of access to information on suspected ADRs reported for medicinal products marketed in the EU by means of a database and data-processing network (EudraVigilance);
 - maintenance of and variations to the terms of the marketing authorisation for centrally authorised products and
 - management of referral procedures for nationally authorised products leading to Commission Decisions binding in all Member States when there is a safety concern which impacts on public health in the Community; and provision of recommendations on measures necessary to ensure safe and effective use of these products.

EudraVigilance was put in place by the EMEA from December 2001 (European Medicines Agency, 2004), enabling the electronic transmission of ADR case reports to a central point accessible by all competent authorities in the EU and exchange of pharmacovigilance information between all stakeholders (marketing authorisation holders, national competent authorities and EMEA). In addition to the case reports arising worldwide post-marketing, EudraVigilance was extended to include clinical trials data as of May 2004. These developments are 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 on ADRs in relation to medicinal products authorised in the EU is provided (European Commission, 2006).

Much of the work of the EMEA is done within its scientific committees. For medicines used in humans this is the CHMP. This committee is supported by several expert working parties, one of which is the PhVWP. The PhVWP currently meets eleven times per year at the EMEA. Its mission is to provide advice on the safety of medicinal products and the investigation of ADRs to enable effective risk identification, assessment and management, in the pre- and post-authorisation phase, leading to recommendations on harmonised and synchronised action. These are ultimately implemented either by the European Commission following a CHMP Opinion for centrally authorised products or by national competent authorities. The PhVWP also takes the lead in the development of pharmacovigilance guidelines.

To facilitate, in addition, 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. Records of this information flow are maintained centrally by the EMEA and followed up by the PhVWP at each of their meetings. The principles and procedures of this system are presented in a guideline (European Commission, 2006).

Pharmaceutical companies holding marketing authorisations in the EU have various obligations in the area of pharmacovigilance that are laid down in Title IX of Directive 2001/83/EC and Regulation (EC) No.

726/2004 and elaborated further in guidelines (European Commission, 2006). In particular, marketing authorisation holders must employ a qualified person who is responsible for

- establishing and maintaining a system that collects and collates all suspected ADRs;
- the preparation of periodic safety update reports;
- responding to requests for additional information from competent authorities; and
- provision to competent authorities of any other information relevant to the risk-benefit evaluation.

In addition, marketing authorisation holders are obliged to report serious suspected ADRs in accordance with the legislation and guidance cited above to competent authorities within 15 days ('expedited reports').

THE PROCESS OF REGULATORY PHARMACOVIGILANCE IN THE EU

Regulatory pharmacovigilance is dependent on the availability of information on the clinical effects of medicines in representative populations as used in normal practice. In addition to systems for collecting and handling suspected ADRs, 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, for example introducing warnings, contraindications, information on ADRs 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 (Jefferys *et al.*, 1998). 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 summarised in Figure 14.1.

RISK MANAGEMENT

With a view to increase proactivity, the recently revised legislation has introduced the concept of

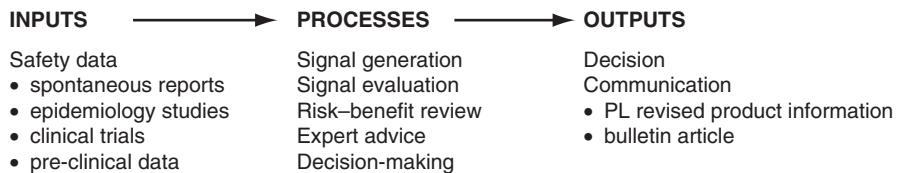


Figure 14.1. Regulatory pharmacovigilance.

risk management which is defined in the EU 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. Some of its elements have already been agreed by the ICH in guideline E2E on pharmacovigilance planning and, together with current thinking, incorporate 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.

DETECTION OF ADRs

Potentially important safety issues can be identified at any stage of drug development. In the post-authorisation 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 recognised 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. In regulatory practice, a signal is an alert from any available source that a medicine may be associated with a previously unrecognised hazard or that a known hazard may be quantitatively (e.g. more frequent) or qualitatively (e.g. more serious) different from existing expectations.

The commonest source for identification of significant safety concerns arising with marketed medicines is spontaneous ADR reporting. These are individual case reports from health professionals 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 ADRs. 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 drug. This approach is underpinned by standard definitions given in EU legislation (Title I of Directive 2001/83/EC) and is also consistent with definitions proposed by the ICH in guidelines E2A and E2D (International Conference on Harmonisation, 2005).

Although formal studies of drug safety are particularly used in the investigation of signals identified by methods such as spontaneous ADR 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 literature 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 (Uppsala Monitoring Centre, 2005) to which EU Member States contribute data. Whatever the source of the signal, the aim is to identify it as rapidly as possible. The next steps are to inform other Member States, gather further information and conduct an evaluation.

EVALUATION OF PHARMACOVIGILANCE ISSUES

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-authorisation studies have been set out in guidelines for marketing authorisation holders (European Commission, 2006). 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 drug-related 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 both at national and EU level.

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 ADR. In particular, hazards may be minimised by targeting the medicine at patients least likely to be at risk of the ADR 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-marketing 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 ADR or the accumulation of important new evidence about a recognised reaction

leads to a need to make changes to the product information and hence to vary the marketing authorisation(s). Variations to marketing authorisations 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 to facilitate rapid implementation. When the competent authorities and companies are in agreement about the nature and impact of a drug safety issue, changes can be made on a voluntary basis by the marketing authorisation 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 authorisation holder or the competent authority can initiate an urgent safety restriction (USR) procedure that enables a change to the product information within 24 hours and is followed within 2 weeks by a formal variation (Commission Regulation (EC) No. 1084/2003; Commission Regulation (EC) No. 1085/2003). 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 authorisation(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 unfavourable benefit-risk balance even in different sub-groups of patients.

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 ADR requires immediate communication, whereas the addition of information relating to a non-serious ADR 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, other relevant health professionals and at patients. The recently revised legislation has introduced new obligations for the Member

States' authorities and the EMEA in relation to such communication to the public. Additional requirements are also imposed on the companies and will even be enforced by penalty legislation. A particularly important aim in communications about drug safety 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, an EMEA/CHMP Working Group with Patient Organisations is in operation since 2003 with one of its aims to provide overall recommendations and specific input to guidelines on communication and to new procedures, for example for testing of product information (EMEA/CHMP Working Group with Patient Organisations, 2005). Similar initiatives have been undertaken at national level in some Member States and there is fruitful exchange of all experience gained.

Any change to the marketing authorisation and product information which 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 'Dear Doctor/Pharmacist' letter (Direct Healthcare Professional Communication). With regard to information targeted at health professionals, the EMEA has initiate dialogue with health professional organisations at EU level to support and complement national activities. 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. Improvements in dissemination mechanisms are planned for the future.

The competent authorities recognise that successful communication about drug safety is a vital component of the pharmacovigilance process and needs EU-wide co-ordination. This is a particular challenge because of the need to translate messages into all the official

languages used in the EU (currently 20), and considerable attention is being paid to improving this aspect of the process. Intensive thought is currently given to the enforcement of existing and establishment of new procedures to optimise EU-wide co-ordination of safety communication as well as to the assessment of public health impact of such communication. In terms of risk minimisation, targeted information to healthcare professionals and patients is seen as an important tool.

FUTURE CHALLENGES

The medicines legislation has recently been reviewed by the European Commission with the resultant changes having come fully into force in November 2005. Although there is no fundamental change to the basic system, many elements have been re-enforced or newly introduced, with the aim to improve pharmacovigilance and to meet the higher expectations of EU citizens. Such expectations also lie in establishing mechanisms for direct reporting of adverse experiences by consumers, and related initiatives have been started at the level of some Member States and through dialogue at EU level. Another important challenge results from the EU enlargement in 2004 and 2007, involving Central and Eastern European countries. Steps have already been taken since 1999 to integrate the new countries in drug regulation and pharmacovigilance activities through an initiative known as the Pan-European Regulatory Forum (PERF). In this context, it is particularly important to have in place agreed standards for the conduct of pharmacovigilance for all the parties involved. The PhVWP is currently developing such standards for regulators through an initiative known as good pharmacovigilance practice (GVP). Particular efforts are also being put into further development of the electronic information network through the EudraVigilance project.

One important limitation of all current pharmacovigilance systems is the difficulty in measuring the effects of the actions taken. It will be particularly important for EU competent authorities to address this using the available electronic epidemiological databases. Expectations of consumers in respect of drug safety have increased considerably in recent years (EMEA/CHMP Working Group with Patient Organisations, 2005) and

are likely to continue to do so. To meet these expectations, processes will need to become even more transparent and to be demonstrably effective. Communication tools also need to be improved, 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 have been brought together to form an EU-wide system that currently, after the EU Enlargement in 2004, covers a population of more than 450 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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15

Spontaneous Reporting – UK

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INTRODUCTION

In the United Kingdom, the Licensing Authority responsible for medicines for human use consists of ministers, including the Secretary of State for Health. The Authority's executive function in the control of medicines is performed on a day-to-day basis by the UK Medicines and Healthcare products Regulatory Agency (MHRA). 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). 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.

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 Vigilance and Risk Management of

Medicines of the MHRA is responsible for monitoring the safety of all licensed medicines in the United Kingdom, 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 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

INTRODUCTION OF THE YELLOW CARD SCHEME

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 responsibilities of this new committee was to collect and disseminate 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 almost 40 years since the introduction of this Scheme, the design of the reporting form has changed progressively, 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 a specialised database to facilitate rapid processing and analysis of reports and detection of signals of drug safety hazards. Four Regional Monitoring Centres (RMCs), introduced in the 1980s, provide valuable support for the running of the Scheme in Merseyside, the Northern region, Wales and the West Midlands (e.g. Houghton *et al.*, 1996). A fifth RMC was opened in Scotland in October 2002 and the Northern RMC expanded its activities into Yorkshire in the September of the same year. The RMCs are now known as Yellow Card Centres.

PURPOSE AND ACHIEVEMENTS 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 used 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 used in patient populations for which it was not intended, may be given for long periods of time, and in combination with other medicines.

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; see the section on 'Weaknesses of Yellow Cards' below). 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 15.1.

WEAKNESSES OF YELLOW CARDS

As mentioned previously, all spontaneous reporting Schemes have a number of limitations; these have been documented previously (e.g. Rawlins, Fracchia and Rodriguez-Farre, 1992; Meyboom *et al.*, 1997a, b). The limitation of most 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-Quejo *et al.*, 1998).

Under-reporting of ADRs is clearly of concern, since it may lead to under-estimation of the significance of a particular reaction. This is compounded by

Table 15.1. Important new adverse reactions identified via spontaneous reporting since 1995 and the resultant UK actions in respect of marketing authorisations/product information.

Medicine	Adverse reaction	Resulting action	Year
Tramadol (Zydol ^{▼*})	Psychiatric reactions	Warnings	1995
Cyproterone acetate (Cyprostat, Androcur)	Dose-related hepatotoxicity	Restricted indications, requirement for monitoring of liver function	1995
Quinolone antibiotics	Tendinitis, tendon rupture	Improved warnings	1995
Tacrolimus (Prograf ^{▼*})	Hypertrophic cardiomyopathy	Warnings, dose reduction and monitoring requirements	1995
Alendronate (Fosamax ^{▼*})	Severe oesophageal reactions	Warnings and revised dosing instructions	1996
Clozapine (Clozaril)	GI obstruction	Improved warnings	1997
HIV protease inhibitors	Hyperlipidaemia and fat redistribution	Improved warnings and monitoring recommendations	1997
Isotretinoin (Roaccutane)	Psychiatric reactions	Improved warnings	1998
Sertindole (Serolect [▼])	Sudden cardiac death	Drug withdrawn [†]	1998
Human clottable protein concentrate (Quixil [▼])	Fatal neurotoxic reactions following unlicensed use in neurosurgery	Improved warnings	1999
Aristolochia in Chinese herbal remedies	Renal failure	Aristolochia banned	1999
Cisapride (Prepulsid, Alimix)	Serious cardiovascular reactions	Use of cisapride suspended in the UK [‡]	2000
Bupropion (Zyban [▼])	Seizures	Improved warnings and revised dosing instructions	2001
Cerivastatin (Lipobay)	Rhabdomyolysis (particularly when used in combination with gemfibrozil (Lopid))	Marketing and distribution of cerivastatin suspended worldwide	2001
Olanzapine (Zyprexa)	Hyperglycaemia, diabetes and exacerbation of diabetes	Improved warnings and monitoring recommendations	2002
Kava-kava	Hepatotoxicity	Supply of Kava-kava prohibited in the United Kingdom	2003

Table 15.1. Continued.

Medicine	Adverse reaction	Resulting action	Year
Aspirin	Reye's Syndrome in children under 16 years	Statutory label warning	2003
Warfarin	Interaction with cranberry juice leading to changes in INR values and bleeding episodes	Warnings	2003
Rosuvastatin (Crestor▼)	Rhabdomyolysis	Revised dosing instructions and improved warnings	2004
Atomoxetine (Strattera▼)	Hepatic disorders	Warnings	2005
Linezolid (Zyvox▼)	Optic neuropathy	Improved warnings and monitoring recommendations	2006
Polygonum multiflorum	Hepatotoxicity	Warnings	2006

* Black Triangle (▼) – drug at the time the major safety issue was identified

† Sertindole was reinstated in 2002 with increased warnings

‡ Cisapride licences have been cancelled

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). There is also evidence to suggest that levels of reporting may vary between different groups of doctors, with hospital doctors reporting less frequently than general practitioners (GPs) (Bateman, Sanders and Rawlins, 1992; Eland *et al.*, 1999).

Various studies have attempted to establish the reasons for under-reporting; recent surveys of attitudes to reporting of ADRs suggest that lack of time and uncertainty as to whether the reaction was caused by a drug are among the most common factors in deterring reporting (Belton *et al.*, 1995; Eland *et al.*, 1999; Sweis and Wong, 2000). Another factor identified by some groups was concern about breaching patient confidentiality (Bateman, Sanders and Rawlins, 1992; Sweis and Wong, 2000).

Average ADR reporting rates for the Yellow Card Scheme (e.g. reports per million inhabitants per year) are among the highest in the world (e.g. Edwards, 1997), especially when compared with other countries with a large population (Griffin, 1986). However, 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 recent figures are more encouraging; an analysis of the reporters of Yellow Cards submitted between 1992 and 1995 showed that around one-third of practising doctors submitted a report during this 4-year period. However, it is clear that many doctors do not contribute to the Yellow Card Scheme; this is unlikely to be simply because these doctors do not see patients who have experienced an adverse reaction.

REPORTING VOLUMES

Since the launch of the Yellow Card Scheme in 1964, over 500,000 reports have been received by the MHRA and the CSM from health professionals, either directly through the Scheme or indirectly via pharmaceutical companies (Figure 15.1). The Scheme is voluntary for health professionals but pharmaceutical companies have legal obligations to report ADRs to the MHRA (Waller, Coulson and Wood, 1996), and in 2003 and 2004 the latter accounted for approximately 30% of all ADR reports received. It can be seen 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 first of these increases coincided with the withdrawal of practolol following its association with oculomucocutaneous syndrome, the

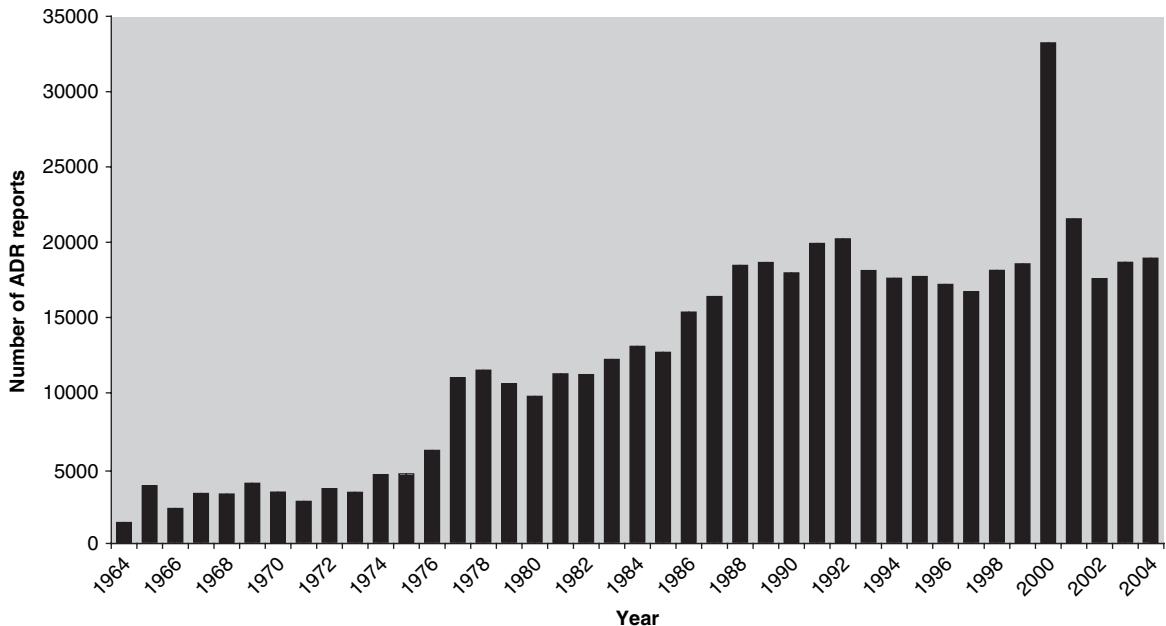


Figure 15.1. Number of Adverse Drug Reaction (ADR) reports received by year since 1964.

introduction of the CSM drug safety bulletin *Current Problems in Pharmacovigilance*, and the inclusion of a yellow page in prescription pads used by GPs, reminding them to report ADRs. The second increase 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, and in prescription pads (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 in the mid- to late 1990s. A number of factors may be responsible for contributing to this decline; for instance, the number of Yellow Cards submitted on forms included in GPs' prescription pads has fallen dramatically in the past 10 years (these 'FP10' forms comprised 10% of all UK reports received in 1991, compared with 0.1% in 2001), suggesting a move from handwritten prescriptions to increasing use of computerised practice systems. Additional factors may include the increasing demands on doctors time and concerns over confidentiality, as evidenced by surveys of factors affecting reporting as described above.

GP focus groups have been used to examine understanding of, and attitudes to, ADRs and reporting via the Yellow Card Scheme. The key findings were broadly in line with published surveys of attitudes to ADR reporting, namely that GPs were too busy to report, and that they were uncertain about how to distinguish adverse reactions from adverse events. Additionally, there was some concern about confidentiality issues associated with supplying patient details, and uncertainty about where ADR reports were sent and how the information would be used.

In 2000, there was a dramatic rise in the number of Yellow Cards, with over 33 000 reports received during this 12-month period. This can largely be accounted for by the reporting of a large number of suspected adverse reactions to meningitis C vaccines, administered to children under the age of 18 in a nationwide immunisation campaign. Nurse reporting was permitted during the campaign and an estimated 18.5 million doses of vaccine were distributed in just over a year. Even when reports for this vaccine are excluded, there was a 16% rise in the number of Yellow Cards received in 2000 compared with that of 1999.

Following completion of the meningitis C immunisation campaign, the number of Yellow Cards returned to previous levels. In 2003 and 2004 the number of reports have steadily increased and this coincides with the formal introduction of nurse, midwife and health visitor reporting in October 2002 and the introduction of electronic reporting during the same time period. It remains to be seen if this level of healthcare professional reporting will be maintained in future years, especially with the introduction of patient reporting.

RECENT INITIATIVES TO ENHANCE THE SCHEME

Although the importance of the Yellow Card Scheme in protecting public health by monitoring the safety of medicines in routine practice is not in dispute, there is a need to tackle continually the issue of under-reporting by addressing some of the factors highlighted in the section on 'Weaknesses of Yellow Cards' above. The environment in which the Scheme operates is very different now, compared with the 1960s. 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 pharmacists and nurses have evolved over recent years. 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. Nurses are now able to prescribe a wide range of 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 recently in order to try to address some issues raised in the section on 'Weaknesses of Yellow Cards' above. 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, and those aimed at facilitation of reporting. Developments

in interpretation of data protection legislation resulted in the introduction of anonymised Yellow Card reporting. Importantly in 2004, an independent review of the Yellow Card Scheme recommended greater access to data for research, and increased patient involvement. 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 is not alone of particular value; the objective is to receive Yellow Card information of suitable quality to enable 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 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 published targets, in order to ensure that data from the reports are available on the database as quickly as possible for inclusion in the signal generation process. Any large increase in the volume of reports can slow down the time taken to make reports accessible for risk detection and may increase the signal-to-noise ratio.

WIDENING THE YELLOW CARD REPORTING BASE

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 RMCs 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). Following the nationwide extension, 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 the light of these findings, and the assumption that community pharmacists are well placed to inform patients about, and be made aware of, any ADRs experienced in association with 'over the counter' products, nationwide reporting by community pharmacists was introduced in November 1999 (Anon, 1999).

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 now supply and administer medicines through patient group directions (PGDs) (Health Service Circular 2000/026). With these new prescribing powers, both hospital and community pharmacists are nowadays important contributors to the Yellow Card Scheme and in 2004, over 3000 ADR reports originated from pharmacists, representing 17% of all ADR reports received by the Agency.

Nurse Reporting

In the past five years the role and responsibilities of nurses have rapidly developed. Nurses have had a more active role in the provision of medicines to patients. This is illustrated by the introduction of independent nurse prescribing from the Nurse Prescribers' Formulary for district nurses and health visitors and the Nurse Prescribers' Extended Formulary (NPEF). Along with pharmacists, nurses are empowered to provide medicines under PGDs, and supplementary prescribing was introduced in April 2003.

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 and 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 to submit spontaneously 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 have been 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 which has recently been 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, they could be important contributors to the Yellow Card Scheme. As a result, the Scheme was extended to all nurses, midwives and health visitors in October 2002 and 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 2004, over 2000 ADR reports were received from nurses comprising 11% of all health professionals who reported via the Scheme that year.

SPECIALIST THERAPEUTIC AREAS

As mentioned above, there is some evidence to suggest that hospital doctors report less frequently than GPs (Bateman, Sanders and Rawlins, 1992; Eland *et al.*, 1999). This may result in under-reporting being a particular problem for medicines where treatment is initiated and monitored by hospital specialists. In addition, in certain situations or patient groups, data to support the safe and effective use of medicines is particularly limited. For such areas of particular concern, an increase in the number of relevant reports may not be achieved simply by increasing the overall reporting base. Rather, in such areas, an approach has been taken to target existing reporting groups to improve the reporting of reactions relevant to these areas. Described here are recent initiatives aimed at improving reporting of ADRs in three areas of particular interest: drugs used in the treatment of human immunodeficiency virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), ADRs in children, and those associated with herbal products, including unlicensed remedies.

The HIV Reporting Scheme

Since the mid-1990s a number of important new drugs have become available for the treatment of individuals

infected with HIV. Some of these drugs have been licensed on the basis of clinical trials that involved small numbers of patients and were designed to show changes in surrogate markers of HIV disease. This meant that at the time of licensing there was very limited safety data available for these drugs.

Following their introduction onto the UK market, it was noted that relatively few suspected ADRs were being reported in the United Kingdom for these anti-retroviral treatments, despite the fact that new safety issues were being identified from worldwide safety data.

In order to address this, the HIV reporting Scheme, an extension of the Yellow Card Scheme, was launched in November 1997 by the MHRA and CSM in collaboration with the Medical Research Council HIV Clinical Trials Centre (Anon, 1998a). The Scheme targeted specialist health professionals (doctors, nurses and pharmacists) working with people infected with HIV; these health professionals were asked to report suspected ADRs on specific reporting forms which did not request the name of the patient, in order to allay concerns over patient confidentiality which might be a serious deterrent to reporting for this particular patient group.

The introduction of this Scheme resulted in a significant increase in the number of UK reports of suspected ADRs associated with anti-retroviral drugs: for instance, during the seven months prior to the launch of the Scheme, 112 reports were received, compared with 207 during the seven months following the launch (Anon, 1998b). Promotion of the Scheme, including the production of a regular newsletter *HIV ADR Reporting Scheme News*, was aimed at maintaining the effectiveness of this initiative.

SUSPECTED ADRS IN CHILDREN

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, of medicines licensed for use in adults, such medicines may well be 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. However, it is notable that under-18-year-olds make up around 20% of the population, but that the proportion of Yellow Card reports received for this age group was somewhat lower in 1997 and 1998 (approximately 8%).

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 to the BPSU (Verity and Preece, 2002). 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 September 2004, the Commission adopted the proposal for a regulation of the Council and the European Parliament on medicinal products for paediatric use, 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, measures to increase the robustness of pharmacovigilance for paediatric medicines will be put forward and a Paediatric Working Party within the European Medicines Agency (EMEA) will be established. In recent years, the proportion of Yellow Cards received by the MHRA in under-18-year-olds has increased marginally to 10% of all UK ADR reports received in 2004, perhaps influenced by the introduction of nurse reporting and a general increased knowledge about the Scheme. There is still room for improvement, but with the advent of the European paediatric regulation and the introduction of patient reporting in the United Kingdom, it is likely that paediatric ADR reporting will continue to increase.

UNLICENSED HERBAL REMEDIES

A survey of the use of unlicensed complementary and alternative medicines in the United Kingdom found that 20% of adults interviewed had used such treatments in the past year, and an estimate of the annual expenditure on these treatments in the United Kingdom suggested that it may exceed 1.5 billion (Ernst and White, 2000). Up to now alternative regulatory routes for herbal products existed in the United Kingdom with only a minority of herbal products licensed for use based on evidence of safety, quality and safety, similar to those required for the licensing of a medicine. Traditionally herbal products have been exempt from licensing requirements by the conditions set out in Section 12 of the Medicines Act and for that reason there is a large variety of unlicensed herbal preparations, including traditional Chinese and Ayurvedic remedies, which are increasingly available. Herbal products may be perceived as ‘natural’ and therefore safe by the general public; many products are available on general sale in pharmacies and health

food shops and are likely to be used by patients to self-medicate without prior consultation with their health professional.

Until 1996, the Yellow Card Scheme collected reports of suspected ADRs to licensed herbal products only; in 1995, less than 0.2% of Yellow Cards were received related to such products. In October 1996, the Yellow Card Scheme was extended to include reporting for unlicensed herbal remedies, following a report from Guy's Hospital Toxicology Unit on potentially serious adverse reactions associated with herbal remedies (Anon, 1996). Although levels of reporting remain low, there has been an almost twofold increase in the reporting of suspected ADRs to herbal remedies (around 40 reports per year until 1998; more than 70 reports in 2001), with such reports accounting for 0.4% of reports received in 2001. This information is important in monitoring the safety of herbal products, many of which are unlicensed and therefore unregulated, and in evaluating how such products might interact with licensed medicinal products, for example the reported interactions between the herbal remedy St John's Wort (*Hypericum perforatum*) and a number of medicines including the oral contraceptive pill (Anon, 2000d).

The safety of unlicensed herbal products was further emphasised when reports of serious hepatotoxicity, including fatal cases and cases resulting in liver transplants, were reported in association with the use of Kava-kava (*Piper methysticum*). As a result the CSM prohibited the use of Kava-kava in unlicensed medicinal products in July 2002 and this was followed by a prohibition order in January 2003 (Anon, 2003). A year later, health professionals were asked to report cases of hepatic ADRs with the use of Black cohosh (*Cimicifuga racemosa*) via the Yellow Card Scheme following cases of hepatotoxicity in the United Kingdom (Anon, 2004).

These safety issues highlighted the urgent need for regulatory standards for the safety and quality of herbal products and for more formal requirements to be made of the manufacturers for the provision of information to consumers. In January 2002, the European Commission adopted formal proposals for a Directive on Traditional Herbal Medicinal Products. Directive 2004/24/EC amending Directive 2001/83/EC, the Community code on medicinal products for human use, was formally adopted and came

into force on 30 April 2004 (Official Journal of the European Communities, 31 March 2004). This new Directive requires that all medicinal herbal products placed on the market in the United Kingdom will be required to be registered under the Traditional Herbal Medicines Registration Scheme (THMRS). The new Scheme requires traditional herbal medicines to meet specific and appropriate standards of safety, quality and traditional use and for the product to be accompanied by information for its safe use. The Directive was implemented in the United Kingdom on 30 October 2005, and a 7-year transitional period for unlicensed herbal medicines allow companies time to adjust to the new requirements. A new UK advisory committee on herbal medicines, the Herbal Medicines Advisory Committee (HMAC), has been established to advise the government on the THMRS, as well as on unlicensed herbal remedies supplied under Section 12 of the Medicines Act 1968. In the light of the large usage of unlicensed herbal remedies, it is important that efforts continue to be made to stimulate reporting in this area; with registration of these products under the new Directive, it is likely that further safety issues with herbal products will be unveiled.

FACILITATION OF REPORTING – NEW TECHNOLOGY AND MEDIA

It seems self-evident that making reporting 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.

In addition to increasing time pressures on health professionals, the recent expansion in the use of information technology means that the majority of GP practices, hospitals and pharmacies are now using computers as a routine tool in their daily work. In the light of this, it is recognised that the paper Yellow Card is no longer the most convenient method of reporting for many healthcare professionals. 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 is printed out and posted to the MHRA. This pilot Scheme was introduced in mid-1998 (Anon, 1997b); to date over 4000 GP electronic reports have been received, and in 2005, approximately 2% of UK reports were received by this route.

Electronic reporting of suspected ADRs to the MHRA became routine for a small number of pharmaceutical companies who have been submitting reports via the MHRA's Adverse Drug Reactions Online Information Tracking (ADROIT) Electronically Generated Information Service (AEGIS) since 1995. Electronic reporting became mandatory for companies under Directive 2004/27/EC from 20 November 2005.

Following on from 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, in 2002 resulting in the launch of the electronic Yellow Card on the MHRA website. To date the MHRA has received over 2500 electronic Yellow Cards and as the move towards a paperless society continues, reporting by this means will undoubtedly continue to rise.

THE ANONYMISED YELLOW CARD

One of the key principles of the Yellow Card Scheme is that reports are submitted and handled in complete confidence. Concerns about confidentiality might deter both doctors (Bateman, Sanders and Rawlins, 1992) and pharmacists (Sweis and Wong, 2000) from submitting Yellow Cards; this issue was also highlighted by the GP focus group work.

An anonymised reporting form was first used in the HIV reporting initiative, as described above, because of particular concerns regarding confidentiality in this patient group. However, patients' rights to privacy are now guarded by data protection legislation based in European legislation; this issue was highlighted by the General Medical Council's Guidelines on Confidentiality (General Medical Council, 2000). This led to the introduction of an 'anonymised' Yellow Card in September 2000 (Anon, 2000b,c), which asks for initials and age (rather than name and date of birth) of the patient. In addition, the 'anonymised' Card

asks reporters to include an identification number or code for the patient; this should enable the reporter, but not the MHRA to identify the patient, and is used in correspondence between the MHRA and the reporter. The use of such an identifier was introduced in order to address concerns that 'anonymised' reporting might lead to a reduction in the ability to detect duplicate reports and to obtain follow-up information from the original reporter. After six months, over 6000 suspected adverse reactions had been reported to the MHRA on the 'anonymised' reporting form; of these, around 77% of forms included an entry in the patient 'identification number' field.

INDEPENDENT REVIEW OF ACCESS TO THE YELLOW CARD SCHEME

In recent years, increasing numbers of requests for access to Yellow Card data have been inundating the MHRA. These ranged from requests for reports on classes of medicines, copies of the whole database for genetics research and requests for the data to develop methodologies for identifying potential drug safety signals. While Agency guidelines are in place for responding to basic requests for Yellow Card data, some of these requests fell outside the established policies on releasing data and it soon became apparent that formalised procedures were required that would allow the data to be used for bona fide research but at the same time protecting the confidential data of reporters and patients. These changing demands on the Yellow Card Scheme raised important ethical, operational and financial issues in relation to public health. The government agreed that the time had come for a review of access to Yellow Card data to consider whether, and under what conditions and for what purposes, the data should be made more widely available. An independent review of the Yellow Card Scheme was announced in July 2003 under the lead of Dr Jeremy Metters. Dr Metters convened a small multidisciplinary steering committee to consider the public health, scientific, ethical, genetic, data protection, legal and other issues that would arise from increasing access to Yellow Card data. The steering committee took into account the views of stakeholders during a 12-week public consultation before the *Report of an Independent Review of Access to the Yellow Card Scheme* was published

in April 2004. The Review recognised the importance of the Yellow Card Scheme for public health and for the benefit of patients and considered that it was imperative that any changes implemented should not harm the Scheme or deter reporters from submitting Yellow Cards. Increasing access to Yellow Card data could be of benefit to public health as long as appropriate controls were set in place. Requests for Yellow Card data were divided into categories, which depended on the level of data requested. The Review recommended that anonymised aggregated ADR data should be proactively published and available via the MHRA website, while requests for data that may potentially identify a reporter or patient or provide an opportunity for the recipient to contact a reporter should be subject to scientific and ethical scrutiny. The Review recommended that an independent scientific committee should be established by the Licensing Authority to evaluate research proposals for these data to ensure they are scientifically robust. Following scientific approval, a research proposal would be ethically reviewed under the established framework of the Central Office for Research Ethics Committees (COREC) system. Regardless of scientific and ethical approval of a research proposal, in line with the provisions of the Data Protection Act 1998, consent from a reporter and patient would always be required before access to their data was permitted.

As a separate issue, the Review recognised the value that patient reporting could bring to the Yellow Card Scheme and recommended that the Scheme should be extended to enable patients to report their experiences directly to the MHRA (see section on 'Focus on Patients' below). In addition, the Review commended the work of the RMCs but put forward that further clarification of the relationship, respective responsibilities and working practices between the MHRA and the RMCs was required. A substantial number of the recommendations of the Review focused on strengthening the Scheme to raise awareness of its role and importance and a communication strategy was proposed to provide better information and education about the Scheme for health professionals, patients and the public.

The MHRA welcomed the Review recommendations and launched a public consultation on six key areas identified from the recommendations of the Review, to coincide with the 40th anniversary of the Yellow

Card Scheme on 4 May 2004. The CSM and the government accepted the main recommendations of the *Report of an Independent Review of Access to the Yellow Card Scheme* in January 2005. While procedures were being set in place to establish a permanent, non-statutory scientific committee, an Interim Committee on Yellow Card Data was convened. The remit of this committee, under the chairmanship of Dr Jeremy Metters, was to advise on development of arrangements for release of Yellow Card and ADROIT data; to advise on protocols and procedures to underpin the operation of the permanent committee; and to consider and advise on the handling of requests for data that the MHRA had already received.

The Interim Committee acknowledged the extremely valuable research potential of the Yellow Card data and considered the implications of releasing the data under the Freedom of Information Act 2005 (FOIA), while at the same time protecting the confidentiality of patients and reporters and their personal data under the Data Protection Act 1998 (DPA). Using the principles of these Acts, requests for Yellow Card and ADROIT data were divided into Category I requests that are generally releasable under the FOIA and not prohibited from release by DPA, and Category II requests that are subject to FOIA exemptions and the restrictions of the DPA.

As recommended in the Review, from January 2005 the MHRA has published anonymised, aggregated Yellow Card data on specific medicines in the form of Drug Analysis Prints (DAPs) on the Yellow Card website (known as Category Ia data). Other types of data that fit into Category I (known as Category Ib data) are not included in the regular publication Scheme, but can be provided by the Agency to individuals on request, in line with FOIA provisions. These generally include a limited range of data fields from anonymised individual case reports. In 2006, a substantive committee, the Independent Scientific Advisory Committee for MHRA database research (ISAC) was established (www.mhra.gov.uk).

FOCUS ON PATIENTS

Since the Yellow Card Scheme was established in 1964, reporting of ADRs has been restricted to health professionals of specific disciplines. With increasing

responsibilities the roles of health professionals, such as pharmacists and nurses described previously, have evolved to place them in more appropriate positions to report suspicions of ADRs and as a result the number of reporters who can contribute to the Scheme has increased. Likewise patients, with easy access to the Internet, have greater knowledge about the medicines they receive and take a more active role in their health. This attitude is also reflected in the government's current policy to provide patients with greater choice over decisions affecting their health. As part of this strategy the government launched its *NHS Plan* in 2000 and within this programme to modernise the National Health Service (NHS) a range of initiatives to improve patient information, patient choice and patient and public involvement in the NHS are proposed. The government recognises that 'choice is central to modernising and improving the delivery of services. In essence, it is about treating people as active, responsible citizens, not passive recipients of services, enabling them to exercise genuine choice over key aspects of their lives' (The NHS Plan – a progress report. The NHS Modernisation Board's Annual Report 2003). The government also encourages wider availability of medicines and the number of drugs that have been reclassified from Prescription Only Medicines (POM) (available only on a prescription) to Pharmacy (P) (available under the supervision of a pharmacist); and the number of drugs that have been reclassified from P to General Sale List (GSL) (available in general retail outlets such as supermarkets) has risen in recent years. Before a change in legal status is granted, pharmaceutical companies have to demonstrate levels of safety dependent on specific criteria and provide appropriate prescribing information. Examples of recent POM to P switches include chloramphenicol 0.5% eye drops for the treatment of acute bacterial conjunctivitis and Zocor Heart Pro (simvastatin 10 mg) to reduce the risk of a first major coronary event in people who are likely to be at a moderate risk of coronary heart disease, while clotrimazole for the treatment of *Candidal vulvovaginitis* (thrush) is an example of a P to GSL switch.

The potential benefit of patient reporting to the Yellow Card Scheme was realised by the MHRA prior to the *Independent Review of Access to the Yellow Card Scheme*, although there were some concerns that the Scheme may become flooded with recognised

non-serious ADRs. To investigate this further, the MHRA undertook a pilot study of patient reporting in South East London with NHS Direct in April 2003, involving staff at the NHS Direct call centre making the reports on behalf of patients. This was not particularly successful as by the end of March 2004 only 39 reports had been received from the NHS Direct centre. During the Review, stakeholders criticised the pilot for not collecting the patient perspective directly from patients who would provide their own account of their experience. The Review recommended that 'A system should be set up for patients to report ADRs directly to the MHRA. Different approaches to patient reporting should be tried but, initially, patient reports should be kept separate from those of health professionals through a parallel system until experience indicates the best method of linking patient and health professional Yellow Card reports to the same ADR.' The MHRA and the government welcomed this recommendation to introduce direct reporting of ADRs from patients to the Scheme, and in September 2004 the CSM Patient Reporting of Adverse Drug Reactions Working Group was established to advise the MHRA and CSM on the development of different arrangements to pilot direct reporting by patients or their carers of suspected ADRs and to communicate about this new initiative. Although patient reporting is still in pilot phase, as from October 2005 patients have been able to report their experiences directly through the Scheme.

Benefits of patient reporting include the identification of ADRs not previously reported and/or specific features of ADRs that health professionals had not considered. For example, it was patients who identified 'electric shock' sensations following the use of selective serotonin reuptake inhibitors (SSRIs). Introduction of patient reporting has also increased general awareness about the Scheme.

The MHRA is continuing to focus on involving patients as it looks towards the future. In association with the CSM Patient Information Working Group the report *Always read the leaflet – Getting the best information with every medicine* was published in July 2005. This report concentrated on strategies to improve the quality and accessibility of medicine information, addressed risk communication and delivered new guidance and recommendations to help improve the quality of Patient Information Leaflets.

Empowering patients with knowledge to understand the risks and benefits of medicines will help patients to make informed choices about the medicines that they are taking. With the introduction of patient reporting, the nature of the Scheme will undoubtedly change in the future.

FUTURE DIRECTIONS FOR THE YELLOW CARD SCHEME

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. Many of these initiatives have been described above but it is also worth mentioning two approaches which have been suggested as ways to enhance reporting, but which are not at present under consideration as future directions for the Yellow Card Scheme. The first of these is payment for the completion of Yellow Cards. This issue 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 and for this reason, payment for the completion of Yellow Cards would be inappropriate. The second approach concerns 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; Wilholm *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; Wilholm *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 causation. 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 compulsory reporting and incentive payments would change the Scheme's fundamental practicalities. The Scheme should remain as a voluntary Scheme and health professionals should consider it to be their professional duty to report ADRs. The Review did, however, recommend that reporters who assist in research based on Yellow Cards should be reimbursed for the time and effort needed to contact a patient and to obtain the patient's consent to facilitate Yellow Card research. As discussed above, procedures for accessing Yellow Card data for research are in the development phase, but it is anticipated that once these systems are in place, the Yellow Card data collected over the past 40 years will be an important resource for research.

The long-term future of the Yellow Card Scheme will be based on further developing electronic reporting and information exchange. Although the MHRA has received electronic reports of suspected ADRs from a small group of pharmaceutical companies since 1995, this continues to be a focus for development. During the late 1990s, EU Competent Authorities, the EMEA and the European Commission have created a central pharmacovigilance database supported by a system of mandatory electronic ADR reporting between the pharmaceutical industry and the 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. To facilitate ICSR reporting by pharmaceutical companies, the MHRA has amended its database dictionary to MedDRA and the pharmacovigilance systems have been redeveloped to support electronic transmission of IC SRs.

Of equal importance is the development of electronic communication between regulatory authorities and health professionals, including a mechanism for electronic reporting of suspected ADRs. With increasing use of computerised software systems by GP practices, hospitals and pharmacies, the inclusion of Yellow Cards on such systems might be one approach, as in the current pilots described above. There are a number of such GP systems; it may be more useful to provide a single method by which all health professionals involved with the Yellow Card Scheme can submit suspected ADR reports, potentially via Internet-based reporting. The secure transmission of reports, through a widely available system must be assured; it is possible that future development of National Health Service electronic record systems may provide a suitable medium for reporting of suspected ADR reports.

The nature of pharmacovigilance within the United Kingdom is also evolving with robust methods for signal detection being developed. 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. In the United Kingdom, proportional reporting ratios (PRRs) were introduced as a statistical method for interpreting spontaneous ADR data (Evans, Waller and Davis, 2001). This statistical method compares the proportion of all reactions to a drug which are for a particular medical condition of interest 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. A tool for prioritising signals arising from spontaneous ADR data is known as impact analysis, which considers the strength of evidence for causality and the public health implications (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. The introduction of new concepts, technologies and regulations, optimised use of spontaneous data and the evolving Yellow Card Scheme continues to underpin these processes with the introduction of patient reporting and its future use as an important research tool.

CONCLUSIONS

The Yellow Card Scheme has been in existence for over four 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 speediness, confidentiality and above all the commitment of health professionals to report their suspicions in the interest of protecting public health.

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16

Spontaneous Reporting – France

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THE FRENCH PHARMACOVIGILANCE SYSTEM

The French Pharmacovigilance System has a number of features that make it stand out: it is based upon a network of 31 Regional Pharmacovigilance Centres (CRPV), co-ordinated by the Pharmacovigilance Unit of the French Agency for the Safety of Health Products (AFSSAPS). Regional Pharmacovigilance Centres and AFSSAPS are connected via a national database, which contains adverse drug reactions (ADRs) reported by healthcare professionals. All reports are assessed before entry into the national database, with a common imputability method. The French organisation is based on a decentralised collection and validation of safety data through the Regional Pharmacovigilance Centres and a centralised evaluation and decision-making process at the AFSSAPS.

HISTORY AND ORGANISATION

To understand the way it functions, and some of the differences with other countries' pharmacovigilance systems, a little history is necessary. After the

thalidomide tragedy, and the other early drug safety scandals or scares, a number of clinical toxicologists and pharmacologists, usually associated with Poison Control Centres (Paris, Lyon, Marseille), decided to set up units to inform their physicians of the risks of drugs, and provide for a local place to report ADRs. In 1973, a national centre was set up by the French Medical Association in collaboration with the French Pharmaceutical Manufacturers Association. The same year, six experimental pharmacovigilance centres were created in France. Over the years, more pharmacologists joined the first ones, and a network of centres appeared. The heads of these centres, at the time without any official remit, met regularly during meetings of the French Association of Pharmacologists. As this network evolved, they had to work out common methodologies. From the mid-1970s the centres were officially recognised, the regular meetings started taking place at the Ministry of Health, and a unit was set up there to co-ordinate activities. In 1979 a decentralised system was put in place with a network of 15 centres, which was thereafter extended to 29 in 1984 and 31 in 1994. Since 1984, prescribers (physicians, dental surgeons and midwives) and marketing authorisation

holders (MAHs) have been required to report ADRs. The national database was rejuvenated in 1985 so that online input became possible, and it could be accessed from all centres. In 1994 the Pharmacovigilance Unit was transferred to the French Medicines Agency (now French Agency for the Safety of Health Products, AFSSAPS). Good Pharmacovigilance Practices were evolved and sent to every prescriber in the country. To implement the European legislation, two decrees came into force which extended the mandatory reporting of ADRs to pharmacists and defined the current general organisation of the French pharmacovigilance system: the decree of March 1995 on general principles and the decree of May 1995 that especially related to human blood products.

At the present time, the 31 Regional Centres have a duty to collect, record and evaluate ADR reports, and input them into the common database, after causality assessment. The Heads of the Regional Pharmacovigilance Centres meet monthly at the AFSSAPS in the Technical Committee, a working group set up to prepare the work of the National Pharmacovigilance Commission (Advisory Board). The Technical Committee is responsible for co-ordinating the collection and evaluation of information on ADRs, conducting surveys and providing recommendations that are forwarded to the National Pharmacovigilance Commission, which recommends action to the General Director of the Agency, to prevent or eliminate drug-related accidents (Figure 16.1).

The AFSSAPS is responsible for implementing the national pharmacovigilance system. It defines the pharmacovigilance trends and co-ordinates the actions of the various partners involved. The Pharmacovigilance Unit of AFSSAPS centralises all the data collected on the territory by the regional pharmacovigilance centres (via the national database) and the pharmaceutical companies (who report directly ADRs to the Unit). This Unit is in charge of the co-ordination of the Regional Centres' activities, the organisation of meetings held by the Technical Committee and the National Pharmacovigilance Commission, and the exchange of information with other competent authorities: the European Medicines Agency (EMEA), other Member States, the World Health Organisation (WHO), competent authorities in third countries (Food and Drug Administration

(FDA), etc.). It also monitors compliance with pharmacovigilance regulatory obligations of each partner involved, especially to ensure that the reporting requirements are fulfilled. The AFSSAPS takes appropriate measures to ensure the safe use of medicinal products after marketing with the same objective: to protect public health.

REGIONAL PHARMACOVIGILANCE CENTRES

The 31 Regional Pharmacovigilance Centres form a network covering the whole country, thereby representing a large monitoring area. These decentralised structures for collecting ADRs encourage exchange of information with healthcare professionals and constitute a particularity of the French system. Regional Pharmacovigilance Centres are located in departments of clinical pharmacology or clinical toxicology in the University Hospitals. They each have a defined geographical area of intervention which is included along with their address and phone numbers in the *Vidal Drug Dictionary*.

They have several missions (Moore *et al.*, 1985):

- Collecting, recording and evaluating reports of ADRs.
- Providing information on ADRs to healthcare professionals, but also to the local hospital director(s) (e.g. in formulary boards), and to the Agency, as required,
- Conducting pharmacovigilance investigations at the AFSSAPS' request.
- Contributing to scientific progress by conducting research on drug-related risks.

Regional Pharmacovigilance Centres are established through a convention between the AFSSAPS and the University Hospital. They are financed by the Agency on the basis of performance, which includes not only the number of reports received and questions answered, but also collective activities and scientific publications.

The University Hospitals also contribute to their financing by seconding personnel and by providing

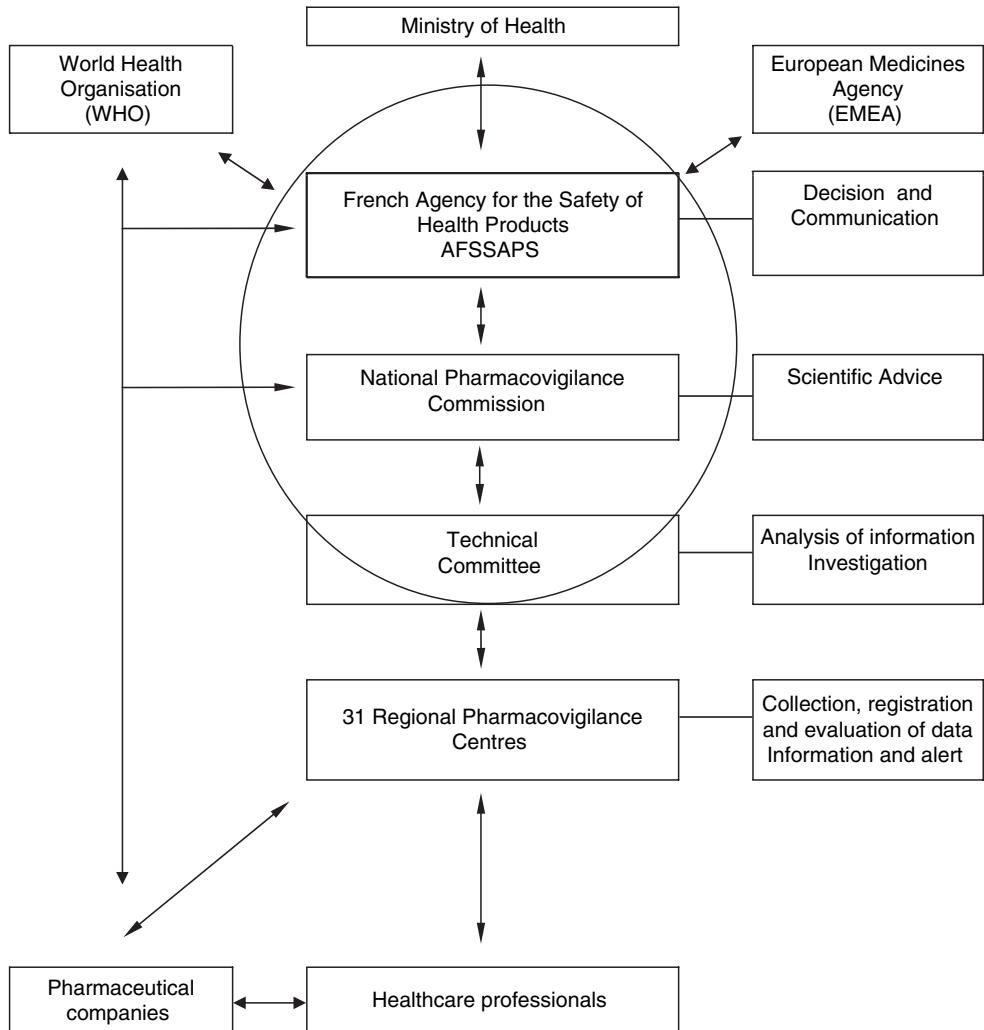


Figure 16.1. French pharmacovigilance systems.

material support, the latter varying according to the Hospital. Personnel in the Centres can be financed through the university and hospital (professors, practitioners, assistants, and medical or pharmacy students), and through the Agency grants.

Regional Centres have a scientific association, included within the French Pharmacological Society, which organises yearly scientific meetings in the Spring, and other work-shops or thematic meetings in the Fall, and co-sponsors with the Agency and the French Pharmaceutical companies yearly methodology workshops.

SOURCE AND MANAGEMENT OF REPORTS

Reports to Regional Centres come from several sources:

- Spontaneous reports sent by healthcare professionals. Prescribers and pharmacists are legally required to report immediately serious or unexpected ADRs to their Regional Centre. However, other healthcare professionals (nurses, physiotherapists etc.) can also report these ADRs. There is

an official form for reporting ADRs to Regional Centres (cerfa n° 10011*01). However, centres usually have their own forms (commonly devised) on to which the information is transferred, and in which raw data (e.g. photocopies of lab tests or hospital discharge letters) can be stored.

- Reports gathered during clinical rounds: since the Regional Centres are in reference (tertiary care) hospitals, the appropriate departments (internal medicine, haematology, dermatology, hepatology, for instance) can be regularly visited or contacted for hospitalised drug-related cases. These departments sometimes have 'drug staffs' where drug-related problems can be discussed with the team from the Department of Pharmacology. In addition, pharmacy students in the clinical wards are often used as pharmacovigilance relays.
- A large number of reports come from the requests for information by health professionals, that is the drug information centre activity. Though a fair number of these questions concern pre-emptive information (what can I prescribe this pregnant women with this condition?), about half concern new medications and suspected drug reactions, usually under the form 'has this ever been reported before?' These actually usually correspond to a specific patient, the prescriber asking the Centre for help in solving a diagnostic problem, where a drug may possibly be involved. The dialogue that ensues between the pharmacologist and the clinician will usually help solve the problem. Since the interaction occurs early, the pharmacologist can suggest further action, such as diagnostic tests, or drug dechallenge, which will improve the case's information content. In this interaction, the clinician receives help for a specific problem, and the Regional Centre 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 type 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.

After assessment of causality using the French imputation method (see below) (Begaud *et al.*, 1985),

reports are input to the national pharmacovigilance database at the Regional Centre. Mean time from receiving the case to input is a few days, with priority given to serious reports, which are identified as such in the database. Centres are required to report all serious reactions to the Agency within 15 days. At any time, every Centre can access the complete database, which is located in the Pharmacovigilance Unit of the Agency.

Though there are no automated alerting processes functioning routinely on the database at this time, it is customary when a new report comes in, especially if it concerns a recently marketed drug, or if the event is serious and unexpected, to query the base for similar cases, possibly using the case–non-case approach (Moore *et al.*, 1993, 1997; Montastruc *et al.*, 2000), to generate some measure of reporting disproportionality that could be indicative of an impending problem. Serious reports are automatically retrieved from the database at the Agency on a daily basis and forwarded from the Agency to the relevant MAH, and in the case of centrally authorised products to the European Medicines Agency (EMEA) 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 Agency, and the submission of Periodic Safety Update Reports (PSURs) according to defined periodicity. Reports from industry are received at the Agency, and input manually to a separate database, which can for the moment be accessed only at the Agency. In accordance with the new European requirements (Regulation (EC) No 726/2004), electronic transmission of ADRs will become mandatory in November 2005. In order to be compliant with ICH standards for electronic reporting of ADRs, AFSSAPS is currently setting up a new pharmacovigilance database. This new single database will receive ADRs from pharmaceutical companies and Regional Centres and will contain all previously recorded case reports.

ALERT MANAGEMENT

Alerts can arise from individual case reports at the regional level, because of the number or nature of

the reports or because of reporting disproportionality. Alerts may also originate from other European competent authorities through the Rapid Alert System or from FDA alerts, from literature data or any other source. Possible domestic alerts are reviewed within the Technical Committee for attribution.

The Technical Committee is presided by the Chairman of the National Pharmacovigilance Commission, and includes a representative of each Regional Centre (usually its director). The Pharmacovigilance Unit of the Agency ensures the secretariat of both the National Commission and the Technical Committee.

During each 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 Centre is designated to take responsibility for the investigation as ‘Rapporteur’. This can be an ‘unofficial investigation’ or an ‘official investigation’. In the former case, the Rapporteur Centre looks at all cases reported to the Centres, and at other sources of information, to recommend whether the alert is or is not worthy of official investigation. If not, it is usually shelved, or kept under distant surveillance in case it reactivates. The MAH is not formally involved in unofficial investigations.

An official investigation can be initiated because of an alert (at the national or European level), or can be systematic in the case of a new drug class, for instance, or if specific problems are anticipated when a drug is put on the market. The rules for these official investigations are outlined in the Good Pharmacovigilance Practices, which have been revised recently to take into account the recent scientific and technical developments of pharmacovigilance activities. It should be used as a reference document to define the roles and responsibilities of interested parties. This document is available on the AFSSAPS’ website: www.afssaps.sante.fr.

When an official investigation is decided upon, the marketing authorisation holders concerned are informed and instructed to make contact with the designated Rapporteur Centre. The cases reported to the Regional Centres and to the MAH are pooled. Duplicates are identified and resolved. All cases are reviewed together by the MAH and the Centre, with

the help of external experts as necessary, and causality is reassessed, using more specific criteria, such as those devised in consensus conferences, national or Council for International Organizations of Medical Sciences (CIOMS)-supported. The population exposure to medication is estimated from sales data, or from more precise data if available, resulting in reporting rates, usually given in number of cases reported per treatment-months of product sold. This estimation is done for the various levels of causality and seriousness. Additionally, indications of risk factors such as age, concomitant diseases or medication are looked for.

The assessment report written by the Rapporteur Centre on the investigation is sent to the MAH for comments, and presented to the Technical Committee. The Technical Committee ensures that the investigation has been carried out properly, validates it or not and submits it for examination to the National Commission, usually after a consultation meeting with the MAH, where the MAH’s proposals or comments are discussed.

The National Pharmacovigilance Commission is composed of representatives of health authorities and research bodies, clinicians, toxicologists, pharmacologists, pharmacists, representatives of consumers and patients associations, and a representative of the pharmaceutical industry. It can be supplemented and guided as needed by invited experts. The Rapporteur Centre presents the assessment report, in the presence of the MAH representatives, who are invited to comment and make their proposals. These are then discussed, first in the presence, then in the absence of the MAH. The National Pharmacovigilance Commission provides advice to the General Director of the Agency on the measures to be taken to prevent, reduce or eliminate drug-related risks. In the case of centrally authorised products, the Commission’s recommendation is forwarded to the Committee for Medicinal Products of Human Use (CHMP) of the EMEA 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 co-operation between Member States ensuring a common evaluation and management of safety concerns.

These processes are relatively similar to the European processes, except that there seems to be greater interaction and co-operation with the MAHs. This is built into the system, and may be related to the fact that many of the industry pharmacovigilance personnel have been trained in the Regional Centres. In addition there are many programmes to enhance industry-regional centre communications, such as commonly organised training courses, and yearly workshops. In fact, the industry is a recognised part of the French Pharmacovigilance System, which has been officially designated as including the Agency, its Pharmacovigilance Unit and the Commissions it harbours, the Regional Centres and the Industry Pharmacovigilance Departments.

RESULTS

In 2004 (Figure 16.2):

The Regional Centres received 20 116 reports that were entered in the national database: 10 002 (50%) were serious. Industry transmitted about the same number of serious reports to the Agency: 10 867 and submitted 2940 PSURs.

Reports sent to the Regional Centres came from specialist physicians: 79%, general practitioners: 8%, pharmacists: 11%, and others (nurses, midwives etc.): 2%, with a majority from the hospital environment which represents approximately 80% of all reports received by the Centres.

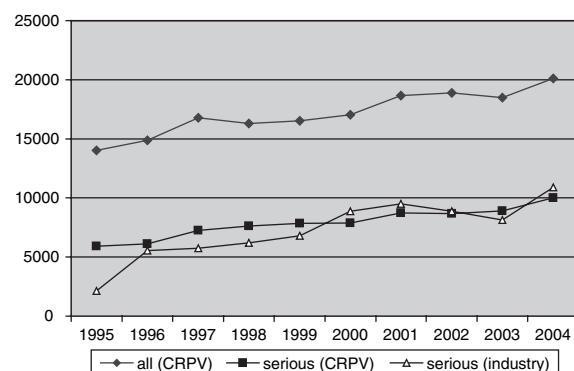


Figure 16.2. Yearly number of all and serious adverse reaction reports sent to regional pharmacovigilance centres (CRPV), and serious adverse reaction reports sent by industry.

- There were 31 261 requests for information, 8151 (26%) of which became reports.
- Centre personnel taught 1363 hours of initial training (medical, pharmacy students and others), 781 hours of complementary training (e.g. in master-level courses), and 805 hours continuing medical education.
- There were 169 peer-reviewed publications and 220 presentations in scientific meetings.

THE FRENCH IMPUTABILITY METHOD

This method was first devised in 1978 (Dangoumau, Evreux and Jouglard, 1978), revised in 1985 (when it was published simultaneously in French and in English) (Begaud *et al.*, 1985). It is the only imputability (causality assessment) method to have legal status. It is probably one of the most widely used, if not *the* most widely used, imputability method, having been applied to more than 100 000 reports, and yet it remains widely misunderstood.

The method was derived when the regional network was developing, to ensure that all the Centres worked and assessed reports in reasonably the same way. It has a few basic principles, designed to ensure the highest possible sensitivity when used routinely on incoming reports. It is because of this that the term ‘causality assessment’ may not really be applicable in that it is not causation *per se* that is assessed, but the possibility of involvement, a subtle distinction.

BASIC PRINCIPLES

The basic principles are as follows:

- The causality is judged only on the data present in the case, in abstraction of all published data concerning the drug-reaction association. Each case is judged on its own merits (intrinsic imputability) to ensure maximal identification of possible new reactions. This also ensures time-independent classification. Previous publications and labelling, which vary over time, are only indicated, and are not an integral part of the imputability.

- The causality is assessed on each drug-reaction pair presented by the patient at the time of the event, or that could be involved (such as previously stopped medication that could result in unidentified withdrawal symptoms).

This method is thus very dependent on the Regional Centre/drug information centre system, where there is early interaction with the reporter, so that information can be accrued in real-time, rather than having to judge a case *a posteriori* on incomplete information, as is usually the case in most paper-based spontaneous reporting systems where the reporter has already made up his mind on causality when reporting, and information is only present on the drug suspected by the reporter who often has no formal pharmacological or ADR-assessment training.

The method relies on a set of criteria that are, in fact, common to all causality assessment methods, so that it is easy to reapply other causality methods if the proper information has been obtained. It is perfectly very general in its definition of criteria, and much attention has been devoted to refining definitions of these criteria for specific reactions, and even for specific drug-reaction associations (Habibi *et al.*, 1988; Fournier *et al.*, 1989; Roujeau *et al.*, 1989; Vigeral *et al.*, 1989; Benichou, 1990; Benichou and Solal-Celigny, 1991).

There are six main criteria, three for chronology (time sequence) and three for semiology (signs and symptoms). These are described below.

TIME SEQUENCE ANALYSIS

The criteria include challenge, dechallenge and rechallenge.

- *Challenge* can be classified into ‘very suggestive’ (when there is an obvious temporal association between drug administration and the onset of the reaction, such as anaphylaxis during intravenous drug injection), impossible (when the drug is given after event onset), and compatible (other cases). The ‘impossible’ category is especially pertinent, since it justifies knowing the reason for which the drug was given to eliminate protopathic bias, the prescribing of a drug for early symptoms

of the event later reported as a reaction (e.g. agranulocytosis attributed to an antibiotic that was prescribed for the sore throat and fever that are the first signs of agranulocytosis, or stomach cancer and H2 antagonists prescribed for undiagnosed dyspepsia).

- *Dechallenge* can be suggestive when the reaction abates when the drug is stopped. It can be non-conclusive when there is no assessable dechallenge (e.g. drug not stopped, or patient dies), or there is no information on dechallenge, or the reaction is irreversible (renal failure, death), or specific treatment was applied to the reaction, and so on. It is against the role of the drug if the reaction persists (if reversible) when the drug is stopped, within pharmacokinetic constraints.
- *Rechallenge* is positive when the reaction recurs when the patient takes the drug again (for whatever reason, bearing in mind recurrent protopathic bias), negative when the reaction does not recur when the drug is taken again at the same dose, for the same duration, with the same concomitant diseases and medication (a rare event), and not assessable in all other cases.

Information on challenge, dechallenge and rechallenge is input into the appropriate three-way table, which results in a grade from CO (drug excluded) to C3 (very suggestive time association or positive rechallenge) (Table 16.1).

SIGNS AND SYMPTOMS

Signs and symptoms are graded in much the same way. Three criteria are assessed:

- Pharmacological plausibility: are the signs and symptoms suggestive of a pharmacological effect of the drug (i.e. a type A reaction), which could be reproduced experimentally?
- Other causes: have other reasonable causes for the event been looked for and eliminated? By reasonable, one means most (90%?) of the usual causes for the disease. There has been much discussion on what reasonable means, and this is probably where the consensus conference criteria are most useful.

Table 16.1. Chronological imputability.

Rechallenge	Challenge						
	Very suggestive			Compatible		Impossible	
	R+	R0	R-	R+	R0	R-	
Decchallenge:							
Suggestive	C3	C3	C1	C3	C2	C1	C0
Inconclusive	C3	C2	C1	C3	C1	C1	C0
Unsuggestive	C3	C1	C1	C1	C1	C1	C0

- Is there a laboratory test that is specific to the drug-reaction pair, and is it positive or negative? The criteria for specificity may vary. For example, if there were signs of toxicity, elevated or null plasma concentrations of a drug would qualify (within pharmacokinetic time frames, of course). This would not apply for an allergic reaction, though null plasma concentration with sufficient sensitivity could perhaps qualify as a negative laboratory test if it effectively eliminates drug exposure within the appropriate time frame.

Again, the results are fed into a three-way table (Table 16.2), resulting in a semiology grading from S1 (doubtful) to S3 (very suggestive). Most cases are S2 (non-specific reaction, no other reasonable cause, no specific laboratory test), or S1 (same but other causes not looked for usually because reaction to the drug is known, and all signs abated when the drug was stopped, before further investigations were made).

This method is not very precise, and is probably much less specific than other methods, and especially

the Bayesian approaches. It has a number of merits, however:

- It is more of a triage method, and can be applied extremely rapidly in the vast majority of cases if there is the appropriate information.
- It is, in fact, extremely useful to ensure that the proper information on a case report is retrieved on an ongoing basis. Using the causality method on a routine basis helps tremendously in making sure all relevant information is retrieved when discussing a case with a reporter. In this it improves the quality of the data, and the later application of any causality method, be it the same with refined criteria, as would be used in an official investigation, or any other, since all methods rely on mostly the same information.
- Its use by all persons involved in the system facilitates communication, by the use of a common language. This was and remains indispensable in a network-based system, where harmonisation of practice is essential.

Table 16.2. Semiological imputability.

Lab test	Signs and symptoms					
	Very suggestive of drug involvement or interaction			Compatible		
	L+	L0	L-	L+	L0	L-
Alternate non-drug explanation:						
Absent	S3	S3	S1	S3	S2	S1
Possible or present	S3	S2	S1	S3	S1	S1

FUTURE PERSPECTIVES

The optimisation of risk management activities and safe use of the medicinal products is a common concern of both the EMEA and the competent authorities of Member States. In order to improve pharmacovigilance activities and to detect signals earlier, additional tools will be introduced by the new European legislation: reinforcement of the evaluation of safety data before granting of a marketing authorisation, submission by pharmaceutical companies of

risk management plans, development of an effective communication on pharmacovigilance issues to healthcare professionals and the public and so on.

Pharmacovigilance must maintain a continuous monitoring system in order to evaluate adverse reactions which the clinical studies conducted before the marketing authorisation would not have identified. The submission of a risk management plan not only with the marketing authorisation application but also after the granting of a marketing authorisation is an important tool contributing to a pro-active approach.

The knowledge of the real conditions of prescription and use of the drugs is necessary to ensure their good use. Thus, it appears essential to conduct pharmacoepidemiological studies to investigate and quantify emerging risk. These studies are integrated in the risk management plans and should complete safety data received from the spontaneous reporting system. To that end, a scientific association (GIS) has been set up between the ministry of Health Directorate General of Health, the INSERM (National Institute for Medical Research), and the National Health Insurance System, to promote the use of the Health Insurance System databases to study post-marketing drug utilisation and risks. A Pharmacoepidemiology network has also been set up by INSERM to help with these studies, and with field studies, as needed.

To improve the efficacy of the pharmacovigilance system, complementary initiatives have been taken by AFSSAPS. The Agency is actively involved in a partnership with patients and consumers associations to ensure a more active participation of these associations in the pharmacovigilance activities. The aim of this initiative is to produce transparent information and to better define the role of associations in the evaluation and the risk management related to the use of medicinal products.

Beyond the management of adverse reactions occurring under the normal conditions of use of the drugs, it is important to take into account all adverse events associated with inappropriate drug use, including medication errors. The Regional Centres are deeply involved in the management of medication errors which can in many cases modify the benefit–risk ratio of the drug and result in the re-assessment of the conditions of use. Afssaps co-ordinates working groups including representatives of Regional Centres, prescribers and pharmacists in order to organise the

collection of data, the production and dissemination of information among them with the aim of preventing medication errors.

In conclusion, the French System is based on a number of specificities which have proven successful.

- The existence of a real network, where alert investigation is done in the Regional Centres.
- The use of common procedures, to ensure quality of data, including the use of the causality method.
- The integration of the Centres in clinical pharmacology department within university hospitals.
- The emphasis of the drug information function, as a continuing source of education.

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Spontaneous Reporting in Germany

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INTRODUCTION

Pharmacovigilance has now been established as a science that has some specific aspects. On the one hand, it is a combination of research in basic life sciences, diagnostic procedures or biotechnological tools, clinical pharmacology and medical practice, biostatistics and epidemiology, and on the other hand, it includes development as well as implementation and use of procedures. This is well reflected in the World Health Organisation (WHO)¹ definition of pharmacovigilance: The overall aim is to protect patients, or rather, users, taking medicinal products from harm. Activities in pharmacovigilance are not restricted to actual pharmacological treatments or diagnostic procedures but also have links to many areas in the overall healthcare systems established nationally, including communication.

Because pharmacovigilance has emerged as a science and its complexity – and uncertainties – have become more and more clear, much progress has

been made to identify and describe the different fields and aspects in more detail and to further develop criteria and principles for activities in the field of pharmacovigilance. On the European Union (EU) level, this has resulted in a large body of regulations, directives, guidelines and many other documents setting standards for pharmacovigilance practice. These rules have now been largely implemented into national legislation. Today, we are operating within a widely different pharmacovigilance system than 15 years ago. Nevertheless, there are, and will remain, differences in the national health and pharmacovigilance systems, and experiences from different countries should be shared to improve the system in general without neglecting national medical traditions.

DEMOGRAPHIC AND ECONOMIC DATA

After the reunification in 1990, Germany now has around 82 million inhabitants. There are major differences in the population density with larger rural areas in the eastern federal countries and larger industrial regions in the west. The average income and

¹ WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

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. Another 1.8 million other medical healthcare professionals contribute to the performance of the health system. There are 21 400 public pharmacies in Germany that are run completely on a private basis. Hospitals mainly have their own pharmacies, and these are not involved in the drug supply to outpatients. About €240 billion were spent in 2003 in the national health system, and around €37.5 billion are paid in total – prescriptions and self-medication – for medicinal products (corresponding to ~15.6% of total expenses).

LICENCES FOR MEDICINAL PRODUCTS IN GERMANY

The former EU Directive 75/319/EC was completely implemented into national law in 1978 with regard to the registration and licensing of all medicinal products as defined in that Directive. Thus, not only chemically defined medicinal products but also herbal medicines and products used within the homeopathic or anthroposophic therapeutic medical concept are licensed, if they fit the definition of medicinal products. The same applies to blood products, vaccines and other biologicals. After the complete re-evaluation of old products already on the market in 1978 was finalised by the end of 2005, around 45 370 medicinal products are presently licensed in Germany. This figure includes generic products, identical drugs of the same Marketing Authorisation Holder (MAH) and parallel imported drugs. This figure divides into

- 290 centrally authorised medicinal products,² including vaccines, monoclonal antibodies and biotechnology-derived products in haemotherapy;
- 33 300 chemically defined medicinal products;
- 1150 blood products, vaccines and other biologicals;
- 2900 herbal drugs;
- 6650 drugs containing only homeopathic preparations and
- 1120 drugs used in anthroposophic therapy.

² Not counting various strengths and pack sizes.

ACTORS IN SPONTANEOUS REPORTING

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, devitalised 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.

REPORTING ROUTES

Spontaneous adverse drug reaction (ADR) reporting began in Germany in the first half of the 1960s. At that time, no national drug safety agency had been established in the Federal Republic of Germany (West Germany) with an official mandate and sufficient expertise and resources to systematically collect and evaluate ADR reports. Since 1978, the responsibilities for collecting ADR reports have been clarified, and the actors now play different roles within the system.

A three-way reporting system is in place. Healthcare professionals can report suspected cases of ADRs (1) directly to one of the two national agencies for human medicinal products, (2) to the Drug Commission of the German Medical Association, mainly used by physicians and not by other healthcare professionals, and (3) to the MAH of the medicinal product suspected to have caused the ADR. However, both national drug agencies are the final and only institution 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 central databases, whichever reporting route is chosen by the individual reporter.

DRUG COMMISSION OF THE GERMAN MEDICAL ASSOCIATION (BUNDESÄRZTEKAMMER)

Historically, the Drug Commission of the German Medical Association began in 1963 with collecting spontaneous ADR reports. This was a consequence of the thalidomide disaster. The Drug Commission of the German Medical Association exclusively receives reports directly from physicians. They give quick confirmation of the receipt of the report and, if appropriate, provide additional information to the reporter. The total number of reports received in this manner amounts to about 2000 per year.

The Drug Commission of the German Medical Association of today is also an expert panel of experienced clinicians with a smaller core group handling the incoming reports and making 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. On the contrary, the Drug Commission of the German Medical Association has access to BfArM's national ADR database and may publish statements based on data evaluation from this database in their own responsibility. There are contractual and legal rules in place that regulate co-operation between the competent authorities and the Drug Commission of the German Medical Association.

REGIONAL PHARMACOVIGILANCE CENTRES

To improve the national pharmacovigilance system, i.e. to broaden the tools on how to get early and proper information on new or serious ADRs that may require regulatory actions, BfArM and PEI will establish a network of regional pharmacovigilance centres. Pharmacovigilance centres will not substitute the spontaneous reporting system (SRS) but will add an additional instrument for detecting ADRs not recognised so far, including frequency estimates. BfArM had in mind the French pharmacovigilance system established in the early 1980s. Because there was a need to investigate whether the French system could be transferred to Germany in parts or entirely, BfArM financed a pilot project to test and evaluate

the feasibility under the specific conditions of the healthcare system in Germany that is different from the system in France. This project ran for 8 years (from 1996 to 2004) and comprised the following main tasks:

- To register all patients with pre-defined trigger diagnoses hospitalised e.g. blood dyscrasias, serious allergic reactions, renal and liver dysfunctions, central nervous system (CNS) effects, etc., but excluding elective hospital stays.
- To select patients with regard to whether the reason for hospitalisation could be an ADR, which would be serious per definition, and then to completely document, follow-up and assess the case.
- To increase and ensure high quality of these reports by a separate quality assurance unit and to report these cases to the national competent authorities, i.e. BfArM or PEI.
- To make estimates on the frequencies of these ADRs on the basis of exact prescription data received from the regional health insurance and pharmacy reimbursement systems, covering the population within a circumscribed region of the respective hospital.

Four university hospitals in East Germany with the support from an information technology (IT) unit in Munich and the quality assurance unit in Wuppertal took part in this project. Important experiences have been gathered during this pilot phase and will now be implemented in a tailored system in Germany. There will be about six to seven regional pharmacovigilance centres of this type covering a population of at least 1.5 million inhabitants. Another five centres of a different type will join the network within the next few years. They will have specific tasks and structures, and two of them are already working: (1) a case-control surveillance system looking in a quantitatively defined population for cases of rare or very rare diseases (presently blood dyscrasias) that are predominantly caused by exogenous agents including drugs, comparing these with a control group from the same population, and (2) a register of non-systematically reported drug exposure during pregnancy with follow-up and pregnancy outcome surveillance. Additional pharmacovigilance centres are planned. They will be concerned with the collection of ADR reports in

paediatric and psychiatric hospital units. The pharmacovigilance centres' network will also include a unit for statistical analyses and another for developing new methods for the quantification of drug risks.

ADVERSE DRUG REACTION DATABASES

THE NEW SYSTEM

The two agencies in Germany have established new ADR databases in their institutions. As both ADR databases are essentially similar, BfArM's database will now be explained in more detail. After a 30-month period of development, the system went into production in March 2005, enabling the agency to fulfil legal reporting obligations towards the European Medicines Agency (EMEA) from May 2005 on. The system is fully compatible with international standards defined in the International Conference on Harmonisation (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. Medical Dictionary for Regulatory Activities (MedDRA) in its latest version for coding medical information, ISO catalogue of country codes, WHO-Drug Dictionary and Anatomical Therapeutic Chemical (ATC) classification to deal with the huge amount of drugs existing globally]. BfArM is aiming to have all ADR information about individual cases covered in the new database that is seen as a major step forwards compared with the situation so far.

The new database is not only a data entry and storage system. In addition, a workflow system has been implemented so that the case reports once entered into the database, manually or electronically, can be processed through electronic tools. This includes entry screens for single case assessment, views on the data fields in a structured way as well as access to scanned images of paper-based reports. In addition, standard forms for routine correspondence, e.g. the confirmation of receipt as well as information to third parties where appropriate, with data dynamically loaded into these forms from the database, are available.

Furthermore, a user interface for data retrieval exists that allows user-friendly stratification of data. Standardised entry screens to formulate routine requests

are available, but users are also allowed to perform queries on the database without using the interface. Retrieval results may be presented in a variety of output reports. This includes various listings, summary tabulations as well as graphical presentations. A set of standard reports may be amended by user-defined reports created by using a report generator that is available for those who work regularly with the database and have knowledge about the details in more depth.

ELECTRONIC SUBMISSION

According to EU legislation, MAHs are obliged to send reports electronically to the responsible authorities and the EMEA. Germany has implemented the rules in a national regulation on the basis of the German Medicines Act. This national regulation became valid on 20 October 2005, and it offers the possibility of switching to electronic reporting not at a defined date but over a period giving companies as well as regulators the chance to cope with challenges the new technology imposes.

Companies with a very low number of reports per year, defined as less than an average of ten reports annually during a period of the last 5 years, may apply for a waiver that allows paper-based reporting despite the legal obligation for electronic transmission. In this case, most reports sent to BfArM or PEI from those companies are closely monitored by both institutes. The waiver may be withdrawn if the number of reports exceed the limits in the future.

Companies that are obliged to report electronically have to undergo a test phase in which cases are submitted to a database that is only designed for user tests and developmental purposes. The tests are focused on technical aspects as well as on content of and coding in the electronic reports. These data are compared with the information provided in the paper forms normally sent. After successful completion of this test that is structured similarly to the EMEA test scenario, companies shall enter into the so-called 'production phase'. BfArM has started this phase of transmitting case reports only electronically in December 2005 with three companies and has now registered about 50 companies for electronic reporting. The first phase of the transition period towards electronic reporting is focused on the major companies

with a high number of reports so that BfArM is able to handle the huge amount of data better than before. The proportion of reports submitted by these large companies ($n = 70$) is expected to equal about 95% of all reports per year. PEI has been receiving reports electronically since February 2005, presently from 20 companies. On a daily basis, BfArM and PEI forward all new reports in their databases electronically to the EudraVigilance database run by the EMEA.

Problems that can be seen after the first months of experience are data inconsistencies across data fields and data coding that appear to be a challenge in the context of the new rules. So far, companies were obliged to transmit all relevant information in accordance with the legal time lines. This allows the provision of data in an unstructured way even if put into appropriate report forms. The new obligations, laid down in ICH guidelines that are referenced by the applicable EU documents, go beyond these requirements stating that information in the narrative should be reflected by accurate coding in the appropriate data fields (ICH E2D guideline). Therefore, the obligation is not only to provide but also to structure information according to the agreed international standards facilitating data retrieval to find the legendary ‘needle in the haystack’. Thus, BfArM sees its role not only in dealing with the new technologies and the huge number of reports but also in monitoring whether the requirements of structuring data are fulfilled and in providing feedback accordingly.

REPORT NUMBERS

With regard to actual figures, BfArM receives about 17 000 national case reports per year, not counting duplicate reporting and follow-ups. Report numbers from foreign countries, EU as well as non-EU, are currently declining and amount to about 120 000 annually, again not counting duplicate reporting and follow-ups. Declining numbers during the past year are because of the legal implementation of the revised EU rules for ADR reporting outlined in the so-called ‘Review 2004’. Most cases are thus received from countries outside the EU.

Unlike in other countries, BfArM receives most domestic cases through pharmaceutical companies. As far as national reports are concerned, 85% of the incoming information derive from this source. The

second largest number of reports is received from drug commissions of healthcare professionals that exist for physicians (see above) as well as for pharmacists and dentists. These sources provide about 10% of national reports with the Drug Commission of the German Medical Association being the most important one. The remainder of cases is received from physicians directly (including from investigator-initiated trials). Direct consumer reports, i.e. reports from patients or their relatives, amount to an only very low number (about 100 per year). This low number sounds surprising because topics of drug safety are often discussed publicly and intensively, including in lay media. On the contrary, direct consumer reporting is not encouraged by our institute. The experience over the past decades has not shown that information has been lost by not having encouraged consumer reporting, i.e. the information has been received through other routes. The BfArM tends more to follow the international recommendations that patients should see their doctors first to seek medical advice and to transmit well-documented case reports that are the result of collaboration between patient and physician. This strategy is encouraged by BfArM and PEI whenever appropriate.

Most of the ADR reports refer to drugs used in cancer treatment (main ATC Group L) and those used in neurology or as analgesics (main ATC Group N). The distribution of suspect/interacting drugs mentioned in case reports – maybe more than one per case – according to the ATC classification is shown in the following figure for the year 2005 (Figure 17.1).

IDENTIFYING SAFETY ISSUES FROM THE SPONTANEOUS REPORTING SYSTEM

TREND AND SIGNAL DETECTION TOOL

Because of the large number of reports, it is almost impossible for the responsible assessors to have an overview about the incoming information based on their experience and memory alone. Different terms are out for the use of computer-based tools in that field: signal generation as well as signal detection. We prefer the term ‘signal detection’ to ‘signal generation’, because the issue is not to generate things that are not there. The issue is to recognise signals when

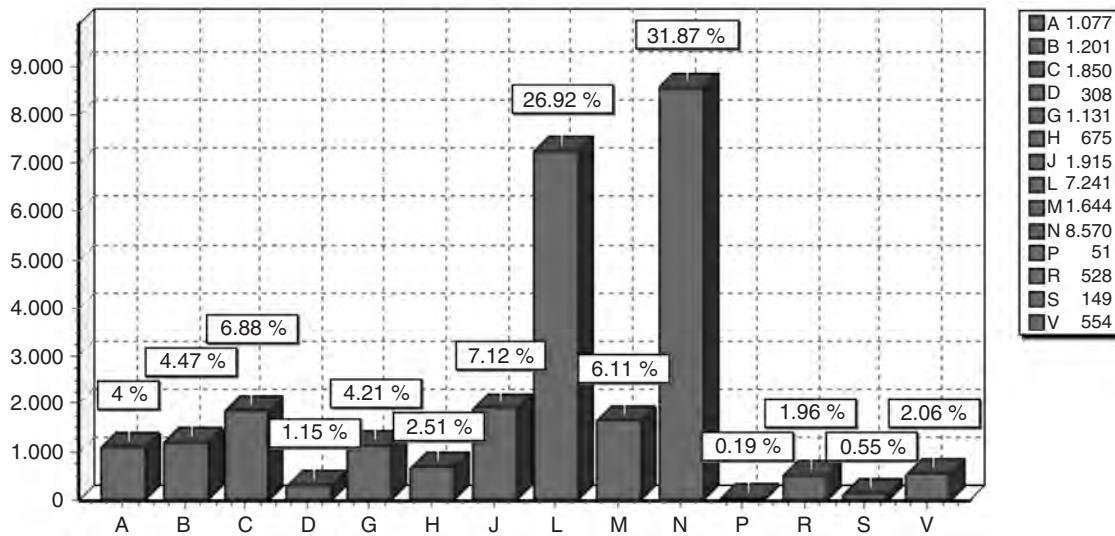


Figure 17.1. Suspect drugs in National ADR Reports according to ATC Main Groups in 2005 (number of underlying case reports: 16 684).

they are present and can be derived from the existing data but which have not yet been detected by individual report review.

The BfArM does not consider a signal detection tool to be a replacement of staff skills and intellectual work in that field. It should rather function as a measure of security – a second safety net. It must be emphasised that the output of such electronic tools needs careful review and assessment by medically qualified staff, because these systems also bear the risk to detect false positive ‘signals’. Certainly, these need to be distinguished from the real ones. To build up the above-mentioned ‘second safety net’ effectively, it is necessary to integrate such tools into the user environment of the ADR database. Ideally, different approaches supportive of daily routine work should be installed.

In BfArM’s new system, three strategies have been implemented that are now in the process of evaluation and refinement for future versions:

1. A tool that detects new substance–ADR combinations reported within a specified period, i.e. those that have not yet been reported at all or very seldom. The term ‘seldom’ is defined by the number of specified substance–ADR associations reported in the whole database. For example a substance–ADR combina-

tion that has been reported within the last month, but which has also been reported 200 times in the period before, would not be considered ‘new’ and would therefore be ignored by this tool. Given that the same association has been reported only once or twice before, the system would generate an output. The time covered and the number of reports necessary to trigger an output are flexible, i.e. can be tested and adapted to find the right balance between results worth being elaborated on further, and noise.

2. A tool enabling the detection of trends. This approach compares substance–ADR associations of equal sequential time. The output shows whether clusters have emerged or whether a continuous increase of report numbers describing a specified association can be observed. Again, the length of time and limits for total numbers are flexible and are currently in the process of being tested.
3. The proportional reporting ratio (PRR) approach that 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. This approach is quantitative and does not focus on trends or new associations (Evans, Waller and Davis, 1998). This tool would generate an output if a specified substance–ADR association in the

database occurs more frequently – beyond a pre-defined threshold – compared with the whole database or ATC group. Again there is flexibility in the determination of thresholds, and tests are necessary to determine suitability and thresholds.

These basic tools will be used for screening. The substance–ADR associations existing in the database for a specified period, e.g. the last quarter, are generated by the computer and are checked against the parameters applied. An output is provided if the criteria are met regardless of a specific user question. They may also be used for specific searches, i.e. the user has the possibility of launching a request for a specific substance–ADR combination applying one or all methods described.

Future versions envisaged will focus not only on specific ADR terms but also on term groupings developed in the CIOMS/ICH Working Group on Standardised MedDRA Queries (SMQs). The SMQs are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification. We expect that the combination of the tools already established together with the methodology of SMQs would enable regulators as well as companies to detect signals with greater sensitivity and hopefully earlier compared with the use of single ADR terms alone.

SINGLE CASE ASSESSMENT

Over many years while BfArM and PEI received spontaneous reports on paper, medical assessors made quality checks of the reports and also a causality assessment of each individual reported case. The cases were categorised according to the WHO scheme used in causality assessment (certain, probable, possible, unlikely, unassessable, unclassified, etc.) (Meyboom *et al.*, 1997). The outcome of the assessment was documented in the case files.

Medical assessors are responsible for and have special expertise in assessing ADRs caused by drugs that belong to one (main) 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, etc., and have the best and complete insight in the related

diseases and therapeutic options in that field. This enables assessors to extend their risk-benefit assessment from the suspected drug to therapeutic alternatives in a comparative way. This is relevant in the risk-to-benefit assessment and in the decision-making process.

In the past, individual case report assessment constituted an enormous workload. In Germany, the revision of national reporting requirements, apart from the very extensive ones laid down in the former Directive 75/319/EC towards the new rules of the EU Directive 2001/83/EC as amended, took place very recently (April 2005). Consequently, BfArM and PEI received a large number of reports on serious ADRs over the past 11 years from EU Member States as well as from third countries.

Following the implementation of Directive 2001/83/EC as amended, into national law that led to a reduced total number of reports and now being able to receive case reports electronically from a relevant proportion of large companies, a tremendous change in the character of work of the assessors and of the workload is expected to occur. It is envisaged that the effectiveness of case assessment is clearly increased and resources are much better used for more and complex risk assessments. Identifying signals of safety problems could take place earlier and quicker that would be to the benefit of the consumers.

RISK-ASSESSMENT PROCEDURES

PHARMACOVIGILANCE MEETINGS

Risk-to-benefit assessment is a complex challenge. It is not only restricted to mere safety data, i.e. number of single case reports, incidences or odds ratios. In the process of assessment and preparation of a decision, other aspects must be regarded and considered as well. Therefore, other opinions and views on the problem perhaps from people outside the agency's pharmacovigilance unit should be requested and reflected.

The pharmacovigilance unit meets regularly once a month with representatives from BfArM's licensing units to exchange information on new safety issues, ongoing risk-to-benefit assessments, internal and external decisions, e.g. from the Committee for Medicinal Products for Human Use's (CHMP) Pharmacovigilance Working Party. These meetings allow

the co-ordination 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 with representatives from the herbal products department, the narcotics department and the legal or pharmaceutical administrative departments.

DECISION-MAKING PROCESS AND THE 'TWO-STEP PROCEDURE'

In general, BfArM and PEI may take regulatory decisions according to four main types of procedures. Type 1 is the Urgent Safety Restriction that leads to an immediate change of the licence followed by a Type II Variation procedure according to EU Regulations 1084/2003/EC or 1085/2003/EC. Type 2 is one of the formal referrals according to Article 31 or 36 of Directive 2001/83/EC as amended or Article 20 of Regulation 726/2004/EC, irrespective of whether rapporteurship has been given to one of the two agencies or not. Type 3 may be a class review outside a formal European referral resulting in changes of the Summary of Product Characteristics (SmPC) or Patient Information Leaflet (PIL) or establishing risk-management plans. Type 4 is a purely national risk assessment that is not extended to other Member States because of lacking community interest. Whatever procedure is chosen or started, BfArM or PEI initiate a formal national procedure, the so-called 'Two-Step Procedure' that helps to exchange information with the stakeholders, to implement once agreed regulatory actions, and to communicate.

Once a safety issue has been identified and action for minimising the risk is considered necessary, the principal type of actions, the scope of the regulatory action, i.e. which drugs are included, and the information from relevant data sources available (preclinical data, clinical data and post-licensing experiences) are compiled. A team including in-house experts in the field drafts a list of questions to the MAHs (all who hold a licence 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, on the basis

of new data or information, concerns whether the risk-to-benefit balance is still acceptable (step one of the Two-Step Procedure). The MAHs have to submit all relevant data requested but have also the opportunity to comment on the concerns and the proposed regulatory action, to submit supportive or divergent data and to propose voluntary action for minimising the risk. The time frame for responses should be adequate and depends on the severity and urgency of the issue.

The MAH's response is evaluated and presented in an agency's pharmacovigilance meeting. The agreed regulatory actions are ordered formally to the MAHs, and detailed reasons are given (step two). 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

'Risk communication' has become an important tool not only to inform patients or their caregivers about the properties of the drugs actually used. Risk communication also contributes to a better understanding of drug therapy, its principle benefits and risks. Also, the enormous change in the public availability of information on drugs through the internet or print media is a challenge. Drug agencies have a lot of information and data from unpublished, pre-clinical and clinical, studies that are not accessible to people in the outside world. They also have easy access to worldwide literature and exchange information with drug agencies worldwide. Presently, major changes in the communication policy are taking place, and the EU-revised Regulations and Directives specify what should and can be communicated to interested parties and the public in the near future.

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, i.e. 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 SRSs. A respective caveat paper, very similar to that used by the Uppsala Monitoring Centre (UMC), is sent out.

CONCLUSIONS

Spontaneous reporting remains an essential pillar in detecting risks, mainly ADRs, associated with the use of drugs. Spontaneous reporting systems have been and will be further refined to overcome, at least partly, the known limitations of SRSs. Electronic tools help to handle the huge amount of data which today can be gathered for one individual case and which can be put together and stored in large databases. Existing statistical methods, which should be developed further, enable drug safety activists to detect signals on drug-related risks earlier. However, it continues to be a major task that information from SRSs inevitably must undergo intellectual assessment by skilled pharmacovigilance experts. It is essential that risk information from SRSs is brought into the context of overall risk-to-benefit assessments. This is a pre-condition for making reasonable and robust decisions that are to

the benefit of the patients and to communicate these properly.

ACKNOWLEDGEMENT

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Spontaneous Reporting – United States

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INTRODUCTION

The US Food and Drug Administration (FDA) is responsible not only for approving drugs for marketing but also for monitoring their safety after marketing (Ahmad, 2003; Ahmad, Goetsch and Marks, 2005). Drug approvals are based on data obtained from clinical trials that are oftentimes limited in size and duration and that have excluded patients with other therapies or comorbidities from study (Rogers, 1987). After marketing, new information relating to drug safety usually becomes available as product use becomes more widespread, and on occasion this may alter the benefit-risk profile of a drug (Friedman *et al.*, 1999; Wysowski and Swartz, 2005).

In the United States, pharmacovigilance is regarded as those aspects of drug safety monitoring and assessment that are related to or dependent upon voluntarily reported cases of adverse drug reactions (ADRs) or that relate to other activities, the primary purpose of which is the generation of a signal or hypothesis of a potential adverse drug effect association. This perspective considers pharmacoepidemiology as being more closely related to population-based, systematic investigations that may range in complexity from purely descriptive to rigorous

hypothesis-testing studies. There is admittedly a gray zone whereby the two approaches blend together.

There are many ways by which drug safety signals arise. The most common is through voluntary or spontaneous case reporting to regional or national pharmacovigilance centers, such as the FDA. Case reports and case series from the literature also contribute to signal development. Other potential sources of safety concerns include pre-clinical animal testing, pre-marketing clinical trials, experience with other drugs in the same class and experience from other national centers around the world. The clinical pharmacology of the drug itself, its pharmacokinetics (absorption, distribution, metabolism and excretion) and pharmacodynamics, may raise other concerns related to organ-specific toxicity or drug–drug interactions.

ADVERSE DRUG REACTION REPORTING IN THE UNITED STATES

The FDA continues to assess the benefit–risk profile of approved drugs throughout the life of the drug, primarily on the basis of ADR case reports (GAO/ HEHS, 2000). In the United States, ADR case reports are

voluntarily sent to the FDA or the drug's manufacturer by healthcare professionals and consumers (Ahmad, Goetsch and Marks, 2005). Drug manufacturers are legally required to submit all ADR reports they receive to the FDA. Under current US regulations (21 CFR 314.80), reports of 'serious' ADRs not presently listed in the drug product's labeling must be submitted to the FDA within 15 calendar days of the company's receipt of them. For regulatory purposes, a 'serious' report is defined as one describing an ADR that is life threatening or that leads to death, hospitalization (initial or prolonged), disability, congenital anomaly or required intervention to prevent permanent impairment/damage. Reports meeting the regulatory definition of 'serious' but describing events already listed in product labeling as well as all reports with non-serious outcomes are submitted to the FDA on a periodic basis that varies depending on the market age of the product.

The FDA has maintained a computerized repository of these voluntarily reported ADRs since 1969 (Ahmad, Goetsch and Marks, 2005; Wysowski and Swartz, 2005). This repository and the system to manage it have grown and changed since then. In 2004, the FDA received approximately 425 000 reports, and the total number of reports in the database now exceeds 3 million, covering all marketed prescription drug and therapeutic biological products in the United States. For most over-the-counter (non-prescription) products, manufacturers are not required to submit ADR case reports to the FDA.

The ADR database has evolved over the years as computer and information technologies have improved. The most recent modification occurred in 1997 when the FDA redesigned the database, now referred to as the Adverse Event Reporting System (AERS), and shifted from using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) to Medical Dictionary for Regulatory Activities (MedDRA) coding terminology (Brown, Wood and Wood, 1999). These changes were implemented for several reasons. Agreements reached through the International Conference on Harmonization (ICH) necessitated a restructuring of the database to meet international standards for electronic submission of ADR reports. This 'ICH compatibility' should facilitate information exchange with industry and with

other national pharmacovigilance centers (Green, 1998). Furthermore, electronic submission of ADR reports has greatly enhanced the efficiency and accuracy of the data entry process. In 2004, manufacturers submitted over 80 000 reports electronically to the FDA. From a pharmacovigilance perspective, electronic submission should result in higher quality data and greater immediate access to this data by those who review or work with the case reports.

ADVERSE DRUG REACTION REPORTS REVIEW PRACTICES AT THE FOOD AND DRUG ADMINISTRATION

Serious unlabeled ADR reports submitted by companies, serious ADR reports (labeled or unlabeled) submitted directly to the FDA by health professionals or consumers and reports of selected 'important' medical events are electronically transferred to the computer 'in-box' of one of approximately 25 safety evaluators, who review them on a daily basis. The safety evaluators are primarily trained clinical pharmacists who are assigned to cover specific groups or classes of drugs or therapeutic biologics. Over time, they acquire in-depth familiarity with the products they monitor.

In reviewing these case reports, the primary focus is placed on identifying previously unrecognized serious ADRs. When such a report is identified, a computer search is made of the entire AERS database for reports of similar cases with the drug in question. These cases are reviewed for clinical content and completeness. If important information is missing or supporting medical records are needed for some cases, then the safety evaluator may contact the reporter, usually a health professional, to obtain the needed data. This is a time-consuming but essential process, especially when faced with a serious ADR associated with a widely used medicine. In parallel with these activities, a literature review is performed, national drug usage data are obtained and, frequently, an epidemiologist within the office conducts an investigation of background incidence rates and risk factors for the clinical event of interest. For example, a case series of pancreatitis in association with the use of

a particular drug product might be supplemented by incidence data from a population-based, randomized survey conducted by the US National Center for Health Statistics.

After a case series is assembled and follow-up completed, it is analyzed for drug relatedness. Several factors are important to this assessment. Temporal association describes the relationship between drug exposure and event. If the adverse effect preceded the drug exposure, then the drug cannot have caused the effect. If the reaction resolves with the withdrawal of the drug, then the ‘dechallenge’ is positive; if the reaction reoccurs with the re-initiation of the drug, then the ‘rechallenge’ is positive. Dechallenge is often cited as the evidence of drug relatedness. However, the lack of resolution (negative dechallenge) should not be viewed as evidence against an association. Many adverse effects, once initiated, follow a course of their own. This is especially apparent with certain blood dyscrasias, serious skin reactions and acute liver failure. Positive rechallenge has traditionally been cited as strong evidence of drug association. Our experience suggests that the absence of reoccurrence should not be taken as evidence against the association. For most recognized and serious ADRs, rechallenge is not intentionally performed.

The timing of onset of the ADR after the beginning of drug use may provide clues as to possible mechanisms (short latency: anaphylaxis; long latency: cirrhosis). It is also important to note if other explanations for the adverse effect are present such as underlying disease states or other medications. 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, herbal or dietary supplements taken by the patient may be linked to the ADR. Disease states and/or other drugs may therefore cloud or confound the relationship between a particular drug and event, complicating the assessment of case reports. Finally, clinical and laboratory features of the ADR and its progressive unfolding may also provide information that distinguishes it from underlying or other disease processes (Meyboom *et al.*, 1997). For example, myopathy

is a recognized consequence of HIV infection but can also result from zidovudine, used in the treatment of HIV/AIDS. Zidovudine-induced myopathy was found to be caused by damaged muscle mitochondria, distinguishable from HIV myopathy based on the presence of ‘ragged-red’ fibers in biopsy specimens from affected patients (Dalakas *et al.*, 1990).

The safety evaluator usually stratifies the cases into those with more complete information in which other potential explanations are absent or extremely remote, cases with incomplete information and cases with other risk factors or potential explanations for the adverse event. The case material is evaluated in combination with drug usage data, epidemiologic information and the published literature. In general, a signal results if there are higher quality, unconfounded cases plus supporting cases with less complete information or confounding factors present. There is no ‘threshold’ number of cases required to indicate the significance of a potential signal; medical judgment is used in each situation. For example, in 2004, the FDA advised healthcare professionals about a new warning for atomoxetine, a drug approved for attention deficit hyperactivity disorder (ADHD) in adults and children. Following receipt of only two reports (a teenager and an adult) in patients who had been treated with atomoxetine for several months, the labeling was updated with a bolded warning about the potential for severe liver injury. On the contrary, it took over 300 cases of serious cardiac arrhythmias and about 80 deaths before cisapride was withdrawn from the market.

An analysis of the safety issue is presented to the medical reviewing division responsible for ongoing regulation of the drug. A decision is then made about whether the signal is strong enough to warrant a regulatory action such as changes in product labeling, further study, issuance of a public health advisory, restriction of use or market withdrawal.

METHODS OF SIGNAL DETECTION AND REFINEMENT

DATA MINING

‘Data mining’ is a technique for extracting meaningful, organized information from large complex

databases and has been used to identify hidden patterns of associations or unexpected occurrences ('signals') in spontaneous reporting system databases. One goal of this developing technology is automated signal generation within spontaneous AERS databases (Bousquet *et al.*, 2005). If this can be reliably achieved, data mining might serve as a potentially useful adjunct to traditional pharmacovigilance practices (Almenoff *et al.*, 2005). Since 1998, 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, Machado and O'Neill, 2002; Szarfman, Tonning and Doraiswamy, 2004).

Importantly, data mining *cannot* prove or refute causal associations between drugs and events. Data mining simply identifies disproportionality of drug-event reporting patterns in databases. The absence of a signal does not rule out a safety problem. Similarly, the presence of a signal is not a proof of a causal relationship between a drug and an adverse event. Hands-on review of the cases is critical to the evaluation of potential 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 include those inherent to spontaneous reporting databases such as under-reporting, influences by media/publicity and litigation. Results obtained from data mining technique should be interpreted with caution and with the knowledge of the weaknesses of the spontaneous reporting system (Anon. Guidance for Industry. E2E Pharmacovigilance Planning. ICH. April 2005; <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0117-gdl0002.pdf>).

CASE SERIES

The most common approach to signal development is based on the evaluation of a series of case reports. Although several criteria (described above) are used in this review, no formal causality assessment algorithm is followed. Many such algorithms have been reported in the literature, but these suffer from important liabilities including inflexibility, lack of sensitivity and lack of validation (Pere *et al.*, 1986; Frick, Cohen and Rovers, 1997). They are also oftentimes

difficult and time consuming to use, may tend to discount even remotely confounded cases and may place excess weight on the presence of positive rechallenge.

Because the AERS database draws on the cumulative experience of nearly 300 million people, it is a rich source of clinical material. A physician in practice may see one case of a rare or unusual drug reaction and may perhaps even publish the case. The advantage of a centralized ADR repository is that it offers the potential of much greater case numbers and with that comes the capacity to describe the spectrum and natural history of the reaction and to identify risk factors for its occurrence.

Several examples help to illustrate this. Based on a review of 121 cases of seizure reported with alprazolam, the importance of the duration of drug use and the sudden cessation of therapy were identified as risk factors for seizure occurrence (Graham, 1989). The 'epidemic curve' derived from these case reports strongly suggested benzodiazepine withdrawal as the underlying mechanism (Figure 18.1). The evaluation of 95 reported cases of hemolysis with the use of the antibiotic temafloxacin resulted in the discovery of hemolytic-uremic syndrome with this drug and identified prior fluoroquinolone use as a strong risk factor for the development of this life-threatening complication (Blum, Graham and McCloskey, 1994). More recently, a review of 89 cases of acute liver failure reported with the use of troglitazone described the clinical spectrum and natural history of this disorder (Graham *et al.*, 2003). Of note, this analysis provided evidence of the inability to predict who was at risk of this frequently fatal reaction. It also demonstrated that liver enzyme monitoring would not

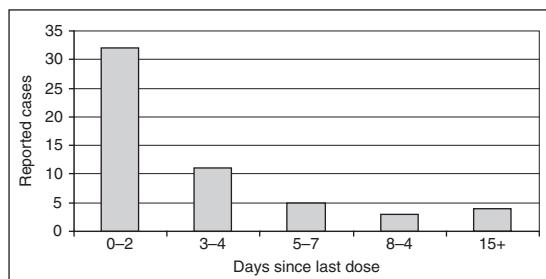


Figure 18.1. 'Epidemic curve' showing reported cases of seizure by time since stopping alprazolam use.

prevent liver failure occurrence with troglitazone. In another instance, a review of 58 case reports suggested a possible association between the use of the antifungal, itraconazole and the development of congestive heart failure (Ahmad, Singer and Leissa, 2001). No evidence of a similar signal was observed with the other azole fungicides.

PROPORTIONAL DISTRIBUTIONS

This approach to signal identification and refinement is similar in concept to proportional morbidity ratios (Rothman and Greenland, 1998). Basically, the number of reports of a given ADR or of a group of ADR terms are viewed as a proportion of all ADRs reported for that drug. The resulting measure can serve to highlight specific drug reactions or show a clustering of different reactions, all of which affect a particular organ or body system. Of perhaps greater utility, a drug's proportional distribution can be compared with that of other drugs in the same pharmacologic class or with drugs from other classes used to treat the same indication. From this type of analysis, one might observe that a particular antibiotic has a relatively high proportion of skin-related ADRs compared with other class members. As with proportional morbidity ratios, proportional distributions are useful in a qualitative sense, revealing potential 'problem areas' for a drug. However, they do not contribute to our understanding of ADR incidence.

REPORTING RATES

In its simplest form, a reporting rate is the number of reported cases of a particular ADR divided by some measure of the suspect drug's utilization, usually the number of dispensed prescriptions. As such, they are not true rates, but convention refers to them thus. An epidemiologic modification of the reporting rate 'denominator' 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.

The reporting rate of an ADR can be compared between different drugs. 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 drug and two other anti-androgens marketed in the United States 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).

Reporting rates must be interpreted carefully because they are not incidence rates. True rates incorporate the element of time and depend upon the complete ascertainment of the event being measured within a defined population (Clayton and Hills, 1993). These requirements do not hold for reporting rates. Using person-time rather than prescription number as the denominator of the reporting rate still does not give rise to an incidence rate because most ADRs are not reported, and hence the reporting rate will seriously underestimate the true incidence. The failure of most ADRs to be reported to the FDA or other pharmacovigilance centers is referred to as under-reporting. This is the single greatest limitation of using spontaneous case reports to monitor drug safety. After an ADR occurs, a series of barriers must be overcome if this event is to reach the 'in-box' of a safety evaluator. These are (a) recognition and correct diagnosis of the clinical event, (b) attribution of that event to a drug exposure and (c) registration of the event (filing a report) with the drug company or the FDA (Graham, Waller and Kurz, 2000). These barriers generally reduce the level of reporting of serious ADRs to the range of 1%–10% (Inman and Adelstein, 1969; Inman and Weber, 1986; Scott *et al.*, 1987; Rogers, Israel and Smith, 1988; Belton *et al.*, 1995; Eland *et al.*, 1999, La Grenade, Graham and Nourjah, 2001).

OBSERVED-TO-EXPECTED ANALYSIS

A natural extension of the concept of reporting rates is the technique of observed-to-expected analysis. This approach to signal refinement is more epidemiologic in nature than the above described methods. To employ this approach, it is necessary to have an estimate of the background rate for the clinical event of interest in the general population. Such rate information may be found in published literature or possibly through other sources such as the US National Center for Health Statistics (La Grenade, Kornegay and Graham, 2000).

The other piece of information that must be obtained is an estimate of the total exposure-time to the drug of interest within the population. This estimate is usually derived from data estimating the total number of prescriptions dispensed for a specific drug, along with an estimate of the average prescription length in days. At the FDA, such data are usually available through a contract with a commercial drug-utilization data vendor. 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, Waller and Kurz, 2000).

Two examples illustrate this method. Returning to nilutamide and pulmonary fibrosis, the person-time of drug exposure in the US population was estimated using commercially available data (Ahmad and Graham, 2003). The background rate for 'idiopathic' pulmonary fibrosis was obtained from a population-based epidemiologic study (Coulas *et al.*, 1994) and was applied to the accumulated person-time of exposure to nilutamide. This analysis found that the number of spontaneous case reports of pulmonary fibrosis with this drug was 15-fold greater than expected.

An evaluation of ADR reports for clozapine 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, Graham and Trontell, 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 is much greater than that obtained. In such instances, one has moved beyond signal towards establishing an association.

'CASE–CONTROL' ANALYSES

Another approach for signal development borrows heavily from the case–control method of standard clinical epidemiology (Breslow and Day, 1980; Kahn and Sempos, 1989). The simplest variant of this approach identifies all ADR cases describing a particular event of interest within a national center's pharmacovigilance database. These will serve as 'cases' in the analysis. All other reports in the database serve as non-cases or 'controls'. Reports listing the drug under investigation are classified as 'exposed', regardless of their status as a case or non-case. Similarly, reports not listing the drug of interest are 'unexposed'. A two-by-two table is created, and an odds ratio is calculated as the cross-products ratio $((a \times d) / (b \times c))$ (Table 18.1). Moore *et al.* (1997) used this approach to chart the emergence of a signal and its progression over a period of months.

A modified version of this approach has been developed at the Medicines and Healthcare Regulatory Agency in the United Kingdom (Wiholm *et al.*, 2000). The proportional reporting ratio is calculated from

Table 18.1. Format of two-by-two table used to categorize adverse event reports for 'case-control' analysis

	Case (ADR of interest)	Non-case (All other ADR reports)	
Exposed	a	b	a + b
Unexposed	c	d	c + d

the same two-by-two table as with the case–non-case method above. However, instead of deriving a cross-product ratio, a ratio of proportions among the exposed and unexposed is computed, analogous to the epidemiologic concept of relative risk ($[a/(a+b)]/[c/(c+d)]$).

The above two approaches rely solely upon data contained within the national pharmacovigilance database. A third variant supplements case reports data with population-based data obtained from large automated healthcare databases (Graham, Waller and Kurz, 2000). This method was helpful in assessing the effect of daily dose and cumulative duration of use on the risk of experiencing withdrawal seizures following abrupt cessation of the benzodiazepine, alprazolam (Graham, 1989). A nested case–control design was used for this study, with all cases and non-cases exposed to alprazolam. From the AERS database, all cases of seizure reported with alprazolam were reviewed, and data on daily dose and duration of use abstracted. Reports were coded into binary categories for each of these two potential risk factors (dose: >4 vs. ≤ 4 mg/day; duration: >4 vs. ≤ 4 months), and the proportion of cases in each category was calculated. From a population-based healthcare database, the proportional distribution of alprazolam users in each of the dose and duration categories was obtained. A two-by-two table was created in which each of the four cells contained the relevant proportion from the 121 AERS seizure reports ('cases') and from the general population of alprazolam users ('controls'). The resulting cross-products ratio yielded an odds ratio of 39 for seizure risk with higher dose alprazolam use (Table 18.2).

An advantage of this approach is that an unbiased measure of exposure is obtained from a general population of drug users that can usually be assumed to be representative of all users nationally. It thereby serves as an unbiased estimate of the source population from which the reported cases emerge. If the probability

of the ADR being reported is unlikely to be influenced by the exposure of interest (e.g. dose), a reasonable estimate of the relative risk may be obtained. In this circumstance, underreporting does not affect the observed result.

SURVIVAL ANALYSIS

One final technique, recently developed to enhance the information content of spontaneous case reports data, employs principles of time-to-event and survival analysis to the evaluation of ADR reports (Kahn and Sempos, 1989; Graham *et al.*, 2003). The technique requires access to nationally representative population-based drug use data to model the pattern of duration of use in the general population. In a clinical trial or longitudinal observational cohort study, patients who drop out before study completion are censored at that point in time, and only the time during which they were in the study is considered in the analysis (Piantadosi, 1997). Life-table techniques are common means of accurately accounting for changes in the size of the population at risk resulting from withdrawals (Clayton and Hills, 1993; Kelsey *et al.*, 1996). By use of this method, one can calculate interval-specific reporting/hazard rates (e.g. for the first, fifth or twelfth month of product use) as well as the cumulative risk of an ADR being reported through a given point in time, such as after 1 or 3 years of continuing drug use.

The method is complex but useful. It was used to demonstrate the association between risk of developing acute liver failure and the duration of use of trovafloxacin, a fluoroquinolone antibiotic. Over about a 2-year period, the FDA received 14 reports of acute liver failure associated with trovafloxacin use (Public Health Advisory, 1999). In an effort better to characterize the contour and magnitude of risk over time, the survival technique was used. For comparison purposes, the background incidence rate for acute liver failure due to "idiopathic" causes was previously estimated at one case per million per year (Graham and Green, 1999). Based only on *reported* cases, the relative risk of acute liver failure was increased from the start of therapy and increased rapidly with increasing duration of exposure (Table 18.3). This technique was also used to show that the risk of acute liver failure was substantially increased with troglitazone use

Table 18.2. 'Case–control' analysis of case reports of seizure with alprazolam by prescribed daily dose

Seizure reports (cases)	General population
>4 mg/d	0.67
≤ 4 mg/d	0.33

Table 18.3. Life-table estimation of reporting rates of acute liver failure with trovafloxacin

Interval (days)	Number of cases	Days of follow-up	Interval hazard rate (per 106 person-years)
1–60	14	60	45
9–60	11	52	73
11–60	7	50	168
15–60	5	46	326
31–60	2	30	1912

during the first month of use and remained elevated for as long as patients remained on drug (Graham *et al.*, 2003).

REGULATORY ACTION BASED ON SPONTANEOUS REPORTS

Identification and evaluation of safety signals from spontaneous reports can result in a range of regulatory actions. These may include one or more of the following:

- Change to the manufacturer's professional and/or patient labeling.
- Implementation of a Risk Management Action Plan (RiskMAP).
- Market withdrawal of the product.
- Further study of the safety concern.

Nearly all postmarketing safety labeling changes for drugs are based on spontaneous case reports. In 2005, the average number of such safety labeling changes for drugs per month was approximately 40. A RiskMAP (Guidance for Industry, 2005) may need to be implemented when labeling and routine pharmacovigilance alone are not considered sufficient to manage the risks of the product. In these instances, further measures, such as targeted education and controlled product distribution, might need to be implemented to help assure its safe and effective use. Withdrawal of the drug from the market may be necessary on occasion. Further study may also be needed or desirable, either alone or in conjunction with any of the above actions, to refine the nature and/or extent of the safety concern. In some

situations, a fair assessment of a safety concern can only be achieved through such study. For example, in situations where the underlying disease being treated and the ADR resulting from treatment are the same, only a well-conducted randomized trial will convincingly establish the drug–ADR association. Such was the case with encainide and flecainide, which were removed from the market after randomized clinical trials identified an increased mortality risk (Echt *et al.*, 1991; Massie *et al.*, 1993). This risk would have been difficult, if not impossible, to identify with spontaneous reports alone. The concept of risk management or risk minimization as applied to pharmaceuticals is relatively new. Research into the effectiveness of various regulatory interventions intended to substantially improve a drug's benefit–risk balance has shown that generally speaking, such interventions frequently are inadequate and do not improve the safety profile of medicines (Graham *et al.*, 2005). Additional approaches to risk management are needed (Andrews, Gilsean and Cook, 2004).

THE VALUE AND FUTURE OF PHARMACOVIGILANCE IN THE UNITED STATES

Pharmacovigilance is the cornerstone of postmarketing drug safety activities in the United States and will likely remain so for the foreseeable future. Nearly all postmarketing labeling changes related to drug toxicity are based on spontaneous case reports. The same holds true for drug withdrawals. Since 1980, there have been 22 major prescription drug withdrawals in the United States (Wysowski and Swartz, 2005). Of these, spontaneous case reports and their analysis were a critical informational component contributing to the withdrawal decision in 20. The two exceptions were encainide and flecainide, where randomized clinical trials identified the increased mortality risk conferred by these approved drugs (Echt *et al.*, 1991; Massie *et al.*, 1993). This should not be a surprise because patients with cardiac arrhythmias under treatment of those arrhythmias will sometimes experience sudden death due to arrhythmias, and death is not infrequent among patients with congestive heart failure. In situations where the underlying disease being treated and the ADR resulting from treatment are the same, only

a well-conducted randomized trial will convincingly establish the drug–ADR association.

As mentioned earlier, data mining is emerging as a potential means of generating new safety signals using existing ADR databases (Lindquist *et al.*, 2000; Almenoff *et al.*, 2005). A variety of methods have been developed, each of which compares every potential drug–ADR combination in the database for statistical evidence of a discrepancy from an ‘expected’ number derived from all case reports in the database. The hope, as yet unrealized, is that such screening will help pharmacovigilance practitioners to identify and respond to previously unrecognized safety problems, and to do so with a shorter lag time. The integration of data mining into routine business practices is beginning to occur at a number of national and international pharmacovigilance centers. However, to date, data mining has not been shown prospectively to improve overall signal detection.

In another recent development, ‘active’ surveillance for ADRs has emerged as a potential complement to the traditional so-called ‘passive’ surveillance afforded by voluntary case reports, such as those collected by national pharmacovigilance centers (Food and Drug Administration, 2005). The intention here is to search prospectively and proactively for ADR signals. Suggested methods include setting-, drug- and outcome-based approaches. Setting-based active surveillance has been pilot tested in emergency rooms and blood banks (Bennett *et al.*, 2000; Budnitz *et al.*, 2005) while outcome-based surveillance has been applied to the problem of drug-induced acute liver failure (Ostapowicz *et al.*, 2002; Larson *et al.*, 2005). The principle of drug-based active surveillance was demonstrated recently in a study of the association between rotavirus vaccine and intussusception (Davis *et al.*, 2005). These authors applied sophisticated statistical methods to automated, longitudinal claims data from a large healthcare organization and showed that it might be possible to detect important safety signals prospectively in real time. The use of longitudinal healthcare data for active surveillance requires much additional work but offers the prospect of a significant advance for pharmacovigilance.

While the utility of case reports is undeniable, there is much that might be done to improve and expand their value. Strategies to improve the level of reporting of serious ADRs need to be developed.

The proverb about ‘strength in numbers’ also applies to pharmacovigilance. A few reports may provide a sufficient basis upon which to modify a product’s label. However, important information regarding the magnitude and duration of risk as well as risk factors for ADR occurrence is more easily and reliably discovered through careful analysis of a larger series of cases. Hand in hand with the value of a larger number of serious case reports is improved quality and completeness of those reports. The more clinically detailed a series of reports is, the greater the range of analytic possibilities. The value of this for regulatory decision-making and risk management efforts cannot be overstated. How to achieve these goals in an environment of immense time constraints and litigation fear is an important challenge for the future.

Another area of potentially great public health value is the expansion of current pharmacovigilance practice to include other venues and types of ADRs. In the United States, the focus of pharmacovigilance has been on the rapid identification of serious *unlabeled* events. Many, if not most of these, fall into the category of ‘unexpected’ or ‘idiosyncratic’ and have been referred to as type B reactions (Meyboom *et al.*, 1997). This is an important endeavor but from a population perspective, the bulk of drug-related morbidity and mortality is because of type A reactions, i.e. those that represent an extension of the drug’s pharmacology. The problem is great enough to represent one of the leading causes of mortality in the United States (Lazarou, Pomeranz and Corey, 1998). Pharmacovigilance strategies in this arena might lead to the identification of ‘problem areas’ and provide the basis for more effective intervention and prevention.

Finally, advances in technology in the 1990s and the advent of the ICH process have created an environment where global pharmacovigilance is now conceivable. A remaining challenge is to make this a reality.

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19

Statistical Methods of Signal Detection

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INTRODUCTION

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; secondly, 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 recognised as early as possible. At the same time, those suspected reactions that are not caused by a medicine should be recognised as such and minimal resource should be spent on investigating them.

Signals of potential harmful effects may arise from literature reports, observational epidemiological studies, randomised 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 concentrate on the analysis of large volumes of these spontaneous reports. Their source will usually be health professionals but may also include patients. The early evidence from spontaneous reports can be regarded as a potential ‘signal’. This has been defined as showing a

'possible causal relationship between an adverse event and a drug. Unknown . . . previously' (Wood, Coulsen and Eccles, 1994). The object is to distinguish the real signals from 'noise' precisely.

The details of spontaneous reporting will not be covered here. The salient feature is that health professionals, particularly doctors, report suspected ADRs centrally; this can be to a regulatory authority or to a company. These reports are processed and entered on to a database. Whether they are reported as suspected ADRs or as adverse events there will inevitably be some background reports that are not caused by the drug. There will often be a very large number of reports, and an essential task is to prioritise those that should be investigated first. The purpose of collecting these reports is to detect signals. Even in countries where reporting of ADRs is supposed to be compulsory, reporting rates will usually be much less than 100%. A typical figure is said to be 10%, but it depends very much on the seriousness and newness of the ADR. In the case of fibrosing colonopathy caused by high-strength pancreatic enzymes, the rate was shown to be 100%.

WHAT CONSTITUTES A SIGNAL?

If resources were available, then every single report would constitute a signal, but in practice, some have used simply the number of reports for a particular reaction/drug combination as a cut-off. This cut-off has been, for example, two or more, or three or more reports. This is a reasonably sensitive but a very non-specific test. The number of reports, whether the signal is a causative effect or not, will depend on the number of patients exposed to the drug. The first step in the process is to attempt to estimate incidence. The number of reports is taken as the numerator but a question exists as to what is the correct denominator. Possible alternatives are as follows:

- Sales,
- Prescriptions written,
- Prescriptions dispensed.

Even if the data on prescriptions dispensed are available, they do not necessarily relate to the important factors related to a causal effect. If it is simply

patient-years of exposure, then the total number of prescriptions dispensed is a reasonable measure. However, this assumes that the risk of having the ADR is constant over time. If this is not so, then we need patient-years grouped by duration of treatment. This requires individual patient-based data or at least the distribution of the number of prescriptions per patient.

A cut-off for a signal could then be an incidence rate that is greater than background. This is the basis of the Poisson method of examining signals. This has utility in some specific areas where the background rate is well known and rare, and where the reporting rate is known to be reasonably high or at least well known. It can be used to compare reporting rates of two drugs using sales data as a denominator.

CLASSIFICATION OF ADR REPORTS

Each report must be assigned to one or more drugs and to one or more medical terms describing the reaction. There is a need for a distinction between a drug reported as being suspected of causing the adverse effect and one that is simply co-medication. This distinction made by the reporter of the reaction may not be made correctly, especially when it is an interaction between drugs that is causing the effect.

For the value of the report to be optimal, both the trade name and the drug substance name may need to be recorded separately. For initial statistical approaches to signal detection the drug substance name is the one that is used.

The minimum information for a valid report is usually an identifiable (but not necessarily identified) patient, a drug and a reaction. The reaction must be classified using some form of medical dictionary. There are several different dictionaries in wide use, including those from the Food and Drug Administration (FDA) (COSTART) and the World Health Organisation (WHO) (WHO-ART). In the United Kingdom, the Medicines Control Agency (MCA) use their own Adverse Drug Reactions Online Information and Tracking (ADROIT) dictionary and a project to unify these dictionaries, based partly on the ADROIT dictionary has been carried out, resulting in the internationally (International Conference on Harmonisation (ICH)) agreed MedDRA.

Most of the dictionaries have a form of hierarchy from the widest grouping – ‘System Order Class’, for example cardiovascular – through ‘High Level Terms’ to ‘Preferred Term’, for example myocardial infarction. A second type of classification relates to the public health impact of a reaction classed as fatal, serious or non-serious. The definition of ‘serious’ is not always consistent between countries or dictionaries but within a particular database it will (or should) be consistent.

CHARACTERISTICS OF SPONTANEOUS REPORTS

It is well known that reporting is biased: severe ADRs are more likely to be reported; known reactions are less likely to be reported. In the United Kingdom, there is a tendency for reporting rates to be higher when a drug is newly introduced to the market, but the effect of media or regulatory action may distort this pattern. The consequence is that reporting rates cannot be relied upon as estimates of the incidence of adverse reactions. This situation will always apply, and although there may be calls from those unfamiliar with pharmacovigilance to improve reporting rates so that spontaneous reports do reflect true incidence, this is not their purpose. They can be used to detect signals, and they are certainly capable of doing this.

Given the biases in reporting rates, one obvious way to assess the strength of a signal is to study the spontaneous reports alone without an external comparison group. This means that many of the biases that apply to reporting rates will apply to all reports, and within the database an increased validity of comparison may be made.

PROPORTIONAL REPORTING RATIOS

Proportional reporting ratios (PRRs) compare the proportion of reports for a specific ADR reported for a drug with the proportion for that ADR in all other drugs (Evans, Waller and Davis, 1998, 2001). The principles are not new, but were set out in a similar way by Patwary (1969) and Finney (1974) for ADR reporting with WHO data. The methods were not fully used subsequently, either in WHO or in the United Kingdom, and were effectively reinvented in 1995 at

Table 19.1.

	Specific ADR	All other reactions
Specific drug	a	b
All other drugs	c	d

the UK MCA, where they have been used routinely since 1997. The PRR can also be seen as a numerical version of the ADR profile; this simply uses a bar chart for a particular drug giving the numbers in each system organ class (SOC). An implicit comparison is made with a bar chart derived from another group of drugs. A similar approach is used in classical epidemiology with death data – the ‘Proportional Mortality Ratio’ (see, e.g., Rothman and Greenland, 1998).

The calculation of the PRR is very simple in principle as shown in Table 19.1:

$$\text{PRR} = [a/(a+b)]/[c/(c+d)]$$

This is analogous to a relative risk. An obvious alternative is to use an odds ratio (ad/bc) that may be regarded as a ‘Proportional odds ratio’ (POR). This has slightly more desirable statistical properties than a PRR, but will be very similar in magnitude since in most circumstances $b \gg a$ and $d \gg c$.

When a reaction is new and rare, then a (in the 2×2 table, Table 19.1) 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 POR is not calculable. However, it is possible to use the table for practical purposes in a way that is not exactly statistically rigorous. The second row can refer to *all* drugs rather than ‘all other drugs’. This means that c is never zero and the POR or PRR is always able to be calculated, and the estimated values are less than they would be otherwise. This conservatism applies when the numbers are small and does no harm when using the PRR or POR for prioritisation.

A more general approach 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_{ADR} . The expected number can then be obtained using the total reports for this drug, N_{drug} :

$$E_{ADR, drug} = P_{ADR} * N_{drug}$$

The deviation of the observed number from the expected number can be expressed as a ratio, that is, the *PRR*:

$$PRR = O_{ADR, drug} / E_{ADR, drug}$$

This approach can more easily be seen to be generalisable to allow the expected number to be calculated in a less crude way. It can be modified to allow for age and sex to be taken into account. This is equivalent to having a set of 2×2 tables stratified by age and sex, where a POR can be derived using a general Mantel-Haenszel estimator from several 2×2 tables (Rothman and Greenland, 1998). 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 simplest way to make such allowances is to calculate statistical significance tests of the hypothesis that the PRR or POR is one. It is also possible to use the equivalent confidence intervals (Tubert-Bitter *et al.*, 1996). The usual chi-square test (corrected using Yates' method to be conservative), or for stratified tables using the Mantel-Haenszel method, can be calculated. This chi-square value indicates the contribution of chance to the magnitude of the PRR. Table 19.2 gives an example of an extreme PRR. The proportion of reports of uveitis with the drug rifabutin is $(41/55) = 0.75$, while the proportion for all drugs is $754/591\,958 = 0.0013$: PRR = 586, $\chi^2 = 22\,736$, $p \ll 0.00001$.

It should be realised that all of this process should be used for the purpose of signal detection, and even more importantly, for prioritisation of the detected

signals 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 POR as the sole convincing evidence of causation is unwarranted. They raise a serious question that merits further study. At the same time, it should be remembered that where the reports are of suspected ADRs, then the reporter suspected a causal relationship and the fear that raised PRRs or PORs will generate too many false positive signals is probably also unjustified.

RATIONALE FOR PROPORTIONAL METHODS

A basic question to be asked is whether the use of the proportion of reports for a particular reaction (compared with all reports) is sensible. As a first step, it is reasonable to examine the trends in proportions of reports over time within a major database. Figure 19.1 below gives the cumulative total number of reports and the cumulative number of reactions reported as suspected ADRs in the UK MCA database (Waller, Coulson and Wood, 1996). This database, called Adverse Drug Reactions Online Information and Tracking (ADROIT), has suspected ADRs reported on Yellow Cards since 1964. Over this period, the number of reports in the database has risen dramatically but the pattern in proportions in different SOC s has remained relatively stable.

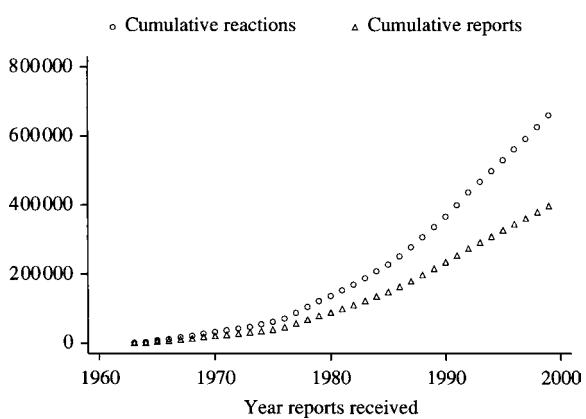


Figure 19.1. The cumulative number of reports and reactions in the UK ADROIT database.

Table 19.2. Example calculation of PRR.

	Uveitis	All other reports	Total
Rifabutin	41	14	55
All other drugs	754	591 958	592 712
Total	795	591 972	592 767

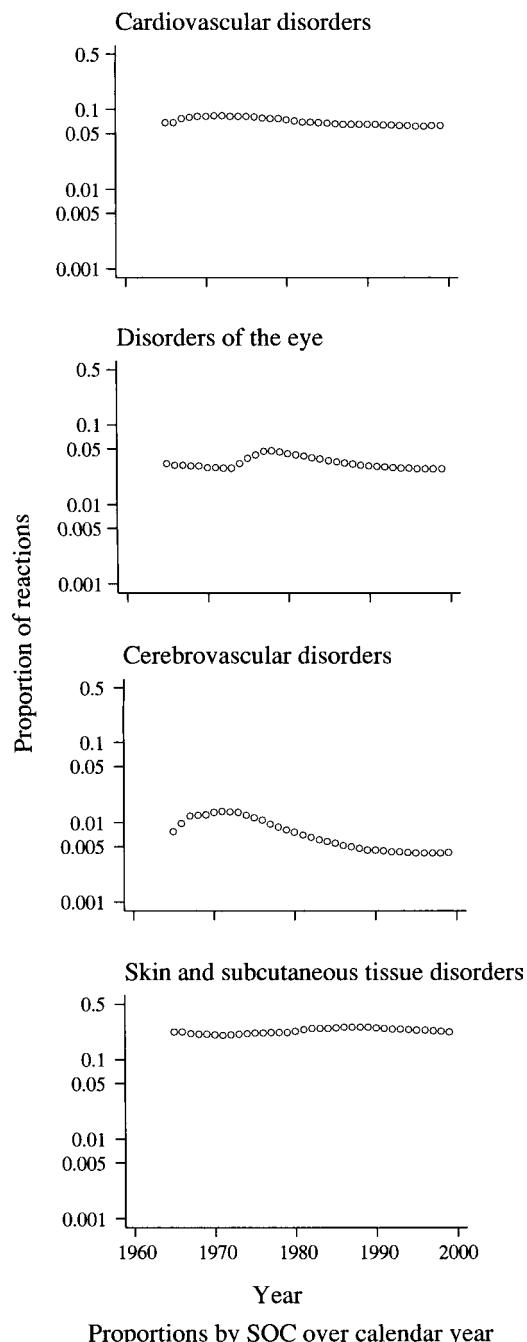


Figure 19.2. The proportions of reactions in some SOCs over time.

Figure 19.1 shows the cumulative number of reports and reactions by year. Figure 19.2 shows the

cumulative proportion (on a log scale) of reactions reported for a cross section of the SOCs. These show that cardiovascular reports are stable at a high level, while 'ear' reports are fairly stable at a low level. Eye reactions show a notable rise in 1974 – a result of practolol. Skin reactions are stable at a high level with a peak in 1982 (benoxaprofen).

THE USE OF PRRS IN MONITORING DRUGS

One method of screening for signals for drugs in the United Kingdom that are under intensive monitoring ('Black Triangle' drugs) is to use both the PRR and the chi-square statistic. A cut-off for each can be used; for example, a $\text{PRR} > 2$ and $\chi^2 > 4$ and the number of reports > 2 . When this method is first used with these criteria on an existing database, many of the signals generated will already be known problems. In the first usage at the UK MCA, slightly more than 60% were known, for example uveitis with rifabutin. About 15% were not believed to be caused by the drug but were events or effects of disease or a function of the patient population being treated, for example haemoptysis with dornase alpha. About 25% were new signals that required more detailed evaluation, for example renal failure with losartan.

In general, the method is used for continuing monitoring so that known problems will not constitute a new signal. The triggers that constitute a signal will then be a change in PRR to raise it above the threshold or a 30% increase in PRR previously above threshold, but where the previous judgement was that the (small) raised PRR was not sufficient evidence of a signal.

FURTHER DEVELOPMENTS AND KEY ISSUES

Further improvements to the sensitivity and specificity of the method include stratifying by age and sex, examining serious or fatal reactions only. (The proportion of reactions that are fatal, stratified by age, is itself a potential signalling method.) Where a drug has a well-known ADR that is reported very

frequently, such as gastrointestinal (GI) bleeding with non-steroidal anti-inflammatory drugs (NSAIDs), this will distort the PRR for other reactions with that drug. The best approach is then to remove the known reactions from the totals for that drug and the database as a whole and recalculate the PRR for all other reactions with that drug. This is simple to do on an *ad hoc* basis but is more difficult to implement in an automated way.

The comparison used need not be the entire database. It is possible to use PRRs within drug classes or indications so that the comparator is all drugs in that class or those used for a particular indication.

The expected number of reactions could also incorporate prior beliefs about the ADR profile, using a fully Bayesian method. (The approaches used at the FDA and WHO do not incorporate prior beliefs.)

The grouping of terms used in the medical dictionary for the database is an important feature. Little empirical study of the effect of choosing different levels in the hierarchy of terms has been done. In most instances, the grouping is at 'Preferred Term' (PT), which is a relatively low level. There are a large number of medical terms at this level, so that the numbers for any particular combination of drug and reaction can be small. This can lead both to the general statistical problem of multiplicity, with many possibilities for signals, and to instability in the PRR based on small expected numbers.

It is possible to use a two-stage process – using, say SOC to screen for raised PRRs, then to re-examine the PRRs using PTs within the SOC where the PRR was raised. The automation of this process is possible in principle, but has not been done yet. An alternative is to use an intermediate level within the hierarchy – a 'High Level Term' (HLT), for example. This has the advantage of being a single stage process and avoids the use of too many terms, reducing the problems of multiplicity and small expected numbers.

The use of the method in general is easiest within a large database that contains a wide range of drugs, but it can be used within a pharmaceutical company database. Here, the potential for incorporating prior beliefs is at its greatest. A further possibility for companies is to use the proportions of reactions from the FDA database, which is publicly available, to calculate expected numbers for their own drugs. Other

regulatory databases are not yet publicly available but increasing transparency may change this in the future.

CONCLUSIONS

The validity of the method has been demonstrated. It detects existing problems; it finds new signals and prioritises them for the benefit of assessors; it is very simple, transparent, and objective; and it can be automated very easily indeed.

The 'Bayesian Data Mining' approach used by the FDA (DuMouchel, 1999) is very similar, but offers a better statistical analysis when very small numbers are involved. It emphasises ranking of the equivalent of the logarithm of PRR. It uses an 'Empirical Bayes' method, which shrinks $\log(O/E)$ towards zero, and the shrinkage is important if E is small, but gives very similar results when observed or expected numbers of reactions are reasonably large. It is slightly more complex in the calculations, and consequently less transparent.

The WHO has a new approach (Bate *et al.*, 1998) based on a Bayesian confidence propagation neural network, but again is very similar to a PRR. It uses the log (to the base 2) of the PRR based on the same 2×2 table as used with PRRs. Its use of Bayes' theorem in a 2×2 table is not controversial and does not incorporate prior belief. The cut-off for a signal is based on the confidence interval around their statistic. The method has the ability to scan the whole database relatively rapidly, forming all tables for combinations of drugs and reactions that occur together and is used routinely.

The major issues are the potential for misinterpretation of the signals and over-reliance on automation. The statistical methods are a first stage of assessment, and careful evaluation using medical scientific knowledge is still required. At the same time, the potential contributions of statistical methods and of statisticians have not been fully realised. The advances in the past few years seem to have been greater than since the mid-1980s, although it is recognised that there has been some re-invention. Further statistical creativity is possible, particularly in integrating spontaneous reporting with epidemiological methods and randomised trial data.

ACKNOWLEDGEMENTS

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Statistical Methods of Evaluating Pharmacovigilance Data

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INTRODUCTION

The three main challenges of pharmacovigilance, that is to detect, to assess and to prevent risks associated with medicines (Bégaud, 2000), may concern both the patient level and the populational level. Similarly, the latter may rely on classical epidemiological studies, for example cohort or case-control, or on cases-only analyses, which is the scope of spontaneous reporting (SR).

In cohort studies (Kramer, 1988), subjects are followed in a forward direction from exposure to outcome (e.g. the occurrence of a given disease), and inferential reasoning is from cause to effect. For example, in the case of a cohort study with a reference group, the subjects can be split, at the end of the follow-up, among the four cells of the following classical two-by-two table:

	Diseased	Not diseased
N_1 (exposed)	a	b
N_2 (not exposed)	c	d
t_0	follow-up	t_1

In case-control studies, subjects are investigated in a backward direction, from outcome (disease) to exposure and inference is from effect to cause:

Exposed	Not exposed	
a	b	N_1 diseased (cases)
c	d	N_2 not diseased (controls)
		← index date past exposure ascertainment →

In both designs, the compared groups are generally drawn from a larger source population, which raises the problem of possible selection biases; however, the subjects are generally exhaustively classified according to a binary variable: to present or not to present the considered disease in cohort studies, or to have been or not to have been exposed to the studied factor in case-control studies. SR, *per se*, is a passive surveillance method involving the whole source-population, for example all subjects of a given

country treated with a given medicine; however, SR suffers two major limitations (Bégaud, 2000):

- it does not provide any direct and reliable information on the size, characteristics and exposure patterns of the source population;
- the term *spontaneous* refers to the random character of the case collection from the exposed population; indeed, reporting assumes that the observer (i) identifies the adverse event, (ii) imputes its occurrence to a drug exposure, (iii) is aware of the existence of a pharmacovigilance system, and (iv) is convinced of the need to report the case if relevant, for example new and/or serious adverse drug reactions (ADRs).

This results in the major plague of this surveillance method: an inescapable *under-reporting*, the magnitude and selectivity of which are unknown and extremely difficult to assess. Indeed, if a number a of cases of a given event have occurred in a population during the ‘follow-up’ period, then it is likely that only a part $k = a/U$ of these cases will be reported, U being the *under-reporting coefficient* varying from 1 to infinity, for example $U = 4$ if 25% of cases have been reported.

Moreover, it is hard to believe that each of the a cases that have occurred have an identical probability $1/U$ to be reported. Many factors have been shown to influence reporting (Pierfitte *et al.*, 1999) such as the age of the patient, the seriousness of the event and its onset delay. Thus, because of a selection bias, k could be a non-representative sample of the source population of cases.

From a biostatistical point of view, the rather bizarre design of SR could be compared to a cohort study without reference group in which:

- the ‘followed’ population is extremely large, that is the whole population of the surveyed territory treated with drugs;
- the characteristics of this population, for example age and gender distributions, concomitant diseases, are unknown as are its characteristics of exposure (indications, dose, duration, co-medications, etc.);
- the number of ‘investigators’ is extremely large, that is all health professionals in the territory;

- the case collection does not rely on a precise protocol and is thus non-systematic and may be subjective.

Moreover, because of the open character of this method of surveillance (any type of drug, any type of event), there is in fact a quasi-infinite number of sub-cohorts, one for each type of drug exposure:

	Diseased	Not diseased	Total
Exposed	a	b	N_1
	t_0	Cohort study	t

	Diseased	Not diseased	Total
Exposed	k	?	?
	t_0	Spontaneous reporting	t

While the cohort study can estimate the risk associated with a given drug exposure by calculation of the incidence rate a/N_{1t} (number of new occurrences of the disease produced by the surveyed population during the period t), to estimate risks from SRs requires rather complex assumptions and calculations.

RISK ESTIMATION FROM SR

ESTIMATION OF THE NUMERATOR

As previously mentioned, the actual number a of cases that have occurred during the surveillance period t could theoretically be estimated by

$$a = k \cdot U,$$

where k is the number of reports during the surveillance period and U is the under-reporting coefficient varying from one (exhaustive reporting) to infinite (i.e. the reporting rate is null).

Unfortunately, it is extremely difficult and/or hazardous to estimate the magnitude of this under-reporting, even if in most cases it can be thought to be

huge, even for serious cases (Alvarez-Requejo *et al.*, 1998; Eland *et al.*, 1999).

For example, in 1998 a nation-wide prospective study conducted in a representative sample of French public hospitals estimated that 128 768 patients (95% CI: 100 916–156 620) were admitted that year in these hospitals because of an ADR (Pouyanne *et al.*, 2000). This study did not consider other aspects of seriousness such as death, nor admissions to private hospitals. Nevertheless, the obtained figure (128 768) was far larger than the number of serious reactions (about 15 000) reported during the same period to the French pharmacovigilance system still considered as particularly efficient.

The *capture–recapture* approach, when applicable, could appear appealing to estimate the total number of cases of a given effect that have occurred in the surveyed population (Jeeger, Schumock and Kong, 1996). This approach derives the size of the source-population from the number of individuals both ‘captured’ by two independent samplings from this population (a more accurate estimate would be obtained by a greater number of samplings, e.g. three or four). To apply this method to pharmacovigilance consists in considering two or more independent sources of reports in the same territory. For instance, if k_1 and k_2 reports have been collected, respectively, during the same period, through two independent sources, for example the regional pharmacovigilance centres network and the concerned manufacturer and if c was the number of duplicates (i.e. cases identified by both sources 1 and 2), then the total number of cases would be

$$a = \frac{k_1 \cdot k_2}{c}.$$

If k_1 and k_2 were large enough (e.g. ≥ 15), the normal approximation can be used to calculate the $1 - \alpha$ confidence interval (CI) for a :

$$\text{CI}_{1-\alpha} = a \pm Z_{1-\alpha} \sqrt{\frac{k_1 \cdot k_2 \cdot (k_1 - c) \cdot (k_2 - c)}{c^3}}.$$

Example: During a one-year surveillance period, 127 cases were reported to the first system and 42 to the second; 12 duplicates were identified. The estimate for the total number of cases is

$$a = \frac{127 \times 42}{12} = 444,$$

and its two-sided 95% CI is:

$$444 \pm 1.96 \sqrt{\frac{127 \times 42 \times (127 - 12) \times (42 - 12)}{12^3}} \\ = [242; 646].$$

One can deduce that the actual number of cases has 95 chances in a hundred of being between 242 and 646. The number of cases identified by SR being $(127 + 42) - 12 = 157$, the reporting ranges between 24% and 65%.

However, the validity of such an estimate requires that reporting to one system or the other be a truly random and independent phenomenon which could be an unverified assumption. For this reason, the safest way is probably to cease to estimate the actual number of cases and to deal with *reporting rates* instead of *incidence rates*!

ESTIMATION OF THE DENOMINATOR

In some countries, the size N and characteristics of the exposed population and its conditions of exposure can be precisely derived from health insurance databases. In this case, except for the poor quality of case collection (i.e. under-reporting), SR approaches the cohort design.

Unfortunately, in most cases, it is necessary to estimate these parameters from sales statistics and/or drug prescription on drug utilization panels (Bégaud, Pére and Miremont, 1993). The use of such aggregated data precludes any possibility of considering some individual or sub-group characteristics in the analysis.

The necessary ‘ingredients’ for computation are: the number of exposure units, for example tablets, capsules, injection doses sold in the territory during the relevant period of time, and the average daily dose (ADD) of the considered drug used in this population, the latter being estimated from prescription panels or other sources. By default, the defined daily dose (DDD) or the recommended daily dose (RDD) can be used as proxy.

Example: 780 000 packages of 20 capsules have been sold in a 1-year period, the used daily dose is 2.1 capsules. This corresponds to the quantity necessary for a cumulative duration of treatment

of: $(780\,000 \times 20)/2.1 = 2\,666\,667$ days, or 87 719 months. In a more epidemiological parlance, the exposure level in the source-population is 87 719 person-months.

As for incidence density calculations, this total probably sums individual exposure periods which are extremely different. Moreover, because of its ecological character, this approach precludes any risk analysis based on the duration of exposure.

To estimate the number of treatments or the number of subjects treated would require knowing the average duration of a treatment (ADT) with the considered drug. In the previous example, if the ADT was 23 days, the number of treatments for the considered period would be: $2\,666\,667/23 = 115\,942$.

However, in the absence of direct information from a health insurance database, the use of measurements made on panels or relatively small samples, both for the average daily dose and duration of treatment, will greatly increase the statistical instability of the estimate. In the previous example, if the 95% CIs were [1.6; 2.7] and [16; 31] for the ADD and ADT, respectively, then the CI for the number of treatments would range from 31 860 to 104 167. For this reason, it is often preferable to keep person-time estimates for further calculations.

ESTIMATION OF REPORTING RATES

As for incidence rates, the number of cases reported during a given period of time is standardized for the corresponding person-time denominator. For example, if 18 cases of severe neutropenia have been reported for a cumulative exposure time (estimated from sales statistics) of 87 719 months, the reporting rate is $18/87\,719 = 2.05$ for 10 000 person-months of exposure. It is sensible to consider that the occurrence of cases in the exposed population and their reporting, both correspond to a pseudorandom process which can be described by an *ad hoc* probability model. Given that, in pharmacovigilance, the source population is generally extremely large and the probability of occurrence very low, the Poisson distribution is expected to be quite a satisfactory model (Snedecor and Cochran, 1989). In these conditions, the calculation of the 95% two-sided CI for the reporting rate consists of considering the lower and upper limits for the Poisson parameter read in a table such as Table 20.1.

Table 20.1. 95% confidence limits, two-sided, left and right one-sided, for m according to the Poisson distribution. To estimate the CI of a proportion p , bounds are divided by N . For a left one-sided interval, the upper bound of np is $+\infty$ and of p is 1. For a right one-sided interval, the lower bound of np is $-\infty$ and that of p is 0 (computations made by the author by using a HP 49G calculator).

m	Two-sided	Left one-sided	Right one-sided
0	—	—	3
1	0.03–5.57	0.05	4.74
2	0.24–7.23	0.35	6.29
3	0.62–8.77	0.82	7.75
4	1.09–10.24	1.37	9.15
5	1.62–11.67	1.97	10.51
6	2.20–13.06	2.61	11.84
7	2.81–14.42	3.28	13.15
8	3.45–15.76	3.98	14.43
9	4.12–17.08	4.69	15.71
10	4.80–18.39	5.42	16.96
11	5.49–19.68	6.17	18.21
12	6.20–20.96	6.92	19.44
13	6.92–22.23	7.69	20.67
14	7.65–23.49	8.46	21.89
15	8.40–24.74	9.25	23.10
16	9.15–25.98	10.03	24.30
17	9.90–27.22	10.83	25.50
18	10.67–28.45	11.63	26.69
19	11.44–29.67	12.44	27.88
20	12.22–30.89	13.25	29.06
21	13.00–32.10	14.07	30.24
22	13.79–33.31	14.89	31.41
23	14.58–34.51	15.72	32.58
24	15.38–35.71	16.55	33.75
25	16.18–36.91	17.38	34.92
26	16.98–38.09	18.22	36.08
27	17.79–39.28	19.06	37.23
28	18.61–40.47	19.90	38.39
29	19.42–41.65	20.75	39.54
30	20.24–42.83	21.59	40.69
31	21.06–44.00	22.44	41.84
32	21.89–45.17	23.30	42.98
33	22.71–46.34	24.15	44.13
34	23.54–47.51	25.01	45.27
35	24.38–48.68	25.87	46.40
36	25.21–49.84	26.73	47.54
37	26.05–51.00	27.59	48.68
38	26.89–52.16	28.46	49.81
39	27.73–53.31	29.33	50.94

In the above example, the 95% Poisson CI for the observed number 18 is [10.67; 28.45]. The CI for the reporting rate is thus 10.67 to 28.45 for

87 719 months, that is 1.2 to 3.2 per 10 000 person-months of exposure. When the number k of reports is large enough, that is 15 or preferably 30, the CI can be calculated by using the normal approximation for a Poisson count (Daly, Bourke and McGilvray, 1991):

$$\text{CI} = k \pm Z_{1-\alpha} \sqrt{k}.$$

In both cases, this CI defines the set of values which could be observed because of the sampling variation, all parameters remaining identical.

STATISTICAL MODELLING OF SR

If N is the size of the exposed population, that is the number of subjects treated or having been treated with the considered drug during the surveillance period, and p is the reference risk of a given event, that is the risk in this population if not exposed, then the number of fortuitous (i.e. non-causal) occurrences of this event expected during the period is $N \cdot p$.

If RR is the relative risk associated with drug exposure and U the under-reporting coefficient, then the expected number of reports is (Tubert-Bitter *et al.*, 1992):

$$m = \frac{N \cdot p \cdot RR}{U}.$$

Referring to the classical Poisson formula, the probability of receiving x reports is:

$$\Pr(k = x) = \frac{e^{-m} \cdot m^x}{x!},$$

and the cumulative probability of receiving at least x reports is:

$$\Pr(k \geq x) = 1 - \sum_{x=0}^{x-1} \frac{e^{-m} \cdot m^x}{x!}.$$

Table 20.2 gives the probability of receiving at least one report according to the value of m . One can see that to have a good chance of detecting an adverse event requires m to be greater than one, that is 1.61 for an 80% chance, 2.30 for 90% and 3 for 95%, respectively.

Table 20.2. Value of the expected number m necessary to have a given probability $\Pr(k \geq 1)$ of observing at least one case of an event (calculations made by using the Poisson formula).

m	$\Pr(k \geq 1)$	m	$\Pr(k \geq 1)$
0.1	0.095	0.9	0.593
0.2	0.181	1	0.632
0.3	0.259	2	0.865
0.4	0.330	3	0.950
0.5	0.393	4	0.982
0.6	0.451	5	0.993
0.7	0.503	6	0.998
0.8	0.551	7	0.999

It should be kept in mind that for serious conditions, the baseline incidence p is usually extremely low, therefore m remains markedly below one, except if N is extremely large and RR/U greater than one, that is if the association between drug exposure and the considered event is strong and the reporting is reasonably good.

Let us take the example of a non-steroidal anti-inflammatory drug for which the average duration of use is two weeks. In a given country, 2.5 million 2-week treatments have been made in one year, corresponding to a cumulative time of exposure of 5 million weeks, that is 96 154 years. Considering the generally recognized value of 7 per million for the annual incidence of agranulocytosis in the general population, the expected number of fortuitous, that is non-causal, associations is $0.0961 \times 7 = 0.67$. According to the Poisson formula (cumulative probabilities), there is only 48% chance that one case or more really occurs by chance in this population. Considering a probable under-reporting, it becomes highly improbable that one or more of such a non-causal association will be reported. For example, if $U = 4$ (25% of cases which have occurred were reported), $m = 0.67/4 = 0.17$. The probability of receiving one report or more under these conditions is 16%. This probability falls to 0.07% for three reports or more, which allows us to exclude the possibility of a non-causal association (Bégaud *et al.*, 1994). This simulation explains the well-recognized value of SR for signal generation (Fletcher, 1991; Tubert-Bitter *et al.*, 1992): for rare events, only causal associations (characterized by a RR far greater than one) have a good chance of being reported, even if the reporting approaches 100%. This

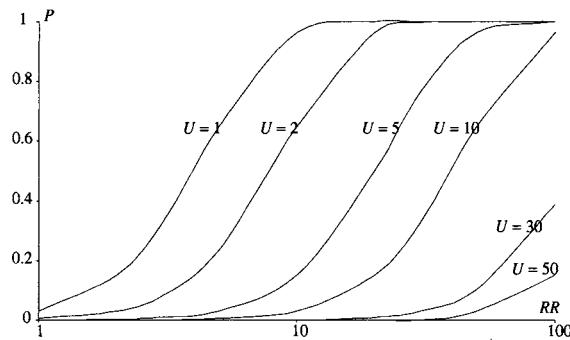


Figure 20.1. Probability P of receiving at least three case-reports according to several theoretical values of RR and under-reporting coefficient U (see text).

is illustrated by Figure 20.1 which plots, for different theoretical values of under-reporting and RR , the probability of receiving three reports or more when the expected number of fortuitous associations is, as above, 0.67.

COMPARING TOXICITY BETWEEN DRUGS

Despite the fact that population databases and health insurance databases are increasingly used for designing comparative pharmacoepidemiological studies, SRs remain the main source for pharmacovigilance decisions. In a classical study, for example a comparative cohort, the incidence rates a_1/N_1 and a_2/N_2 measured in each group (exposed and not exposed to the studied drug, respectively) are compared. In the framework of SR, the validity of such a comparison is jeopardized (i) because of the absence of information on the actual number of cases which have occurred during the considered period of time, and (ii) because of the questionable character of the estimates of the denominators N_1 and N_2 . We will address both issues separately.

THE PROBLEM OF UNDER-REPORTING

As discussed above, it is highly probable that the number of reports involving Drug 1 (k_1) and Drug 2 (k_2), respectively, are only a part of the numbers a_1 and a_2 of cases which have occurred. The issue is that the magnitude of this under-reporting may differ

across the two drugs compared (Bégaud *et al.*, 1991). If the respective values of under-reporting coefficients, U_1 and U_2 , were assessable, one could write:

$$a_1 = U_1 \cdot k_1 \quad \text{and} \quad a_2 = U_2 \cdot k_2.$$

Therefore, the relative risk for Drug 1 compared with Drug 2 would be:

$$RR = \frac{U_1 \cdot k_1 / N_1}{U_2 \cdot k_2 / N_2} = \frac{U_1 \cdot k_1 N_2}{U_2 \cdot k_2 N_1}.$$

Let us note that if $U_1 = U_2$, then the estimate of the RR remains identical, whatever the magnitude of under-reporting. Thus, a comparison based upon the number of reports would lead to the same estimate as if based on the actual number of cases. The only consequence would be a dramatic decrease in the statistical power of the comparison test because it was computed on smaller samples.

This is illustrated by Table 20.3 showing the values of the statistic of a chi-square test performed on the basis of a theoretical number of 120 cases for Drug 1 and 60 for Drug 2, respectively; the number of patients treated being chosen identical ($N_1 = N_2 = 300\,000$) for simplification purposes. One can see that a complete reporting leads to a χ^2 statistic of 20 which allows one to conclude that Drug 1 is more toxic than Drug 2 with a high confidence level ($p < 10^{-4}$). This conclusion would be reversed if the under-reporting affected Drug 1 predominantly, for example if $U_1 = 10$ and $U_2 = 2$. In this case, one would conclude that there was a significantly higher toxicity of Drug 2 ($p = 0.006$).

Table 20.3. Values for the chi-square statistic computed on the basis of 120 cases for Drug 1 and 60 cases for Drug 2, respectively (the exposed population size being the same for both drugs: 300 000 patients) according to several theoretical values of the under-reporting coefficient U (bold figures correspond to differences which are significant at the 0.05 level).

		U_1				
		1	2	5	10	20
U_2	1	20	0	15.4	32	44.2
	2	54	10	0.67	7.7	16
	5	88.3	32	4	0	2
	10	103	44.2	10.8	2	0

Moreover, for an equal but more marked under-reporting, for example $U_1 = U_2 = 10$, a statistical comparison based on the numbers of reports would not allow one to conclude there was a significant difference (χ^2 statistic = 2; $p = 0.16$).

An elegant approach for ‘neutralizing’ the effect of an unbalanced under-reporting has been proposed by Tubert-Bitter *et al.* (1996). It consists in expressing the CI for RR as a function of $U = U_1/U_2$:

$$\text{CI}_{RR} = \left[U \times \frac{N_2}{N_1} \times \frac{k_1 - Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}}{k_2 + Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}} ; U \times \frac{N_2}{N_1} \times \frac{k_1 + Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}}{k_2 - Z_{\alpha/2} \sqrt{\frac{k_1 k_2}{k_1 + k_2}}} \right].$$

Example: The Committee on Safety of Medicines (CSM) (1990) has published complete data on post-marketing surveillance of non-steroidal anti-inflammatory drugs (NSAIDs) in the United Kingdom, for two drugs launched approximately at the same date, piroxicam (1980) and diclofenac (1979). The number of serious gastrointestinal reactions reported to the CSM during the same time interval (5 years) was 538 for 9.16 million prescriptions for piroxicam versus 68 for 3.25 million prescriptions for diclofenac. The RR estimated from these data is $U \times [(538 \times 3.25) / (68 \times 9.16)] = 2.81U$ and the corresponding 95% two-sided CI is calculated as:

$$\left[U \times \frac{3.25}{9.16} \times \frac{538 - 1.96 \sqrt{\frac{538 \times 68}{606}}}{68 + 1.96 \sqrt{\frac{538 \times 68}{606}}} ; U \times \frac{3.25}{9.16} \times \frac{538 + 1.96 \sqrt{\frac{538 \times 68}{606}}}{68 - 1.96 \sqrt{\frac{538 \times 68}{606}}} \right] = [2.23U; 3.72U].$$

Assuming that the reporting ratios were the same for both drugs ($U = U_1/U_2 = 1$), the 95% CI for RR [2.23; 3.72] does not include one. Therefore, the null hypothesis H_0 : ($RR = 1$) will be rejected and piroxicam considered more gastrotoxic than diclofenac as long as $U > 1/2.23$. Reporting 2.23 times lower for diclofenac than for piroxicam would have precluded this conclusion, while it would have been reversed

(diclofenac more gastrotoxic than piroxicam) by a reporting 3.72 times lower for diclofenac.

The calculation process does not impose assignment of *a priori* values for U_1 and U_2 . The only assumption required is the order of magnitude of the ratio $U = U_1/U_2$, regardless of the individual and unknown values of U_1 and U_2 .

As to the context, the concern is to know whether it is plausible to consider a marked difference in reporting across the two compared drugs. It is generally acknowledged that under-reporting is roughly of the same order of magnitude provided that the two drugs belong to the same therapeutic class, have been launched approximately at the same date, are compared for the same type of events and do not differ with regard to the information provided for the potential reporters (Griffin, 1984; Haramburu, Bégaud and Moride, 1997; Pierfitte *et al.*, 1999). For instance, in the CSM (1990) data, benoxaprofen was launched in the United Kingdom approximately at the same time (1980) as diclofenac (1979), the number of serious reactions (of any type) involving benoxaprofen was 332 over 1.47 million prescriptions versus 128 over 3.25 million prescriptions for diclofenac, which leads to a RR value of $5.73U$ (95% CI: $4.72U - 7.11U$). This gives some credibility to the decision to withdraw benoxaprofen from the UK market in 1984 because of unacceptable excess toxicity.

COMPARABILITY OF DENOMINATORS

Another source of bias when comparing the toxicity of drugs is the non-coherence of denominators. It is therefore crucial to ensure that under the null hypothesis of a non-difference in toxicity, the risk of an adverse event is expected to be the same for the two drugs compared.

A typical example relies on different durations of exposure. Let us take the example of anaphylactic reactions which, by definition, are expected to occur at initiation of the treatment. Ninety-two reactions were reported for drug A and 242 for drug B. On the basis of a total exposure (estimated from sales statistics) of 2.8 million months and 1.9 million months, respectively, the risk appears to be 3.9 times greater for drug B. However, this conclusion could be reversed if the number of first users was much greater for this drug because of shorter duration of treatment. It

could happen, even if the two drugs belong to the same pharmacological and/or therapeutic class. For instance, such differences are observed with analgesics or NSAIDs: for more or less obscure reasons, some are used chronically when others are preferred for the treatment of acute pain. Therefore, it is a safe practice, before any decision-making, to try to obtain relevant informations on the utilization patterns of the drugs compared in order to avoid gross misinterpretation errors.

CONCLUSION

Despite the relatively soft character of the data analyzed, simple statistical calculations may apply to SR. Their main interest is to make SR more reliable for alert processes. Moreover, they can avoid major biases and misinterpretation, especially when comparing the toxicity across drugs.

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Data Mining in Pharmacovigilance: A View from the Uppsala Monitoring Centre

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BACKGROUND

The WHO has defined a signal as: 'Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously'. An additional note says: 'Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information' (Edwards and Biriell, 1994).

A signal is therefore very tentative in nature; the first expression that something might be wrong with a medicinal product, or a hint given by new information which might support or explain a medicinal product–adverse reaction relationship already known.

Both quantitative and qualitative factors come into the decision of whether something is a signal or not (Edwards *et al.*, 1990). Many algorithms have been proposed for determining causality between a drug substance and an adverse reaction, but there is no perfect way of doing this, which fits all possible situations. Perhaps the use of the Bayesian approach proposed and developed by Auriche (1985)

and Naranjo and Lanctôt (1991) is the most attractive since Bayesian logic allows one to build up a pattern of probability which changes according to the addition of new information. This intuitively fits the clinical diagnostic approach, and is transparent.

Apparent causality in a single case, or even a series, is not the only issue in comprehensive early signal detection. One might exclude many of the case reports with limited information, yet, because a case record does not allow for remote assessment of the case, does not mean that the original observer was incorrect; only that one cannot confirm the observation. Thus the quantity as well as the quality of reports of associations is valuable. The use of 'poor quality' reports as a trigger for a signal should be considered more carefully if the clinical event is serious. Early warning is more important, and a signal based on doubtful evidence should promote the search for better.

There may be certain items of information within a set of reports which triggers consideration of a signal other than just the medicinal product and clinical event. It might be the apparent over-representation of

higher doses of the relevant drug, concomitant treatment, or certain patient characteristics.

The above are just some of the common reasons for someone to consider during the evaluation of an early signal. There are many others such as the finding of a problem with one medicinal product which triggers a search into products with similar effects. What is clear is that there are very complex interacting patterns of information which may trigger ideas.

Apart from the complexity of possible important patterns in data, the volume of case reports on suspected medicinal product adverse reactions is massive. The WHO Programme for International Drug Monitoring database currently holds 3.5 million case reports. There is more in the published literature and even more from varieties of clinical studies. One begins to see the problem as looking for the proverbial ‘needle in a haystack’ (Edwards, 1997).

If the above does not make the problems daunting enough, we must see medicinal product safety in the context of the use of those products. We need to know not only the numbers of people exposed to the products, but also, why they were used, in what kind of patients, for what reason and with which outcome.

The human brain is excellent at finding significant patterns in data: humans would not have survived if that were not so! On the other hand the vast quantities referred to above cannot be usefully observed, let alone held in the memory for a person to analyse. Many people are involved in pharmacovigilance, but we are not yet wise enough to divide up the great task we have. Even if we did, there would still be a place for bringing the data we have to us for analysis in ways which allow us to see patterns more easily, and without our preconceptions blinding us to see things only in a certain way, conditioned by our experience.

It is true that in looking for patterns by sifting through large amounts of data, one is likely to eventually come up with something which *looks* significant: data ‘dredging’ or ‘trawling’ or a ‘fishing expedition’ is bound to catch something, but not much that is useful. In trying to find signals this view is too rigid; firstly, since one acknowledges that an early signal is tentative and that it simply urges for further work to be performed on that hypothesis. Secondly, from experience, a principal argument has evolved in drug safety,

that, if important signals shall not be missed, the first analysis of information should be untrammelled by prejudice and rigid protocols. Thirdly, and notwithstanding the second point, data mining is not necessarily a random rummaging through data in an aimless fashion, which is what the term ‘dredging’ implies. It is certainly true that the involvement of objects and the characterisation of any relationships in advanced pattern recognition is largely unsupervised, but the level of supervision and the kind of logic that is applied to data is flexible and transparent: this can be compared with the conventional use of ‘mining’ which is defined as ‘*a system of excavations made for the extraction of minerals*’. In essence we consider that data dredging should be used as a pejorative term for unstructured fiddling about with data, or worse, the application of a structure to data to make it fit a biased hypothesis in a way to give added credibility to the result. Data mining on the other hand should be considered as a term for the application of quantitative methods to analyse large amounts of data in a transparent and unbiased fashion, with the aim of highlighting information worth closer consideration.

DATA MINING

In this chapter we are going to use the term ‘data mining’ for 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, Mannila and Smyth, 2001) and a key component of the knowledge discovery process (Fayyad, Piatetsky-Shapiro and Smyth, 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. Although data mining of drug utilisation information, and other relevant data sets such as those relating to poisoning, medical error and patient records, will add greatly to pharmacovigilance (Anonymous, 2003; Bate *et al.*, 2004), research in this area is still preliminary and will not be discussed in detail here.

In principle the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre, UMC) has been doing data mining since the mid-1970s, using an early relational database. As

with many automated systems, the relational database to a very large extent replicated a manual approach. In this instance it was the Canadian ‘pigeon hole’ system (Napke, 1977), where reports were physically assigned a slot, which encouraged visual inspection. Thus observation could be made of when certain categories of report were unexpectedly high. From the UMC database, countries in the WHO Programme for International Drug Monitoring have been provided with information, reworked by the UMC, on the summarised case data that is submitted from each national centre. This information has been presented to them according to agreed categories and classifications as determined amongst Programme members from time-to-time. This kind of system suffers from the following limitations:

- It is prescriptive, the groupings being determined on what is found broadly useful by experience
- Each category is relatively simple, but the information beneath each heading is complex, and formatted rigidly
- There is no indication of the probability of any relationship other than the incident numbers in each time period.

This system does not even have all the user-friendliness of the pigeon hole system, which allowed a user to visually scan the amount of reports as they were filed to see the rate of build up in each pigeon hole. Admittedly, the sorting was relatively coarse, but the continuous visual cue given by the accumulation of case reports was very useful. In improving on the pigeon hole system and adapting it for the ever-increasing amounts of data involved, one can imagine a computer program being able to survey all data fields looking for any pair of events that stand out as occurring together more frequently than expected. Different measures of association have been proposed for the purpose of analysing disproportional reporting of ADR terms with drug substances. The proportional reporting ratio (PRR), which is akin to a relative risk, and the reporting odds ratio (ROR) are classical statistical measures of association that can be combined with for example chi-squared tests for associations to guard against spurious findings. Bayesian and empirical Bayesian approaches take this one step further by providing shrinkage estimates such

as the Information Component (IC) (Bate *et al.*, 1998; Orre *et al.*, 2000) and the EBGM (DuMouchel, 1999). These are typically closer to the null hypothesis of independence than classical estimates and less volatile when data is scarce. As such, they provide robust measures of association that account for both significance and strength. Furthermore, a Bayesian approach is intuitively correct for a situation where there is a need to continuously re-assess probability of relationships with the acquisition of new data and over time. In Bayesian inference, new data modifies the prior probabilities to posterior probabilities, and the posterior probabilities can be used as prior probabilities in subsequent analyses. The process can be iterated indefinitely.

The next level of complexity is to consider the effects of adding other objects as variables. Complex pattern recognition in spontaneous reporting data may extract information related to ADR syndromes, patient risk groups, drug interactions and data quality problems. It typically increases the computational demands and often requires more sophisticated quantitative methods. The UMC has chosen the Bayesian Confidence Propagation Neural Network (BCPNN) as the most favourable framework for development in this area. This is a statistical neural network consisting of a matrix of interconnected nodes that represent different data fields. It is trained according to Bayes law based on the data provided to it. The use of Bayesian logic seems natural since the relationship between each node will alter as more data is added. The network ‘learns’ the new weights between nodes, and can be asked how much those weights are changed by the addition of new case data or by the consideration of higher-order associations.

DESCRIPTION OF DATA MINING METHODOLOGY USED BY THE UPPSALA MONITORING CENTRE

The UMC is, as the WHO Collaborating Centre for International Drug Monitoring, responsible for the technical and scientific maintenance and development of the WHO International Drug Monitoring Programme. The Programme now has 76 member countries, annually contributing around 250 000

suspected adverse drug reaction (ADR) reports to the WHO database in Uppsala.

One of the main aims of the international pharmacovigilance programme is to identify early signals of safety problems related to medicines. To aid this, a new ADR signalling system has been provided for national monitoring centres and authorities based on automated exploratory data analysis. It complements the previous signal detection procedure which involved the examination of unwieldy, large amounts of sorted and tabulated material by an expert panel. An overview of the new signalling approach, including results from the first part of an evaluation including a comparison against another signalling system has been published (Lindquist *et al.*, 1999).

The UMC's main purpose is to find novel drug safety signals: new information. From experience a principal argument has evolved in drug safety, that, if important signals shall not be missed, the first analysis of information should be free from prejudice and *a priori* thinking. Quantitative filtering of the data focuses clinical review on the most potentially important drug adverse reaction combinations (Bate *et al.*, 1998; Lindquist *et al.*, 1999, 2000; Orre *et al.*, 2000). Human intelligence and experience is able to operate better with a transparent filtering method in the generation of hypotheses.

The BCPNN is a computational framework based on a statistical neural network where learning and inference is done using the principles of Bayes law. The network can take real, discrete and binary variables as input. It is in its most simple feed forward implementation equivalent to the naïve Bayes classifier, which is a standard prediction algorithm that has proven efficient in many applications (Domingos and Pazzani, 1997; Hand and Yu, 2001). The BCPNN can also be implemented with feedback loops between the input and the output layers as a form of Hopfield network for unsupervised pattern recognition (Lansner and Ekeberg, 1989). As such, it has been demonstrated useful in identifying ADR syndromes based on spontaneous reporting data (Orre *et al.*, 2005). The BCPNN has also been extended to a multilayer network (Holst, 1997), which has been successfully applied to areas like diagnosis (Holst and Lansner, 1996), expert systems (Holst and Lansner, 1993) and data analysis in pulp and paper manufacturing (Orre and Lansner, 1996). Related research has produced

methods to handle uncertainty in Bayes classification (Norén and Orre, 2005).

The BCPNN is transparent, in that it is easy to see what has been calculated, and the results are reproducible, making validation and checking simple. The network is easy to train; it only takes one pass across the data, which makes it highly time efficient. Because only a small proportion of all possible drug-adverse reaction combinations are actually non-zero in the database, the use of sparse matrix methods makes searches through the database quick and efficient.

The weights in the BCPNN are referred to as Information Components (IC). They are the basis for the data mining method used to screen the WHO database for unexpectedly strong dependencies between variables (e.g. drugs and adverse reactions). They can also be used to study how dependencies in the database change on addition of new data. The IC between drug x and ADR y is defined as (Bate *et al.*, 1998; Orre *et al.*, 2000):

$$IC = \log_2 \frac{p_{xy}}{p_x p_y}$$

where

p_x = probability of drug x being listed on a case report

p_y = probability of ADR y being listed on a case report

p_{xy} = probability that drug x and ADR y are listed on the same case report.

In principle, the IC value is based on:

- the number of case reports with drug x (c_x);
- the number of case reports with ADR y (c_y);
- the number of reports with the specific combination (c_{xy}); and
- the total number of reports (C).

Positive IC values indicate that the particular combination is reported to the database more often than what can be expected based on the general reporting of the two terms in the database. The higher the IC value, the more the combination stands out from the background. An adjusted IC estimate can also be calculated to control for possible confounding variables (Norén,

Bate and Orre, 2004). Stratified analyses are part of the routine data mining of the WHO database but the first pass analysis is unadjusted since it remains unclear how to best use adjustment in routine data mining (Bate *et al.*, 2003).

From the IC probability distribution, expectation and variance values are calculated using Bayesian statistics. Thus estimates of precision (standard deviations) are provided for each point estimate of the IC, allowing both the point estimate and the associated uncertainty to be examined. The interpretation of the probability distribution is intuitive: the standard deviation for each IC provides a measure of the robustness of the estimate. The higher the c_x , c_y and c_{xy} levels are, the narrower the confidence interval becomes. If a positive IC value increases over time and the confidence interval narrows, this indicates an increased certainty of a positive quantitative association between the studied variables.

The BCPNN framework provides an efficient computational model for the analysis of large amounts of data and combinations of variables, whether real, discrete or binary. The efficiency is enhanced by the IC being the weight between nodes in the neural network. The BCPNN can be used both for data analysis/data mining, prediction and unsupervised pattern recognition. Bayesian statistics fits intuitively into the framework of a neural network approach as both build on the concept of adapting on the basis of new data. The method has also been extended to detect dependencies between several variables (Orre *et al.*, 2000). Pattern recognition by the BCPNN does not depend upon any *a priori* hypothesis, as an unsupervised learning approach is used. This is useful in new syndrome detection, finding patient age profiles of drug-adverse reactions, determining at-risk groups and dose relationships; and can thus be used to find complex dependencies which have not necessarily been considered before. Naturally, changes in patterns may also be important.

The automated routine data mining of the WHO database is based on using the BCPNN to scan incoming ADR reports and compare them statistically with what is already stored in the database. A new quarterly output to national pharmacovigilance centres contains statistical information from the BCPNN scan. It also contains frequency counts for each drug and ADR

Table 21.1. Triage criteria.

Substantial increases in IC values over time
New drugs and critical terms
Geographical spread
Special interest ADR terms
Lack of documentation in the literature

listed, both individually and occurring together. The figures from the previous quarter are also included and the data is provided in a computerised format. Drug-adverse reaction combinations with IC values above a certain threshold are selected for further consideration ('associations'). As an important complement, a triage algorithm has been designed to focus attention on the most urgent issues from an international perspective (Ståhl *et al.*, 2004) (see Table 21.1, for the fundamental triage algorithm criteria). The case series thus highlighted by the UMC are forwarded to a panel of clinical reviewers for evaluation and expert opinion. As previously, signals of possible safety problems are circulated to all national centres participating in the international pharmacovigilance programme for consideration of public health implications. Drug safety issues first highlighted with the UMC's data mining system have also been published in the mainstream medical literature (Coulter *et al.*, 2001; Sanz *et al.*, 2005).

Automated duplicate detection is another important area of application for data mining methods in pharmacovigilance. The analysis of spontaneous reporting data is sometimes impaired by poor data quality, and the presence of duplicate case reports is an especially important data quality problem. Sometimes different sources provide separate case reports for the same ADR incident and other times there are mistakes in linking to existing database records any follow-up case reports submitted to update the original report. With the ultimate aim of improving data analysis in the WHO database, the UMC has developed a statistical method for automated duplicate detection in spontaneous reporting data (Norén, Orre and Bate, 2005). The primary aim is data cleaning, which is an important component of the knowledge discovery process (Fayyad, Piatetsky-Shapiro and Smyth, 1996), but duplicate detection can also be considered as a form of data mining in its own right.

'VALIDATION' OF THE DATA MINING APPROACH

Critics of data mining can reasonably suggest that, with all the possible relationships in a huge database, many medicine-adverse reaction associations will occur by chance, even though they seem to be significantly associated. The Bayesian methodology used by the UMC can take account of the size of the database in assigning probabilities, and its current implementation is optimised for the WHO database. While the aim of the quantitative analysis is hypothesis generation and most false positives can be expected to be identified as such in the clinical review, one must be as sure as possible that national centres and reviewers are not provided with what amounts to a huge amount of useless probabilistic information. On the other hand it is clear that finding signals early will necessarily entail some false positives.

Determining the performance of the BCPNN is a difficult task because there is no 'gold standard' for comparison. Also there are different definitions of the term signal. According to the definition used in the WHO programme a signal is essentially a hypothesis together with data and arguments, and it is not only uncertain but also preliminary in nature: the situation may change substantially over time (Edwards and Biriell, 1994; Meyboom *et al.*, 1997).

Practically, signals can only be validated by increasing recognition with time. What is meant by 'recognition' is problematic in itself. In order to gain more insight both into the BCPNN performance and the 'validation' problem in general, we felt we would achieve a reasonable estimate of the predictive power of the BCPNN tool by checking historical associations identified by the BCPNN against standard reference sources (Lindquist *et al.*, 2000). Martindale has worldwide coverage, recognition and wide availability and was used as a standard for well known, recognised ADRs. The US Physicians Desk Reference, though not international, gives very recent information on drugs. It has a comprehensive ADR listing, generally more inclusive than that of Martindale. However, PDR includes suspected adverse reactions, whether substantiated or not. We considered an ADR listed in PDR an indication of a possible drug-ADR relationship.

Two main studies of the performance of the BCPNN were reported in the same paper (Lindquist *et al.*, 2000). The first study concerned a test of the BCPNN predictive value in new signal detection as compared with reference literature sources (Martindale's Extra Pharmacopoeia from 1993 and 2000, and the Physicians Desk Reference from 2000). In the study period (the first quarter year 1993) 107 drug-adverse reaction combinations were highlighted as new positive associations by the BCPNN, and referred to new drugs. Fifteen drug-adverse reaction combinations on new drugs became negative BCPNN associations in the study period.

The BCPNN method detected signals with a positive predictive value of 44% and a negative predictive value of 85%. Seventeen as yet unconfirmed positive associations could not be dismissed with certainty as false positives.

The second study was a comparison of the new BCPNN with the results of the former signalling procedure. Of the 10 drug-adverse reaction signals produced by the former signal detection system from data sent out for review during the study period, 6 were also identified by the BCPNN. These 6 associations have all had a more than ten-fold increase of reports and 4 of them have been included in the reference sources. The remaining 4 signals that were not identified by the BCPNN had a small, or no, increase in the number of reports, and are not listed in the reference sources.

The length of time chosen for the retrospective check against the literature was not arbitrary, but based on the assumption that 7 years would be enough for ADRs to be included in the reference sources, allowing for the maximum reporting for new drugs to have taken place (the Weber effect). We know however that one new association appeared in Martindale between 1999 and 2000, and 7 years still may not be long enough. Publishing delay must be considered in the use of these reference sources, but this is minimised now by their availability online using an Internet browser.

The use of our selected literature sources as a 'gold standard' is open to debate. The literature is not intended as an early signalling system, and uses many sources for its information other than the WHO database: the biases affecting inclusion and exclusion of ADR information therefore may be very differ-

ent. Factors such as those affecting the differential reporting to WHO and the inclusion of new information in the reference sources will have an effect which is independent of the performance of the BCPNN. The BCPNN is run every quarter, and we selected just one quarter: since the BCPNN is used in continuous analysis, the specificity and sensitivity are subject to necessary time-dependent changes in classification of 'positives' and 'negatives'. It is difficult to consider something as a 'non-association' because of this time dependency, and it is clear that there is an asymmetry in the effect of time on our results. This is explicable using the following logic.

Exceptionally high reporting of an ADR-to-product combination, which causes the combination to stand out from the background of the whole database will cause any other product-to-ADR combination containing the product or ADR to stand out slightly less. It is not common for alterations in the background to significantly alter the status of an association. On the other hand it is more common for the reporting of a particular ADR and medicinal product to increase at a rate which is broadly related to the incidence of the ADR to the point where it becomes an association. Publicity about an ADR may affect this rate dramatically, but this by no means invalidates the association, only complicates its interpretation. Another asymmetry is that the negative associations are a selection of all non-associations. This assumes that definite negative associations represent all non-associations, though it is clear that some non-associations will become positive associations in time. Thus a non-association can be either a combination of an ADR term with a medicinal product which is not a positive association and remains stable or one which is statistically a negative association at a high probability. Considering all this, we have in this study defined the inverse of a positive association as a definite negative association. This again shows the difficulty of evaluating a signalling system.

An assumption was made that a substantial increase in the number of reports of an association over the period indicated ongoing clinical interest in an association. More reports may be seen as a support for the validity of the associations, though there is often a tendency for ADRs that are becoming well known to be more reported anyway.

An obvious limitation of any quantitative analysis of spontaneous reporting data is the dependence on the terminology used for recording of adverse reactions. There are only few examples of work done on any of the medical terminologies in use or proposed to determine their relative value in searching for new drug signals (Brown, 2002).

Although we found that the use of the BCPNN gave a 44% positive predictive value, and a high negative predictive value of 84%, the normal methods for assessing the power of a method are difficult to apply to the BCPNN, because of the reasons above. It is for this reason that 'validation' is placed in quotation marks in the title of this section. The BCPNN is not a panacea for drug safety monitoring. The drug-ADR combinations which reach significance do so only in comparison with the background experience of 3+ million case reports. This is particularly important for commonly reported ADRs, which, however serious, would not reach significance until the quantitative experience for a drug and such an ADR is excessive. We have stressed (Lindquist *et al.*, 2000) that the BCPNN has its limitations, is not a substitute for expert review, but has a place particularly where large volumes of data are involved. It is reassuring, however, that all signals identified in the previous system that went on to become frequently reported in the WHO database were also identified in the retrospective BCPNN analysis.

On the other hand, the BCPNN has the power to analyse signals further. We are developing its use for looking at complex variables and in unsupervised pattern recognition to see whether parameters such as gender, age, other drug use increase the strength of association, and whether 'syndromes' of reported terms are present (Orre *et al.*, 2005). However, a very large amount is necessary initially, as with any subdivision of data, to attain statistical significance in subsets. This is a major advantage of using the large pooled WHO database, and we are trying to maximise this potential.

COMPARISON OF METHODS

In this chapter we have concentrated on the use of the BCPNN, partly because it is the most examined system used at present. As mentioned above, in various centres, different measures are used to quantify

the extent to which a certain adverse drug reaction (ADR) is reported in a disproportionate relationship to a certain drug compared to the generality of the database that is standing out from the background of all reports.

There have been a few studies (Kubota, Koide and Hirai, 2004; van Puijenbroek *et al.*, 2002) comparing the BCPNN with other methods. In the van Puijenbroek comparative study, the level of concordance was measured of the various estimates to the measures produced from the BCPNN. The investigation was performed on the data set of the Netherlands Pharmacovigilance Foundation (Lareb), which maintains the spontaneous adverse drug reaction reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. In essence all the other methods highlighted the same combinations as the BCPNN, and indeed more with lower numbers of cases. When the 'disproportionality' was based on relationships with four or more reports (about 11% of the Lareb database), all the methods were comparable. It was only at low count values where any difference could be detected.

The above finding is significant. The precise method used for data mining should be based upon the benefits and drawbacks of each. Crucial to the Bayesian method is the initial setting of the *a priori* probability. How this is set determines the performance of the BCPNN at low counter values. At the UMC we chose an *a priori* probability of independence which is consistent with the WHO definition of a signal and the previous publication (Edwards *et al.*, 1990), suggesting that normally more than one report would be needed to trigger an expert to think that they had found a signal, unless there was something exceptional *qualitatively* about a report (such as a case with proven, true re-challenge). Moreover the WHO database has many more incident reports than the Lareb database so that as greater numbers of reports are submitted, little time will be lost in finding the signal even though the BCPNN requires about three or more reports to trigger.

It is clear that the other methods may be just as suitable as the BCPNN for routine use to identify cases on a continuous basis which deserve follow-up for more information. The trade-off between sensitivity and specificity of the other methods, however, needs to be investigated further for predictive value

at a practical signal detection level. Table 21.2, taken from the comparisons paper, gives a very good idea of some of the comparative benefits of the methods.

THE LIMITATIONS AND USE OF DATA MINING

Data mining is intended to alert the observer to unusual relationships within a data set. It is essential to understand that in pharmacovigilance, what is reported and contained within the data set does not represent the true epidemiology of adverse reactions to medicines. There is the very well-known problem of underreporting, but more than that, many countries ask health professionals to be selective in their reporting to cut down the 'noise'.

In the past, it has seemed reasonable for pharmacovigilance experts to reduce their workload and avoid having to see multitudes of reports of more trivial or well-known adverse reactions, but this has both health and methodological consequences. It is often forgotten that 'serious adverse and unexpected' reactions can be preceded by less serious phenomena. The best known is the xerophthalmia related to practolol being the harbinger of sclerosing peritonitis. Also, the persistent reporting of a well known, to experts, adverse reaction–product combination can be important since it may indicate that practitioners in the field are concerned about it for some practical reason. The reasons may be that they see the reaction more frequently than they think they should, that there is something unusual about the duration or severity, or that there are systematic errors associated with the use of the product which lead to problems (similar confusing labelling of different products, for example) (Biriell and Edwards, 1997).

Data mining should allow for much easier and useful handling of large amounts of information. Since the 'triaging' of information is done automatically, there is no longer any need to specify that only serious and unexpected reactions need be reported. Indeed, data mining in pharmacovigilance will function better for us if there is a large amount of 'ordinary' adverse reaction information to serve as the background. If we just record the serious and unexpected, only the more serious and unexpected will stand out, progressively.

Table 21.2. 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	<ul style="list-style-type: none"> • Always applicable • Large numbers of calculations can be made efficiently • Can be used for pattern recognition in higher dimensions 	Relatively non-transparent for people not familiar with Bayesian statistics
Reporting odds ratio	Point estimate	1	Cells b and c have to contain reports	<ul style="list-style-type: none"> • Easy applicable • Different adjustments possible in logistic regression analysis • In logistic regression analysis, interaction terms can be used for the analysis of drug interactions and syndromes • Easy interpretation 	<ul style="list-style-type: none"> • 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 a,b,c and d of the contingency table
Proportional reporting ratio	Point estimate	1	Cell c has to contain reports	Easy interpretation	Cannot be calculated for all drug-ADR combinations (see conditions of use)
Yules Q	Point estimate	0		Always applicable	Difficult to interpret
Poisson	Test		Only for rare events	Correction for different covariates can be easily established in Poisson regression	Only p-value provided
Chi square (Yates correction)	Test			Always applicable	
Yules' Q-1.96se	Test		Cells a,b,c and d have to contain reports		Standard deviation cannot always be calculated
ROR-1.96se	Test		Cells a,b,c and d have to contain reports	Correction for different covariates can easily be established	Standard deviation cannot always be calculated
IC-2std	Test		None	Always applicable	

This slow shift of emphasis would be deleterious for public health.

Data mining has its main future in the detection of complex patterns in the data. It is possible that, if doctors reported all the medicinal product safety

issues that concern them, we would be able to identify some issues of use and poor use of medicines which could be addressed (Edwards and Aronson, 2000).

One problem with data mining is the temptation to turn it into data dredging. There is a difference: data

mining uses objectively predetermined (if flexible) logic to examine relationships in data transparently with the aim of generating hypotheses for further evaluation. Data dredging is based upon a series of prejudiced queries which might imbue chance relationships with plausibility, and in which a strict logic or strategy is not followed.

Data mining is proving to be a useful tool. Its full potential has not yet been reached, and it may be that some of the current drug regulations and attitudes may need to be reconsidered as its use becomes more widespread. In spite of its potential as the primary search tool in pharmacovigilance, it is clear that its use must be accompanied by the wise interpretation of the information. Since no database is representative of what truly happens, other observations, monitoring and epidemiology must continue to be used in a complementary way. Only by the interactive interpretation of findings using different observational methodology are we likely to even approach the truth.

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Pharmacovigilance in the Netherlands

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HISTORY AND ORGANIZATION

HISTORY

In the Netherlands, consideration regarding the surveillance of adverse drug reactions developed at a relatively early stage. In the early 1950s, at a time when international literature had included only incidental reports of 'side effects', Leo Meyler laid the basis for paying more systematic attention to adverse drug reactions. In 1951, he published his book in Dutch: *Schadelijke nevenwerkingen van geneesmiddelen* (literally: *Harmful Effects of Prescription Drugs*). The second edition, fully revised with a number of supplements, appeared in 1954.

In his preface to the first edition, Meyler wrote the following (here in translation):

The prescribing of drugs will always entail a greater or lesser degree of risk, and in each case the physician must ask himself whether the nature of the condition about which he is being consulted justifies taking such a risk.

Meyler's work was prompted by his own experiences with tuberculostatic preparations. He also warned against the inappropriate use of drugs.

Meyler based much of his work on reports in various medical journals, at a time when the Internet or other conveniences of modern times were non-existent. The first English edition of Meyler's seminal work was published in 1952 as *The Side Effects of Drugs: An Encyclopaedia of Reactions and Interactions*. Its fourteenth edition, edited by Graham Dukes, appeared in 2000. Dukes has been the editor since the eighth edition, published in 1978, of what now has become the standard reference work in its field. Dukes' own scientific background was largely gained in the Netherlands.

ORGANIZATION OF PHARMACOVIGILANCE IN THE NETHERLANDS

Following the thalidomide affair of the late 1950s and early 1960s, the Netherlands decided to adopt a more systematic approach to the safety of prescription medicines. The Dutch Medicines Evaluation Board was founded in 1963. Based on the American model of the Food and Drug Administration, this board would assess new pharmaceutical preparations for both effectiveness and safety prior to marketing authorization. Also in 1963, the Royal Dutch Medical

Association (KNMG) joined the government in setting up a reporting system for adverse drug reactions. In 1965, the task of processing reports was taken over by the National Drug Monitoring Centre, which was part of the Public Health Supervisory Service and came to acquire an extremely good reputation (Meyboom, 1996). With a relatively small staff, Lareb produced a significant number of publications calling attention to the potential adverse effects of prescription drugs (de Koning, 1994). Each year, the National Drug Monitoring Centre received approximately 1000 reports from interested doctors.

In 1986, a number of pharmacists called for greater attention to be devoted to the potential adverse effects of prescription medicines. These pharmacists were convinced that greater awareness of the possibility of adverse effects would improve the quality of pharmacotherapy as a whole. Their initiative led to the creation of the Netherlands Pharmacovigilance Centre Lareb in 1991. A new aspect was that pharmacists too felt their responsibility in the identification of adverse effects and would consider it their task to call attention to such effects (van Grootenhuis *et al.*, 2002, 2003b).

In 1995, European legislation having been made more stringent, the Dutch government decided to restructure the system of pharmacovigilance in the Netherlands. Lareb was designated the national centre for all reports of suspected adverse drug reactions concerning registered drugs. Currently, the Health Inspectorate is responsible for monitoring the quality of pharmacovigilance.

The Medicines Evaluation Board plays a central coordinating role. It receives reports from Lareb, as well as those made directly by the pharmaceutical industry, and it advises the Medicines Evaluation Board. The Medicines Evaluation Board makes the final decision regarding marketing authorization for the Netherlands. Where deemed necessary it is empowered to require amendments to a drug's 'Summary of Product Characteristics' and in serious cases may revoke a drug's marketing authorization altogether. The Medicines Evaluation Board includes a pharmacovigilance department primarily concerned with adverse drug reactions and with maintaining international contacts in this field. Many decisions are taken at European level by the European Medicines Agency (EMEA).

SPONTANEOUS REPORTING IN THE NETHERLANDS: THE NETHERLANDS PHARMACOVIGILANCE CENTRE LAREB

INTRODUCTION

The organization of the reporting of adverse drug reactions in the Netherlands can be characterized as follows:

- a strong involvement of reporters (physicians, pharmacists and patients);
- a strong relationship with the scientific world, resulting in a scientific way of working and the development of new approaches for the processing and the analysis of the data;
- a principal choice for transparency: Lareb want to be accountable for the reports it received and the results of its analyses.

In all these Lareb's renewed website (www.lareb.nl) plays a vital role.

DIRECT RESPONSIBILITY OF DOCTORS AND PHARMACISTS

Lareb is an organization which was founded by doctors and pharmacists and which is still the responsibility of doctors and pharmacists. All large medical and pharmacists' associations and patient organizations are represented on its administrative board. Lareb maintains the national 'spontaneous' reporting system for the Netherlands. That this task falls to an independent centre rather than the government sets the Netherlands apart from most other countries. Although some (such as Germany, New Zealand and Great Britain with its Drug Safety Research Unit) have organizations investigating adverse drug reactions that are allied to universities or professional organizations, the involvement of professional practitioners is particularly prominent in the Netherlands. The government restricts itself to a supervisory and coordinating role, while it also provides funding for Lareb's activities.

The Dutch model has a significant number of advantages and works very well in practice. It is doctors and pharmacists who encounter adverse drug reactions in day-to-day practice. Given co-responsibility for the proper monitoring of drug safety, they will be more

inclined to contribute. This enhances the premise that doctors and pharmacists are themselves responsible for the safe and responsible use of prescription drugs. The barriers to reporting suspected adverse reactions will be significantly lowered if those reports are made to a peer group organization. After all, the occurrence of an adverse reaction may cause the doctor or pharmacist to ask himself (or herself) whether he should assume partial responsibility for this reaction. It is possible that some would be less eager to report an adverse drug reaction to a 'higher authority' such as the government. Reporting adverse drug reactions is voluntary in the Netherlands.

REPORTING BY PATIENTS

Since April 2003 patients are allowed to report experienced adverse drug reactions to Lareb. They may do so through an adjusted web form at Lareb's website. The first year (1 April 2003 till 1 April 2004) Lareb received a total of 276 reports from patients. The second year, 726 patient reports were registered (van Grootenhuis, Passier and van Puijenbroek, 2005).

In general, the reports are of a good quality. It is the patient who uses the drugs and experiences any adverse drug reactions personally. Therefore, it is obvious that patients are involved in the prevention of adverse drug reactions and are willing to report their experiences.

In the past, involvement of patients played an important role in drawing attention to the adverse reactions of DES, benzodiazepines and antidepressants. Another consideration is the fact that more and more drugs are available without a doctor's prescription. To obtain information on adverse reactions of 'over the counter' drugs, patients' reports may play an important role.

The important question: do patients' reports add to the reports of doctors and pharmacists is not unanimously answered in literature. The fact that this question cannot be answered without prior practical experience was an important argument for Lareb to decide to accept patients' reports (van Grootenhuis *et al.*, 2004a).

Both in patients' reports and reports from health professionals, the part of reports concerning females is higher than that concerning male patients. The mean age of the female patients is comparable in patients'

and health professionals' reports; the mean age of male patients is a bit lower in patients' reports. Lareb's decision to let patients report only via the website may have put a disadvantage to, for example, the elderly.

Analysing the severity of the adverse drug reactions, 29% of the patients' reports appears to be 'serious' versus only 21% of the adverse drug reaction reported directly by health professionals. A report is considered 'serious' when the adverse drug reaction led to hospitalization, death of the patient, a congenital anomaly or persisting disability, according to the CIOMS criteria.

Arranged into system organ classes, the five most reported adverse drug reactions received from patients as well as doctors and pharmacists show a remarkable similarity. In both groups disorders of the nervous system are most frequently reported, whereby dizziness and fatigue were often reported by patients.

When the reports are classified into drug classes, according to the ATC system, patients as well as health professionals report most often on psychotropic drugs. Patients appear to report mainly on adverse reactions of antidepressants. The second most frequently reported drugs by patients are sex hormones, a drug class not in the top ten of the health professionals' reports.

On the basis of these positive findings in the first year, Lareb decided to continue accepting patients' reports. Reporting patients receive a personal reaction with comments on the content of the reported adverse drug reaction. When analysing data from Lareb's database, patients' reports are seen as full reports. However, the source of a report is always mentioned, so this can be considered during analyses. The reliability of the reporting system as a whole has improved, since patients' reports are taken seriously.

REGIONAL ORGANIZATION

The Netherlands Pharmacovigilance Centre Lareb, in which several professions meet, has an extensive network of doctors and pharmacists. This is indeed facilitated by the Lareb's regional organization under which the Netherlands is divided into five regions. The Lareb's headquarters in 's-Hertogenbosch acts as one regional office, with the other four in university hospitals throughout the country. Each regional office

has a regional coordinator, responsible for maintaining contact with the doctors and pharmacists in that region.

Furthermore, the regional coordinator personally assesses some of the incoming reports in order to remain involved in the Lareb's 'core business' and will contribute to relevant publications wherever possible. A meeting of all Lareb's scientific staff is held monthly at the headquarters, providing an opportunity for consultation and further 'in-service' training. Lareb is a small organization, with a staff of only 19. Some work part-time. There are five supportive (administrative) staff members, the remainder are all doctors, pharmacists or medical biologists by profession. Details can be found on Lareb's website at www.lareb.nl.

MARKED INVOLVEMENT OF PHARMACISTS

In the context of pharmaceutical patient care, pharmacists in the Netherlands are highly involved in ensuring the safe and responsible use of medicines. Pharmacists played an important part in setting up the Lareb Centre. Today, pharmacists (see Figure 22.1) provide about 40% of the reports the Centre receives.

Most reports are made by community pharmacists, which perhaps can be expected given the

Lareb's background. Hospital pharmacists lay somewhat behind in this respect. Accordingly, Lareb has joined forces with the Netherlands Society of Hospital Pharmacists in attempting to encourage greater involvement on the part of its members. One of the objectives is to establish a protocol in hospitals whereby house pharmacists are not only expected to provide effective pharmacotherapy, but will also play a coordinating and facilitating role in terms of the collation and forwarding of adverse drug reaction reports. A survey held in early 2001 indicated that 97% of hospital pharmacists are eager to report any adverse reactions; they know what must be reported and in what way. In practice, the complaint that pharmacists provide little or no clinical information in a report has not appeared much of a problem. Often, the good cooperation between doctors and pharmacists ensures adequate information to be given, particularly if the relevant report is made in a hospital situation. If necessary, it is possible to contact the prescribing doctor to obtain further information. The fact that pharmacists are able to provide a complete picture of a patient's prescription history is a significant advantage.

THE GENERATION OF SIGNALS

The primary objective of any reporting system is to generate a 'signal': an early indicator or warning of a potential problem. This may be compared to the task of a fire-watcher, who looks for smoke and, if he thinks he spots it, must then determine whether there is indeed a fire and where that fire is located. Sometimes additional research is needed. In pharmacovigilance, it falls to the Medicines Evaluation Board to determine whether there are sufficient arguments to shout 'fire!', whereupon it will take the necessary measures.

Computer automation plays an important role in the internal report assessment process, with all incoming reports undergoing a set sequence of events. The information on the report forms themselves, together with that in any other relevant documentation, is stored in digital form next to archiving the paper copies of the reports. At the time of writing (early 2005) Lareb's database contained over 50,000 reports.

Reports received by Lareb are first assessed by one of its staff doctors or pharmacists. They examine the probability of a causal link, and will use the

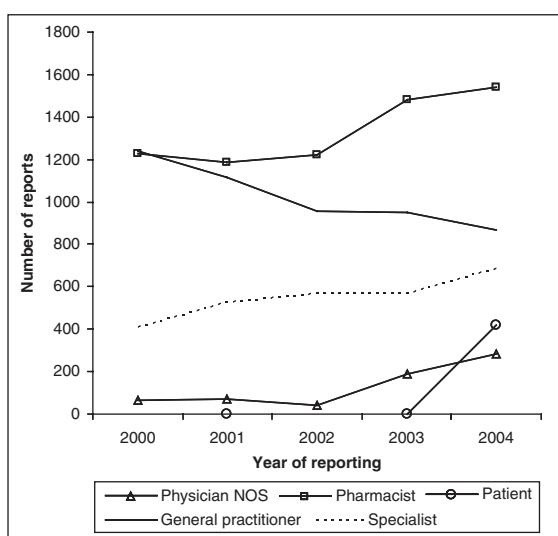


Figure 22.1. Sources of reports.

current literature, previous reports and the description of the drug's pharmacological mechanism to assist them. The results of their assessment are notified to the reporter as well as to the government. Next to the initial assessment, feedback-information is provided to the reporter. Furthermore, the assessors also focus on the possibility of the existence of possible signals in this stage. In addition, serious reports are also assessed by one of the senior staff members, who also pays special attention to the possibility of the existence of a signal.

The reports and their subsequent assessments are discussed in a weekly assessment meeting. The aim of this meeting is primarily the detection of possible signals. It is determined whether or not further action is necessary. Such further action may entail more detailed analysis of the relationship between the reported reaction and the suspect drug or follow-up information to be provided by the reporter. Research within Lareb has revealed a number of factors that can play a significant role in the decision to conduct further analysis. These include the seriousness of the reported reaction, whether or not the association has been reported disproportionately, the presence of a so-called WHO critical term and whether or not the reported ADR is labelled in the Summary of Product Characteristics (van Puijenbroek *et al.*, 2001b).

The weekly assessment meeting also makes use of information obtained through automated quantitative signal generation and external sources of information. A Reporting Odds Ratio is calculated for all reports, providing a statistical indication of the reporting frequency of each of the suspected reactions compared with other reports in Lareb's database (van Puijenbroek *et al.*, 2002; van Puijenbroek, Diemont and van Grootenhuis, 2003). The results of the Bayesian Confidence Propagation Neural Network analysis, submitted quarterly by the World Health Organization Monitoring Centre in Uppsala, are also automatically linked to each report. Based on the information on suspected and concomitant drug the existence of possible pharmacodynamic or pharmacokinetic drug-drug interactions is automatically highlighted by the computer system. Also the possible involvement of the cytochrome system in drug-drug interactions or the possibility of a genetic polymorphism of the cytochrome system in the pathogenesis of adverse drug reactions is automatically monitored

for. Finally prescription-data provided by the Dutch Health Care Insurance Board (CVZ) are linked to the reports, providing information about the number of prescriptions and the number of ADR-reports per 100,000 prescriptions. The latter information enables the assessors to identify possible unexpected increases in the number of reports which may be indicative of the existence of a signal. Besides providing a valuable aid to case-by-case analysis, quantitative information can also be used to distil useful information from a large collection of data. Such information will not be provided by a single case analysis. Lareb is particularly interested in the possibilities for identifying specific syndromes and in detecting *interactions* between drugs (van Puijenbroek *et al.*, 1999, 2000). Ongoing research is being conducted on whether certain risk factors for drug reactions can be identified using the information filed in the database.

After assessment the reports are filed in the Lareb-database. An anonymized copy of the reports fulfilling the definition of a 'serious' report according to the CIOMS criteria is forwarded to the Marketing Authorization Holder of the product in the Netherlands. In addition a copy of all reports is forwarded to the WHO collaborating centre in Sweden (the Uppsala Monitoring Centre). Since April 2005 serious reports are also forwarded to the European Medicines Evaluation Agency to be filed in the Eudravigilance database.

The increasing number of reports asks for the development of methods that enable a triage of reports with and without a high signal value. In this triage process, results from disproportionality analysis will be combined with more clinical and pharmacological-oriented information. It is to be expected that the development of this system will be completed by the end of 2005.

TRANSPARENCY

Lareb has made a principal choice for maximal transparency. In this decision, Lareb's website (www.lareb.nl) has a central place. At this website, all reports received by Lareb can be examined per system organ class and per drug class. By clicking on the individual case reports, more detailed information is available: demographic characteristics, information about (concomitant) medication, reported adverse drug reactions and the outcome of the reactions is provided. All

reports and publications written by Lareb on received adverse drug reactions can be viewed. Also, one can find standardized information on frequently occurring adverse drug reactions. Naturally, reporting through the website is possible; for *health care professionals* and *patients* different web forms are available. The main part of the website is translated in English, since it may be interesting for other countries to view the reports and other information owned by Lareb.

Doctors and Pharmacists

Because Lareb itself is an organization of doctors and pharmacists, it has easy access to practitioners in the field. Partly in view of the fact that doctors and pharmacists report suspected adverse drug reactions on a purely voluntary basis, it is important to inform and remind them of the importance of reporting. In addition to the feedback it provides, both direct and in the form of publications, Lareb offers targeted information to potential reporters in the form of mailings and presentations. The report form itself has a carefully designed layout and is distributed in various ways, such as regular inclusion with the *Drug Bulletin* and the annual *Farmacotherapeutisch Kompas*, the pharmacopoeia which forms a standard desk reference book for 90% of Dutch doctors. An increasing number of reports is received in an electronic format via the Lareb website.

It is important that the reporter can rely on respect to privacy and confidentiality. Lareb does not receive any information about the identity of the patient and no information about the reporter will be given to third parties. The Dutch law is strict on privacy.

An important means of communication with the reporting parties is the 'feedback report'. Receipt of each report is acknowledged. Furthermore, the assessment made by Lareb and the conclusions drawn with regard to the reported adverse drug reaction are notified to the reporter. Lareb strongly believes that the feedback provided stimulates additional reporting in the nearby future. Once a health professional submits an initial report to the Netherlands Pharmacovigilance Centre, the chance that he will report again within a year is relatively high (Figure 22.2). A study analysing the chance for reporters to submit another report in the nearby future shows that especially pharmacists tend

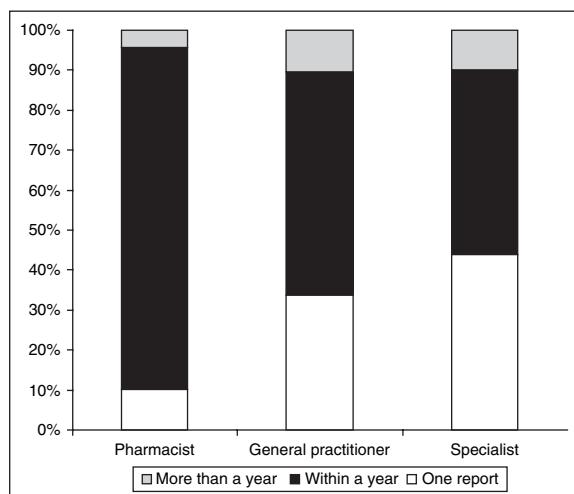


Figure 22.2. Proportion of reports that submits another report to the Netherlands Pharmacovigilance Centre within a year or within more than a year. Data are stratified by type of sender (pharmacist, general practitioner or specialist). Initial report was submitted between 1 January 2000 and 1 January 2003.

to report again within a year after the initial report has been received.

Besides wishing to encourage reporting, Lareb believes that it is important to raise the level of awareness among doctors and pharmacists with regard to adverse drug reactions. This will not only lead to a better standard of reporting, but will serve to significantly reduce the harmful effects of prescription medicines as well. Doctors will prescribe more critically and will be more inclined to consider adverse drug reactions as the cause of complaints at an earlier stage in their differential diagnosis. Consequently, they will be able to either discontinue use of the drug or to adapt the dosage to avoid both unnecessary costs and unnecessary impact in terms of patient health.

The Government

Because Lareb is an independent organization working on behalf of the government, good communication with that government is very important. Reports are forwarded to the Medicines Evaluation Board Agency weekly. Every six weeks, a meeting is held with Lareb, the Agency and the Health Inspectorate. Besides possible 'signals', these meetings also discuss

international developments. Lareb participate in the meetings of the Medicines Evaluation Board.

Given European developments, a more intensive cooperation is foreseen for the near future.

Marketing Authorization Holders

Needless to say, Lareb maintains close contact with the pharmaceutical industry, which also has a vested interest in effective pharmacovigilance. All serious ('15-day') reports are forwarded to the relevant Marketing Authorization Holder, as required by international legislation. These reports are anonymous, neither the patient nor the reporter can be traced. Similarly, all serious reports made directly by the pharmaceutical industry to the government are entered into Lareb's database. If such is wanted by the Marketing Authorization Holder also less serious reports will be sent to them. All articles concerning a specific preparation are submitted for comment to the relevant Marketing Authorization Holder prior to publication.

RESULTS

The 'output' of Lareb can be assessed by looking at both the quantity and quality of incoming reports, aspects that owe much to the efforts of the Centre. Other criteria include the number of publications for which the Centre has been responsible and the number of notifications of possible signals it has made.

Reports: Quantity

The number of incoming reports continues to increase each year. The development in the number of reports included in the database is shown in Table 22.1.

Reports: Quality

Although an adequate number of reports is necessary to ensure a reliable reporting system, Lareb attaches greater importance to the *quality* of those reports. All age groups are represented in the reports. Due to recent publications, the relative proportion of children (age under 16 years) and elderly (age over 65) has risen in the past years (Figure 22.3). The steady increase in these age groups is especially important

Table 22.1. Total reports and percentage of serious reports according to the CIOMS criteria.

Year of reporting	Health professional (% serious reports)	Marketing Authorization Holder*	Total (% serious reports)
2000	2947 (17.4)	400	3347 (27.3)
2001	2901 (16.9)	959	3860 (37.5)
2002	2795 (15.8)	1337	4132 (43.0)
2003	3193 (18.3)	1007	4200 (37.9)
2004	3801 (23.4)	1245	5046 (42.3)

* Since all reports received from Marketing Authorization Holders are 'serious' reports, the percentage is not mentioned.

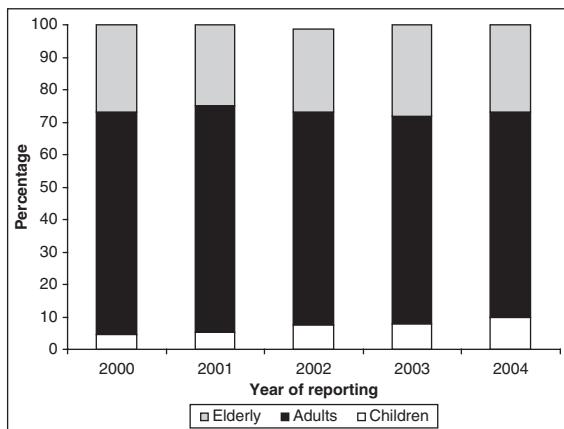


Figure 22.3. Proportion of reports related to children (<16 years of age), adults and elderly (>65 years of age) submitted to the Netherlands Pharmacovigilance Centre Lareb between 2000 and 2004.

since these patients appear to be the most vulnerable to adverse drug reactions.

The quality of reports has also risen each year. Quality is continuously assessed according to a number of criteria, one of which is the extent to which the report is documented. In an increasing number of cases, reports are accompanied by adequate clinical information, including the specialists' clinical notes to the patient's family practitioner. The fact that more complete information is now available may be partly attributed to the greater number of reports being made by hospital practitioners.

Having adopted a scientific and academic level as the basis for its working methods, Lareb is regarded

as a serious partner by other parties, particularly the professional organizations. The scientific quality of Lareb's work is monitored by a Scientific Advisory Board, comprising experts in various disciplines. Each year, Lareb publishes over 30 articles in international or national journals, among which is the Dutch *Drug Bulletin*. Publications by Lareb can be downloaded from the website www.lareb.nl. Lareb also takes care of more than 30 presentations to groups of doctors and/or pharmacists and is frequently represented at international scientific conferences. Five theses have been published in relation to Lareb in the past years (De Koning, 1994; Egberts, 1997; Meyboom, 1998; van Puijenbroek, 2001a; van Grootenhuis, 2003a) and Lareb has contributed to several other theses and publications.

FURTHER INITIATIVES IN PHARMACOVIGILANCE IN THE NETHERLANDS

Besides the spontaneous reporting system and the activities undertaken by, or under the auspices of, the government, there are various other pharmacovigilance initiatives in the Netherlands. Of these, the most notable are those undertaken by the marketing authorization holders and universities.

MARKETING AUTHORIZATION HOLDERS

Needless to say, pharmaceutical companies in the Netherlands must comply with international legislation relating to pharmacovigilance. Reports that meet the criteria of the Council for International Organizations of Medical Sciences (CIOMS) must be sent to the Medicines Evaluation Board within 15 days. Those reports will also be included in Lareb's database. In addition, Marketing Authorization Holders are required to submit periodic safety update reports, including all information known to them concerning the safety of the preparations for which they hold marketing authorization. The Netherlands does not have a tradition of reports being made directly to the pharmaceutical industry by doctors or pharmacists; the vast majority of reports concerning suspected adverse drug reactions pass through Lareb.

UNIVERSITIES

Three Dutch universities have departments of pharmacoepidemiology. The Department of Pharmacoepidemiology of the University of Utrecht developed the PHARMO system, which is operated independently. It is a record-linkage system that uses information provided by a number of pharmacists in combination with hospital clinical records. The department of Epidemiology and Biostatistics of Rotterdam's Erasmus University is responsible for the Integrated Primary Care Information (IPCI) system. It relies on digital information recorded by general practitioners. In cooperation with the Department of Social Pharmacy and Pharmacoepidemiology of the University of Groningen, Lareb has done a pilot in order to investigate the viability of an intensive monitoring system which uses the initial signals notified by pharmacists as well as responses to surveys conducted among general practitioners (van Puijenbroek, Diemont and van Grootenhuis, 2003). It is believed that in the future such a system can result in a first impression of possible adverse reactions of newly authorized preparations.

SUMMARY AND FUTURE DEVELOPMENTS

The Netherlands can now look back on 50 years of systematic attention for adverse drug reactions. This began with the first edition of the book now popularly known simply as 'Meyler's', and has developed to a stage at which the emphasis is on effective pharmacovigilance and at which 'Meyler's' is now the work of several different authors. On behalf of and in co-operation with the government, Lareb maintains the spontaneous reporting system for the Netherlands. A notable characteristic of the Dutch situation is that doctors and pharmacists are themselves responsible for this system, with pharmacists taking a significant role. Transparency and patient reporting are new developments in the reporting system in the Netherlands.

Besides continued consideration for both the quantity and quality of reports, the future is likely to see further development of automatic signal generation and even greater concern for good communication with potential reporters, in order to increase awareness

of adverse drug reactions. Developments at the European level are certain to have a significant influence in this regard.

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23

CIOMS Working Groups and their Contribution to Pharmacovigilance

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INTRODUCTION

The term ‘CIOMS’ is in daily use in international pharmacovigilance departments. For example, CIOMS forms are used for expedited case reporting, CIOMS line listings are used for presenting groups of cases, and CIOMS frequency definitions are used in product information labelling. The aim of this chapter is to describe who or what CIOMS is and to examine the contributions that the individual working groups have made to present-day pharmacovigilance practice.

The Council for International Organisations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organisation which was established in 1949 under the auspices of the World Health Organisation (WHO) and the United Nations Educational, Scientific and Cultural Organisation (UNESCO). It is responsible for the collection and dissemination of informed opinion on new developments in biology and medicine, and exploring their social, moral, administrative and legal implications. In 1977 it was recommended that CIOMS should facilitate discussions between national regulatory authorities and pharmaceutical companies on policy matters by providing an independent forum. It

also convenes groups of experts to make recommendations on specific topics when appropriate.

In 1986, CIOMS set up the first pharmacovigilance working group to discuss international reporting of adverse drug reactions (ADRs). By the end of 2005, six further working groups had completed recommendations and suggested guidelines for harmonisation of various aspects of pharmacovigilance (Table 23.1).

Table 23.1. The CIOMS initiatives.

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

CIOMS drug safety working groups are composed of pharmacovigilance specialists from regulatory agencies and pharmaceutical manufacturers principally from North America and Europe. Historically, members were selected for their personal expertise and contributions rather than to represent specific organisations. Observers from organisations such as the WHO and the International Federation of Pharmaceutical Manufacturers Association (IFPMA) are also invited. The size of the groups has usually been restricted to 20–30 members to ensure optimum discussion and completion of tasks. Considerable overlap of membership between consecutive working groups has enhanced productivity. Consultation with various specialists has also occurred when appropriate.

Each working group is co-chaired by a member from a regulatory agency and a pharmaceutical manufacturer. Win Castle deserves particular mention for co-chairing all the working groups until her retirement in 2000. Her enthusiasm, determination and hard work often provided the impetus necessary for the successful completion of each initiative.

As the CIOMS working groups have no legal jurisdiction, reliance is placed on other bodies to incorporate the CIOMS recommendations and guidelines into a regulatory or legislative framework. For example, the International Conference on Harmonisation (ICH) has progressed the CIOMS initiatives on expedited and electronic reporting as well as having used the CIOMS II recommendations as the basis for the requirements for periodic safety update reports (Table 23.2). The ICH process is based on five steps:

1. Step 1 – Technical discussion by the Expert Working Group who produce a preliminary draft document;
2. Step 2 – The consensus text is released for a 6-month period of consultation;
3. Step 3 – Formal consultation outside ICH;
4. Step 4 – Sign off of finalised text;
5. Step 5 – Implementation.

Therefore, Step 4 is the stage at which the document is finalised and released with the intention that the countries represented by the ICH (Europe, the United States and Japan) will incorporate the requirements into their local legislation and regulations.

Table 23.2. Uptake of CIOMS initiatives by ICH.

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

The acceptance, adaptation and utilisation of CIOMS principles by other bodies will be discussed later in this chapter.

CIOMS I – EXPEDITED REPORTING OF INDIVIDUAL ADRS

RATIONALE

It is well established that continuous ADR surveillance is critical to assuring the safety of approved drugs in clinical practice. Prior to 1984, regulatory authorities restricted their requirements for the receipt of individual ADRs to domestic reports only. However, between 1984 and 1987 the United Kingdom, France, the United States, Italy and Germany introduced regulatory requirements for the submission of foreign reports. That is, manufacturers were required to report ADRs occurring in one country to the regulatory authorities in other countries where the drug was also marketed. As each regulatory authority had different requirements regarding time frames, formats and definitions, and were concerned about different types of ADRs, manufacturers were confronted with many problems.

The purpose of the CIOMS I working group was, therefore, to develop an internationally acceptable

reporting method so that manufacturers could report post-marketing ADRs rapidly, efficiently and effectively to regulators.

PROCESS

On the understanding that the CIOMS members would modify their own international reporting procedures accordingly, the working group set out to define what constituted a reportable individual reaction, the elements of a report and the procedure and format for submitting individual reports. As most reporting depends on legal requirements, it became clear that the regulators needed to reach consensus. When this had been achieved a pilot test was undertaken to demonstrate the feasibility and utility of standardised reporting. The effort was geared towards the international exchange of post-approval reports of suspected, unexpected (unlabelled) serious ADRs. The manufacturers in the working group reported local cases according to the domestic requirements in that country and then entered the cases on to single common forms and submitted them to the other regulatory authorities represented on the CIOMS working group. Reports received from a country outside the participating six were entered on a single report and submitted to all six regulators.

The advantages of standardisation to the manufacturers were that it avoided a multitude of different requirements from different regulators, eased communication of reports between international corporate affiliates, and lessened regulatory ambiguities. From the regulatory perspective, standardisation could improve standards and reporting compliance by manufacturers and facilitate the exchange of information between regulators.

RECOMMENDATIONS

The CIOMS recommendations for the case criteria for expedited reporting of a foreign ADR were defined as follows:

- serious;
- medically substantiated;
- unlabelled (unexpected);
- suspected to be product-related;
- occurring with a marketed product; and
- in an identifiable patient.

Such reports were to be submitted in English on the prescribed CIOMS form within 15 working days of receipt. The subsequent amendments to these recommendations are mentioned later in this chapter.

CIOMS reports were, and still are, restricted to ADRs and not 'events'. This implies that a physician or other professional healthcare worker has judged it a reasonable possibility that the observed clinical occurrence was caused by the drug. In addition, it was emphasised that manufacturers should not select cases for reporting based on their own causality assessment. All spontaneous reports of serious unlabelled reactions made by a medical professional should be considered as CIOMS reports. Submission of such a report does not necessarily constitute acceptance of causality by the manufacturer.

As product labelling differs from country to country it was suggested that manufacturers should review all serious reports and then decide on a country-by-country basis, either centrally or at affiliate level, whether the reported ADR is labelled or not. It was also agreed that there should be a minimum of four pieces of information before a report is considered to have reached the standard threshold for reporting. These are an identifiable report source; a patient (even if not precisely identified by name and date of birth); a suspect drug; and a suspect reaction.

CIOMS reports should be submitted to regulatory authorities as soon as they are received and in no case later than 15 working days after receipt. The 15-day period begins as soon as a company, or any employee in any part or affiliate of a company, receives the report.

The CIOMS I report was published in 1990 (CIOMS, 1990).

INCORPORATION IN REGULATION

Many of the CIOMS I criteria for expedited reporting were incorporated into ICH E2A, *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, which reached final agreement in October 1994 (ICH, 1994). This document expanded on the CIOMS I definitions and terminology. In particular, it introduced the concept of the 'medical' seriousness category that recognised that events may not be immediately life-threatening, or result in death or hospitalisation, but may jeopardise the patient

or require intervention to prevent such outcomes. Although ICH E2A focused on pre-approval clinical trials, its definitions and other criteria have been applied by regulators to expedited reporting of both pre- and post-marketed products. The reporting time frame was reduced from 15 working days to 15 calendar days, with 7 days for the initial report on fatal or life-threatening suspected adverse reaction cases from clinical trials. More recently, ICH E2D, *Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting*, which reached step 4 agreement in November 2003 (ICH, 2003a), formally applied the ICH E2A concepts to the post-approval phase of the product life cycle as well as incorporating many of the good case management practices proposed by CIOMS Working Group V.

CIOMS IA – HARMONISATION OF DATA ELEMENTS AND FIELDS FOR ELECTRONIC REPORTING OF INDIVIDUAL ADRS

CIOMS IA was completed in 1995 but the final report was never formally published by CIOMS. The initiative was run in parallel with the CIOMS III working group but is presented here, out of chronological order, because it was an extension of the CIOMS I initiative.

The vision of CIOMS IA was for the more efficient and rational exchange of safety information by electronic rather than paper submission of expedited reports. Ideally, submission would be to a single shared database accessed by all regulatory authorities and with appropriately restricted access for manufacturers. This would enable the entry of individual cases only once by either a manufacturer or regulatory authority, facilitate the entry and speed of availability of follow-up information, ensure that everyone had access to the same data at the same time and reduce the administrative processes associated with hard-copy reports. Increasing the efficiency of the process and standardisation of the data elements and fields would theoretically increase the time available for signal detection and evaluation activities.

CIOMS IA produced detailed definitions of the data structure required for both administrative and case details for electronic reporting of individual expedited

ADRs. This even included the specifications for the standard units for laboratory data. Many of these definitions and recommendations were incorporated into a similar project initiated under ICH around the same time as CIOMS IA was active; the former reached final agreement in July 1997 as ICH E2B (ICH, 1977). The document was subsequently revised in November 2000 to clarify some of the issues raised during pilot feasibility studies and became ICH E2B (M) (ICH, 2000).

Although the single database envisioned by CIOMS IA does not exist, electronic expedited reporting now occurs in Europe, Japan and the United States.

CIOMS 11 – PERIODIC SAFETY UPDATES

RATIONALE

This initiative was started in November 1989 at a time when several countries had requirements for periodic safety updates; however, individual local regulatory authorities were requesting that data (both foreign and domestic) be presented according to different inclusion criteria, formats and time intervals. Due dates were often determined by the national licensing approval date and therefore varied between individual formulations of the same drug substance. Preparation of these summarised safety updates had become a significant administrative burden for manufacturers. Figure 23.1 shows the report preparation schedule for a fictitious drug with different due dates and periods for review.

The purpose of the CIOMS II working group was to explore the possibility of developing a harmonised

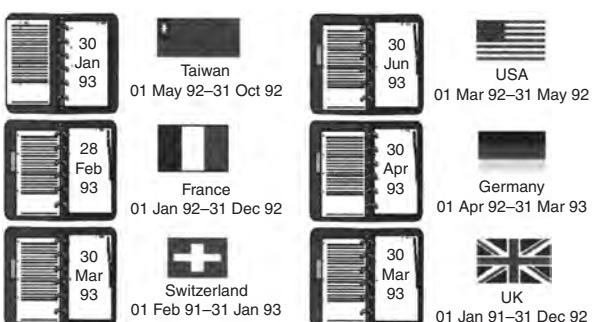


Figure 23.1. Report schedule for Qweasytrol.

approach to preparing periodic safety updates that would meet most existing needs and forestall any diversity in future requirements. It was also hoped that if the guidelines on this approach were adequate and reasonable other regulatory authorities would adopt them in the future. Standardisation would also enable pharmacovigilance staff to focus on reviewing the data rather than generating a battery of different reports.

PROCESS

The working group undertook a survey of the currently existing requirements for periodic safety updates, noting the diversity and identifying the questions which needed to be addressed in defining the content and format, and what might be considered to be the essential elements. After considerable debate and compromise on several controversial issues relating to scope and content, a series of proposals was then drafted in preparation for the pilot phase. Each manufacturer representative undertook to draft a single prototype summary-report on one of their own drugs using the proposed guidelines. Each report was then sent personally to each regulator in the working group and a 'sanitised' version was sent to the other manufacturer representatives. All members of the working group took part in the critical evaluation of each pilot report to examine the feasibility (data availability), resources required in compilation and utility to the regulators of the information provided. On the basis of the experiences gained in the pilot study, the guidelines were refined and used to produce a model report on a fictitious drug (Qweasytrol) for inclusion in the final report.

RECOMMENDATIONS

The underlying principles of CIOMS II periodic safety updates were that they should be prepared to standard criteria that are practical and achievable, while containing sufficient information to reassure regulators that the manufacturer regularly reviewed its safety data. The safety updates should be as brief as possible; it was recommended that the narrative content should not exceed about 10 pages. Data for all formulations of the same drug (including combination products) should be included in one report and the same report

should be submitted at the same time to all regulatory authorities with a requirement for safety updates.

Scope

The proposal was that the guidelines should be applied to safety summaries produced for all new chemical entities licensed for the first time in 1992. Subsequent updates would be based on 6-month interval data with cumulative data only included where it gave a perspective on safety issues. Each subject drug would have an international birth date (IBD), the first approval date for the first formulation of the drug anywhere in the world, that would determine the date at which 6-monthly reports commenced. A data-lock point (DLP) 6 months after the IBD would be used to 'freeze' the database. Normally, the manufacturer should make the report available within 45 calendar days of the DLP.

It should be emphasised that periodic safety summaries were not intended for the first communication of urgent safety information. This should be reported separately in the usual expedited manner.

Content

The working group proposed that the periodic safety update was presented in nine sections as follows:

1. Introduction
2. Core data sheet – the reference document for determining 'expectedness'
3. The drug's licensed status
4. Update on regulatory or manufacturer actions taken for safety reasons
5. Patient exposure
6. Individual case histories (CIOMS line listing)
7. Studies
 - newly analysed studies containing important safety information
 - targeted new safety studies
 - published safety studies
8. Overall safety evaluation
9. Important information received after the DLP.

It was proposed that the individual case histories received during the 6-month period of review, and

meeting specified criteria, should be presented in body system order of the most serious presenting sign or symptom in a CIOMS line-listing format. The criteria for case inclusion were as follows:

- unlabelled, serious attributable cases from studies (published or unpublished);
- all serious and non-serious unlabelled spontaneous reports (including relevant medically unconfirmed consumer reports);
- serious published case histories;
- serious cases from other sources (e.g. from regulatory authorities).

The CIOMS line listing should consist of:

- Company reference number
- Country of origin of report
- Source of report (e.g. physician, literature)
- Age of patient
- Sex of patient
- Dose of drug
- Duration of treatment prior to event (time to onset)
- Description of reaction (as reported)
- Outcome.

A comment column was also suggested for use by the manufacturer to highlight important case information such as concurrent medication or underlying disease. It could also be used for the causality assessments (imputability) required by the French regulatory authority.

The overall safety evaluation should be a concise critical analysis and opinion explicitly including:

- increased frequency of known toxicity;
- drug interactions;
- overdose and its treatment;
- drug abuse;
- positive and negative experiences during pregnancy and lactation;
- effects of long-term treatment;
- any specific safety issues relating to the treatment of special patient groups (e.g. elderly, children).

Finally, the evaluation should indicate whether the interim safety data remained in line with the cumulative experience to date or whether any modifications were necessary to the company's core safety information.

The CIOMS II report was published in 1992 (CIOMS, 1992).

INCORPORATION IN REGULATIONS

The CIOMS II proposals for periodic safety updates were rapidly incorporated into the European Draft *Notice to Applicants* but with a few significant modifications, including the concept of a European rather than an international birth date. This effectively implied that periodic safety reports currently scheduled to the IBD had to be rescheduled to the first European approval date – a step away from the vision of harmonisation. A European schedule for the frequency of submission was also included which stated that 6-monthly reports were required for the first 2 years after approval, followed by annual reports for 3 years and then 5-yearly thereafter. As individual countries began to implement their own periodic safety update requirements they requested this schedule based on their own local approvals. The scope of CIOMS II was also expanded to include all marketed products, not just those approved in or after 1992.

Before the European requirements could be finalised, ICH E2C adopted many of the CIOMS II principles in the *Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* document that reached Step 4 in November 1996 (ICH, 1996). This included further modifications to the CIOMS II scope and format, including some reordering of the sections and introduction of new materials such as the summary tabulations to complement the line listing in section 6. Figure 23.2 shows the ICH E2C table of contents and highlights the changes from CIOMS II. There was also an additional requirement to explain to local regulators any differences between the local product information and the company core safety information.

Fortunately, ICH E2C reverted to the IBD for scheduling reports and the time for submission after the DLP was increased to 60 days. However, while this may be achievable for 6-monthly reports, there is concern because the ICH E2C format is now being requested for periodic safety updates covering longer periods (including the 5-year reports for local product renewals in Europe).

While ICH E2C has been implemented in Japan and included in Volume IX of the *Rules Governing*

1. Introduction
- 2.* World-wide Market Authorisation Status
- 3.* Update on RA or MAH actions for safety reasons
4. Changes to reference safety information(new)
5. Exposure data
- 6.* Individual case histories (summary tabulations)
- 7.* Studies
- 8.* Other information
- 9.* Overall safety evaluation
10. Conclusion

Appendices—including CCSI
* ICH E2C amendments to CIOMS II

Figure 23.2. ICH E2C – Table of contents.

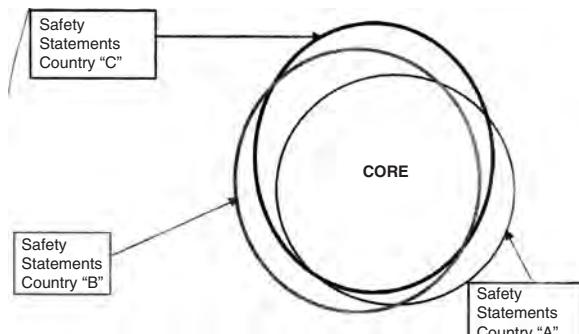


Figure 23.3. CIOMS III – The vision.

Medicinal Products in the European Union – Notice to Marketing Authorisation Holders: Pharmacovigilance Guidelines, by 2005 the US Food and Drug Administration (FDA) had only issued draft periodic reporting requirements based on ICH E2C for consultation.

In summary, the principles and guidelines proposed by CIOMS II achieved a harmonised approach to preparing periodic safety updates that met most existing requirements in 1992. However, they were unable to forestall the diversity of future requirements following their incorporation into regulatory requirements around the world. In 2003 an addendum to ICH E2C was produced to provide practical guidance for the preparation of periodic safety update reports. This included many of the proposals on good summary reporting practices recommended by the CIOMS V Working Group but the diversity of requirements continues unabated.

CIOMS III – CORE CLINICAL SAFETY INFORMATION

RATIONALE

CIOMS II introduced the concept of the core data sheet. It is a document prepared by the pharmaceutical manufacturer, containing the minimum essential safety information, such as ADRs, which the manufacturer stipulates should be listed in all countries where the drug is marketed (see Figure 23.3). It is also the reference document by which ‘labelled’ and ‘unlabelled’ (or listedness and unlistedness for ICH E2C) are determined. Thus, it should focus

on the important information required for rational clinical decision-making and harmonise safety statements worldwide for public health and regulatory purposes.

The CIOMS III working group set out to propose principles and guidelines for consistent decision-rules on the content of the Core Safety Information (CSI), standard terms and definitions, and a standard format. One of the major concerns was to minimise confusion among prescribers and other healthcare professionals due to inconsistencies between the safety information presented in different countries and by different manufacturers.

It was therefore hoped that regulatory authorities would harmonise their basic requirements for safety information in their local data sheets. However, the working group acknowledged the possible need for cultural differences due to medical and legal differences.

The first edition of the CIOMS III report published in 1995 (CIOMS, 1995) focused on CSI for marketed products, including the initial CSI that is prepared in conjunction with the first market authorisation submission, review and approval. During CIOMS V discussions it was proposed that the same basic philosophy and practices be applied to the safety information provided to clinical investigators during a development programme. The concept of development core safety information (DCSI) as a discrete, focused section of the Investigator’s Brochures, which would have the same format as, and would evolve into, the CSI at initial marketing of the product, was therefore agreed. A second edition of the CIOMS III report was issued in 1999 (CIOMS,

1999) including the new proposals for Investigator's Brochures.

PROCESS

The task of the working group was to develop proposals for standard principles and guidelines addressing the what, when, how and where of CSI. The summary of product characteristics (SPC), the official document of the European Union, was used as a model to try to answer the following general questions:

- What evidence is needed, and how should it be used, to influence a decision on whether an adverse experience should be included, excluded or removed from the CSI?
- At what point in the accumulation and interpretation of information is the threshold crossed for inclusion or change in the CSI?
- What 'good safety-labelling practices' can be specified concerning the clinical relevance of information, how it is expressed and the appropriateness of 'class-labelling'?
- What should the sections of the CSI be called, how should they be defined and where should specific information be located?

At the beginning of the process the group hoped to develop specific threshold criteria, or an algorithm, for determining when information should be included in the CSI. However, this was not possible and it became necessary to rely on collective judgement to reach consensus. A series of case scenarios were created from real-life examples for which the decision to amend a data sheet was equivocal. Each member of the group was asked individually to make decisions on the available data. In addition, each person was asked to list the factors taken into consideration when reaching their conclusions. A total of 39 factors were identified and each member of the working group was asked to rank the factors in order of importance. As expected, there was a considerable divergence of opinion but overall the mostly highly ranked criterion for a positive decision was the presence of positive rechallenge information. The reader is referred to the original report for the remaining factors and their respective rankings.

RECOMMENDATIONS

The working group formulated a total of 65 proposals relating to general principles of good safety information and the what, when, how, where and who (responsibilities) for CSIs. A selection of the most useful principles is given below.

What?

- The CSI should be determined by the needs of healthcare professionals in the context of a regulatory and legal environment.
- Include what is practical and important to enable the prescriber to balance risks against benefit and to act accordingly.
- Avoid including events, especially minor events, that have no well-established relationship to therapy.
- There is a legal duty to warn but this must be balanced against the need to include only substantiated conclusions in the CSI.
- The CSI should include important information which physicians are not generally expected to know. (The converse is also true.)

When?

- As soon as relevant safety information becomes sufficiently well established it should be included in the CSI.

It was not possible to define this more precisely but the working group introduced the concept of 'threshold'. This is dependent on the quality of information available and the body and strength of the evidence according to the 39 criteria (plus two additional ones subsequently identified) in the ranking exercise described above. Situations in which the threshold should be lowered were identified. In general, information should be added sooner whenever it is likely to help the physician make a differential diagnosis related to an adverse event, spare extra tests, lead to the use of a specific targeted test or facilitate early recognition of an event. Similarly, the threshold should also be lowered if the ADR is medically serious or irreversible, if good alternative drugs are available, a relatively trivial condition is being treated, or the drug is being used for prophylaxis.

How?

- Keep ADRs identified in the initial CSI (pre-marketing experience) separate from those identified subsequently.
- ADRs should be listed by frequency in body system order.
- Whenever possible, an estimate of frequency should be provided, expressed in a standard category of frequency.

While the working group recognised that precise frequency rates can only be obtained from studies and are limited to the more common reactions, it was agreed that estimates of frequency in a standard format should be provided whenever possible. Although it is difficult to estimate incidence on the basis of spontaneous reports due to the uncertainties in estimating denominator and the degree of under-reporting, the group recommended the standard frequencies shown in Table 23.3.

Finally, the working group defined the safety sections of the CSI, providing guidance on the information which should be included in each section and outlined the responsibilities of the company for remaining diligent and proactive, including undertaking the scientific investigation of signals. The shared responsibility of healthcare providers, patients, editors of medical journals and regulators is also addressed.

INCORPORATION IN REGULATION

Since the standards proposed by the CIOMS III working group would require continuous evaluation, updating and refinement, it was suggested that they

Table 23.3. CIOMS III standard frequencies.

Incidence	Standard frequencies
Very common*	>1/10 (10%)
Common (frequent)	>1/100 and <1/10 (1–10%)
Uncommon (infrequent)	>1/1000 and <1/100 (0–11%)
Rare	>1/10 000 and <1/1000 (0.01–0.1%)
Very rare*	<1/10 000 (<0.01%)

* Optional categories

be retained as guidelines and not adopted as regulations. They have been used as the basis of the European Labelling Guidelines and many regulatory authorities have adopted the standard categories of frequency. However, during the most recent redrafting of the European Labelling Guidelines there was discussion regarding their appropriateness when spontaneous reports are the only source of data for estimating frequency.

CIOMS IV – BENEFIT–RISK EVALUATION

RATIONALE

CIOMS IV can be regarded as a logical progression from both CIOMS II and III. The aim of the working group was to develop guidance for regulators and manufacturers on assessing the balance between benefits and risks of marketed products with a newly established or suspected major safety problem. It would also provide guidance for deciding what options for action should be considered and on the decision-making process should such action be required. Pragmatic approaches to reassessing the benefit–risk relationship, producing a standard report and good decision-making practices are highly desirable, but no standard existed. Although most signals will not warrant formal benefit–risk evaluation, it was recognised that any concepts proposed by the working group would be useful in any periodic or special evaluation of relative benefits and risks.

PROCESS

In formulating its proposals the working group developed, reviewed and made use of actual case histories taken from the experience of companies and regulators in several countries. These examples were used to illustrate basic principles and methodologies as well as to suggest ways of displaying data in connection with benefit estimation, risk estimation and benefit–risk evaluation.

Guidance on the decision-making process and the use of outside experts was supported by information from a survey of regulators and companies in which details of recent significant safety issues and the decision-making process were requested.

RECOMMENDATIONS

The proposals are very different from the usual case-specific ADR evaluations undertaken in pharmacovigilance departments. Conventionally, these reports focus on the ADR of concern and provide relevant details of pre-clinical, clinical trial and post-marketing experience. The benefit–risk assessment proposed by CIOMS IV takes into account not only the new signal but also the overall safety profile of the product relative to that of an appropriate comparator. It examines not only the benefits and risks to the individual being treated but also the net benefits across individuals being treated or, as with the case of vaccines, the net benefit to society.

The outline for the recommended standard format and content of a benefit–risk evaluation report is as follows.

Introduction

- Brief description of the drug and where marketed.
- Indications for use, by country if there are differences.
- Alternative therapies, including surgery.
- Very brief description of the major safety problem.

Benefit Evaluation

- Epidemiology and natural history of the target disease(s).
- Purpose of treatment (e.g. cure, prophylaxis).
- Summary of efficacy and general toleration data compared with other treatments or no treatment.

Note that benefit does not equate only with clinical trial efficacy data. It also includes additional measures such as quality of life, compliance with therapy, outcomes and experience in the ‘real world’.

Risk Evaluation

- Introduction.
- Weight of evidence for the suspected risk.
- Detailed presentations and analyses of data on the new suspected risk.
- Probable and possible explanations.
- Preventability, predictability and reversibility of the new risk.

- The issue as it relates to alternative therapies and no therapy.
- Review of the complete safety profile of the drug, using diagrammatic representations when possible ('risk profiles'); when appropriate focus on, for example, the three most common and the three most medically serious ADRs.
- Provide similar profiles for alternative drugs.
- When possible, estimate the excess incidence of any adverse reactions known to be common to the alternatives.
- When there are significant adverse reactions that are not common to the drugs compared, highlight important differences between the drugs.

Benefit–Risk Evaluation

- Summarise the benefits as related to the seriousness of the target disease and the purpose and effectiveness of treatment.
- Summarise the dominant risks (seriousness/severity, duration, incidence).
- Summarise the benefit–risk relationship, quantitatively and diagrammatically if possible, taking into account the alternative therapies or no treatment.
- Provide a summary assessment and conclusion.

Options Analysis

- List all appropriate options for action.
- Describe the pros and cons and likely consequences (impact analysis) of each option under consideration, taking alternative therapies into account.
- If relevant, outline plans or suggestions for a study that could provide timely and important additional information.
- If feasible, indicate the quality and quantity of any future evidence which would signal the need for a re-evaluation of the benefit–risk relationship.
- Suggest how the consequences of the recommended action should be monitored and assessed.

It will be noted that the emphasis of the benefit–risk evaluation is on quantification wherever possible and an example of a report prepared to CIOMS IV specifications would have been useful. There are examples of previous benefit–risk evaluations that illustrate

the various methodologies that have been used but they are not necessarily directly applicable to a manufacturer faced with a request for an urgent assessment. In particular, it would have been valuable to include some guidance on how to create summary metrics that combine benefit and risk data to allow straightforward quantitative comparisons of different treatment options. An example is given in terms of potential lives saved as the result of treatment versus potential lives lost as a result of adverse reactions. The CIOMS IV report calls for additional research and development of appropriate methodologies and metrics to introduce more science and less art to this important area.

While the logic behind the inclusion of most of these points is self-evident, it is recognised that obtaining the necessary information, especially on the risks and benefits of other manufacturers' new products as comparators, is either very difficult, or impossible, in practice. For older, but not new, products this information may be found in the literature (see dipyrone example).

The CIOMS IV report was published in 1998 (CIOMS, 1998).

INCORPORATION IN REGULATION

While regulatory authorities occasionally request CIOMS IV style benefit-risk assessments for specific issues with marketed products, their current focus is on risk management. ICH E2E, *Pharmacovigilance Planning*, reached step 4 in November 2004 and provides guidance on the Safety Specification and Pharmacovigilance Plan that are submitted at the time of a licence application. These documents summarise the important identified risks of a drug, important potential risks, important missing information including the potentially at-risk populations, situations where the product is likely to be used but have not been studied pre-approval and the manufacturer's plan for discharging these risks. In Europe, Safety Specifications and Pharmacovigilance Plans were required for all new drug applications from November 2005. It is of interest that, although represented on ICH E2E, the FDA has introduced its own requirements for risk management planning that are not in line with those proposed by ICH.

CIOMS V – GOOD CASE MANAGEMENT AND REPORTING PRACTICES

RATIONALE

This was probably the most ambitious of the CIOMS initiatives to date. It addressed many of the new challenges faced in pharmacovigilance, such as the Internet as a source of individual case reports, together with many of the older unresolved issues from previous CIOMS initiatives (e.g. reporting and labelling of deaths). The completed report was intended as a handbook for pharmacovigilance departments and still offers many pragmatic solutions to a number of issues. The title *Current Challenges in Pharmacovigilance: Pragmatic Approaches* (CIOMS, 2001) was, therefore, an apt one.

OVERVIEW

The report is divided into the following five main subject areas:

1. Sources of individual case reports.
2. Good case management practices.
3. Good summary reporting practices – periodic safety update reports (PSURs) reconsidered.
4. Population exposure data.
5. Worldwide clinical safety reporting regulations.

It is not the intention to review the details of all the topics in this chapter but some of the recommendations and guidelines are of particular interest and will be highlighted for the reader.

Sources of Individual Case Reports

Consumer Reports

The value of consumer reports has always been a point of issue between Europe and North America. The CIOMS V consensus was that it is the quality of the report and not the quality of the reporter that is important. It was agreed that medical confirmation should be sought for consumer reports and that it is important to distinguish between verification (i.e. that the events as related by the consumer occurred) and confirmation of a suspected ADR (i.e. attribution). It may even be appropriate to submit a consumer report

to the regulatory authorities as an expedited report when medical confirmation is not obtainable if the case might influence the benefit–risk relationship or has implications for labelling changes.

Literature

Companies should routinely search at least two internationally recognised databases for case reports not less frequently than monthly. The clock-start date for reporting is the date the reference was identified. If the paper is not in English it may be appropriate to translate the abstract or relevant sections only. Automated searches should be supplemented to include publications relevant to the drug or circumstances. That is, it is not adequate to search only for references specific to a particular drug (e.g. salbutamol) when class review may be appropriate (e.g. beta₂ agonists). It was not considered necessary to monitor the lay media but if information is made available on a case, then attempts should be made to ascertain details.

Internet

It was not considered necessary to surf the Internet beyond the company's own site(s) but it is advisable to screen the latter daily for ADR reports. There was also a suggestion that it may be useful to visit known sites from which patients may obtain information on specific drugs and diseases. There was some concern over the validity of case reports posted here, since the reporter may not always be identifiable. It was agreed that if the site is secure the company could encourage ADR reporting via its 'home page'. This could be used to advantage in gathering good quality data by ensuring that some fields were made mandatory for completion.

Solicited Reports

Patient support programmes are frequently used by pharmaceutical companies to obtain follow-up data on product use (e.g. smoking cessation help lines). During the course of conversation the patient may mention the occurrence of an adverse event. It was agreed that the source of this report is neither truly spontaneous nor from a clinical trial. An additional case source, the solicited report, was proposed. It was suggested that these cases be collected and processed

separately and that a company causality assessment is required before expedited reporting of serious solicited reports.

Disease-Specific Registries and Other Databases

As there are a large number of external databases it is unreasonable to expect companies to review them for *ad hoc* signals. However, they should be proactively monitored when there are known specific problems (i.e. when there is a hypothesis). As databases are used to generate signals there is no need to report individual cases on an expedited basis. However, if an increased frequency of a serious ADR is determined in an epidemiology study it may be appropriate to notify the regulatory authority. Since individual case report forms are not always appropriate, CIOMS V introduced the concept of a '15-day letter of prompt notification'.

Good Case Management Practices

Clinical Evaluation

This is important for determining any further action required to characterise a case, in particular to establish the accuracy of the diagnosis and appropriate coding. It also enables the case to be suitably prioritised for follow-up and/or expedited reporting. It was recognised that many companies are coding every event of which they become aware, even if not causally related to the drug. The concept of an 'incidental event' was introduced. This is an event which, although it occurs in reasonable temporal association with the use of a drug, is not the intended subject of a spontaneous report and there is no implicit or explicit expression of possible drug causality by the reporter or the company. Cases in which only the incidental events are serious should not be submitted as expedited reports.

Seriousness

CIOMS V recommended the universal adoption of the ICH E2A definition of seriousness, including medically important events. For consistency it was suggested that all companies maintain a list of terms which should always be considered serious. However, it was recognised that this could never be fully

comprehensive and that it does not replace medical judgement.

Cases with a fatal outcome are only serious when the ADR is a direct or indirect cause of death.

Expectedness

Events are only expected when they are included in the ADR section of the reference safety information (RSI). If they differ in nature, severity, specificity or outcome, then they are unexpected. Class labelling and statements such as ‘relationship not established’ or ‘observed with similar frequency to placebo’ do not imply expectedness.

Principles of Reporting Deaths

This was perhaps the most contentious of all the discussions. Some regulators considered that they needed to know about all reports of deaths, while manufacturers generally maintained that they would be swamped with reports, especially for drugs used in serious medical conditions. It was upheld that cases with a fatal outcome were only serious when the drug caused or contributed to death but there was general disagreement about whether this could always be determined from individual case details, or implied if the case was a spontaneous report. Further discussion centred on whether death was considered expected or unexpected if it was not specifically mentioned in the label (e.g. ‘anaphylaxis’ versus ‘anaphylaxis, sometimes fatal’). It was agreed that physicians should be aware of medical conditions frequently associated with a fatal outcome and therefore the working group decided actively to discourage indiscriminate labelling of deaths. The final outcome of this discussion was to recommend that fatal reports should be expedited until labelled and that all reports with a fatal outcome should undergo special medical review.

Follow-up

Guidance is given on prioritising cases for follow-up, the highest priority being given to all serious cases; unexpected cases; special interest cases and those which are uninterpretable in order to seek clarification. As always, the topic of whether cases should be followed to resolution was raised as there was concern that a non-serious rash, for example, may

become Stevens–Johnson Syndrome. It was suggested that when a letter of acknowledgement was sent, as is good practice, the reporter should be asked to notify the company if any further information becomes available on the case.

Good Summary Reporting Practices: PSURs

Whilst agreeing that the full ICH E2C format PSUR should be produced every 6 months for most drugs, the working group recognised that this presents a number of practical difficulties in terms of format and content. At one extreme, there are high volume reports that may contain thousands of ADR case reports or an unmanageable volume of publications. At the other extreme, there are older drugs with a well-established profile for which there is little or no new information to report. Modifications to PSUR content are proposed for the former high volume reports and recommendations for simplifying reports, with an example, are given for the latter. It is emphasised that the working group is not suggesting new format reports but simply offering pragmatic suggestions for adapting the ICH E2C content and format in certain circumstances.

One of the greatest dilemmas in producing PSURs is fulfilling the different frequency and periodicity requirements for different regulatory authorities in different countries. For example, in Europe, the schedule for submission changes to annual after 2 years and then 5-yearly after the first renewal. Under ICH E2C provisions, regulators who do not wish to receive 6-monthly reports are expected to accept two 6-monthly reports as an annual report or the appropriate series of reports as a 5-year report. The working group therefore proposed the use of the *summary bridging report* to facilitate the review of a series of reports. The summary bridging report 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. An example is presented in the final report.

The concept and use of the IBD for PSURs have not been fully accepted by all regulators. Some require that PSURs are scheduled according to the local approval date and, in addition, not all companies will have synchronised 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, the working group recommended the use of an *addendum report*. This is an update to the most recently completed scheduled PSUR when a regulatory authority (or the company) requires a safety update outside the usual reporting cycle, and more than a brief amount of time has elapsed since the most recent PSUR. The working group proposed the minimum information for inclusion in the addendum report.

Finally, other issues of practical importance in managing the preparation of PSURs that are not directly related to format and frequency are discussed. Many of these topics were issues raised in a survey undertaken by the working group to identify the current PSUR burden to industry.

WORLD-WIDE CLINICAL SAFETY REPORTING REGULATIONS

This chapter summarises the diversity of current regulatory reporting requirements, pre- and post-marketing, for expedited and periodic safety update reporting, many of which purport to be based on existing harmonisation initiatives. It is hoped that the plea for improved harmonisation will be heeded.

The CIOMS V report was published in 2001 (CIOMS, 2001).

INCORPORATION IN REGULATION

The CIOMS V Working Group addressed a range of the challenges that frequently arise in routine pharmacovigilance and therefore it is not surprising that their recommendations have been incorporated into more than one ICH guideline. As mentioned previously in this chapter, the practical guidance on the preparation of periodic safety update reports was used in the addendum to the ICH E2C guideline and the definitions and standards, including the new sources of individual case safety reports (e.g. Internet, solicited sources) and good case management practices, were used as a basis for the ICH E2D guideline on post-approval safety data management. Finally, CIOMS V is referenced under the design and conduct of observational studies in the ICH E2E guideline on pharmacovigilance planning.

CIOMS VI – MANAGEMENT OF SAFETY INFORMATION FROM CLINICAL TRIALS

RATIONALE

Pharmacovigilance has traditionally focused on detection and evaluation of signals in the post-approval environment in order to secure early detection of new adverse reactions or patient subgroups of exceptional sensitivity, and to introduce measures to manage those risks. It was and remains the vision of CIOMS VI even though there are some important differences between pre-marketing and post-marketing safety monitoring and management that there should be a much stronger and closer relationship between them. In providing practical, and sometimes completely new approaches for managing safety information in the clinical trial setting, CIOMS VI enables a more seamless transition in conducting high quality pharmacovigilance from the development stage to the post-approval period. The sixth CIOMS working group addressed the collection, monitoring, analysis, evaluation and overall management of safety information from clinical trials. The output of the CIOMS VI working group is dedicated to the many thousands of patients and other volunteers who generously participate in clinical research programmes so vital for the development and advancement of medicines.

PROCESS

In 2000–2003, drug regulatory authorities, pharmaceutical companies and clinical investigators were challenged by several new national, regional and international guidelines and regulations, including those dealing with ethical aspects of biomedical research. Implementation of ICH Guideline E6 on GCP was completed, the World Medical Association's Declaration of Helsinki was revised in 2000 (and subsequently clarified in 2002 and 2004), the European Commission published the Clinical Trials Directive in 2001 and its guidances in 2003, and CIOMS published the revised International Ethical Guidelines for Biomedical Research Involving Human Subjects in 2002. Moreover, the working group reviewed new developments in drug safety regulations and concepts and in risk-management put forth by the US FDA and the EU EMEA. Similarly, it was also kept up to date on

new initiatives in Japan, Australia and South America. All these aspects are reflected or referred to in the final report of the working group.

A survey of pharmaceutical companies on their safety practices during clinical trials was conducted in early 2003; the results of that survey helped inform the working group's deliberations. The topics covered in the survey included broad organisation and policy issues (regarding, e.g., risk management, Investigator's Brochure management) as well as case processing and data management issues (e.g. causality assessment, study/case blinding, use of AE terms and coding dictionaries, and much more).

OVERVIEW

The report is divided into the following six main subject areas:

1. Ethical Considerations for Clinical Trial Safety Management.
2. Good Pharmacovigilance and Risk Management Practices: Systematic Approach to managing safety during clinical development.
3. Collection and management of safety data during clinical trials.
4. Identification and evaluation of risk from clinical trial data.
5. Statistical analysis of safety data in clinical trials.
6. Regulatory reporting and other communication of safety information from clinical trials.

Ethical Considerations for Clinical Trial Safety Management

The key messages of this chapter are that for anyone designing and conducting a clinical trial, the fundamental principle should be that any study that is not scientifically sound can be considered unethical.

It also endorses the concept of transparency of results and outcomes for all clinical research, especially safety data.

Systematic Approach to Managing Safety During Drug Development

This chapter is destined to become one of the most influential pharmacovigilance texts in recent memory.

It recommends that sponsors of clinical trials ensure that a well-defined and well-structured process is in place that will allow them to readily identify, evaluate and minimize potential safety risks relative to potential benefits for study subjects in pre-approval trials. Such a process should start before initiating the first Phase I study and continue through post-approval use of the drug or biologic in the general population.

A dedicated Safety Management Team (SMT) should be formed for each development programme, to review all the available safety information on a regular basis so that decisions on safety can be made in a timely manner. It also recommends that these reviews generally take place at least quarterly pre-approval and be co-ordinated with pre-approval and, if applicable, post-approval periodic reporting. Quarterly and *ad hoc* safety reviews should consider the overall evolving safety profile of the investigational product, make necessary changes to the Investigator's Brochure (IB), Development Core Safety Information (DCSI) and informed consent, determine if any changes to the conduct of the trials need to be considered, and initiate prompt communications to investigators, ethics committees and regulators when appropriate. The team should be empowered to make decisions that will accomplish the goal of minimizing risk while maximizing benefits to subjects in clinical trials, as well as anticipating the use of the product once marketed.

A formal Development Risk Management Plan (DRMP) should be created and modified as needed during a clinical programme. In the initial planning stages of a new clinical development programme, one goal is to gather the necessary knowledge and information to adequately plan the optimum programme from the standpoint of safety. The plan should include early documentation of known, anticipated and potential risks along with plans for addressing them during development and, where appropriate, the DRMP would eventually evolve into a post-marketing risk management plan that will accompany the registration application.

All pertinent data must be readily available to the safety team from the clinical trial and safety databases as well as from other relevant sources, such as the pre-clinical toxicology department (e.g. carcinogenicity and development and reproductive toxicology), *in*

vitro mutagenicity studies, and pharmacokinetic and drug-interaction studies.

It is important to incorporate epidemiology into the development planning process, not only for defining the natural history of the disease being treated, but for anticipating important confounding factors and background rates of occurrence of concurrent illnesses. Understanding these will help to put the evolving safety profile into proper perspective.

When planning for the development of virtually any new medicinal product, there are certain categories of potential toxicities that should always be considered. These include abnormalities in cardiac conduction, hepatotoxicity, drug-drug interactions, immunogenicity, bone marrow toxicity and reactive metabolite formation.

Collection and Management of Safety Data During Clinical Trials

In early phases of drug development, it is generally necessary to collect more comprehensive safety data than in post-marketing studies. In addition, certain drug types may require longer routine follow-up as in the case of vaccines, immunotherapies and some biotechnology products. As a general rule, it is recommended that safety data event-collection should continue after the last dose of the drug for at least a further five half-lives of the experimental product. Also, investigators should be instructed to always be diligent in looking for possible latent safety effects that may not appear until after a medication is discontinued.

There are no definitive methods for distinguishing most adverse drug reactions (i.e. events that are causally attributable to study therapy) from clinical adverse events that occur as background findings in the population and have only a temporal association with study therapy. The CIOMS VI Working Group thus recommends that:

- All adverse events, both serious and non-serious, should be collected for any clinical trial during development, regardless of presumed relationship to the study agent by the investigator or sponsor, in order to allow for subsequent assessment of causality using standardized methods for individual cases and aggregate data. This applies not only to the

experimental product but to placebo, no treatment or active comparator.

- Causality judgments based on analysis of multiple cases/aggregate data, rather than on individual cases, are almost always more meaningful and typically have a greater impact on the conduct of clinical trials, including changes to informed consent documents, study design and core safety information. However, causality assessment of individual adverse events by the investigator may play a role in the early detection of significant safety problems, and these are the only source of information on rare events.
- The investigator should be asked to use a simple binary decision for drug causality (related or not related) for serious adverse events. One possible approach that has been suggested is to ask simply whether there is a ‘reasonable possibility’ or ‘no reasonable possibility’ that the study treatment caused the event. Alternatively – ‘Was there a reasonable possibility?’ Yes or No.

In order to assure standardized signal detection and evaluation processes, data quality and completeness are paramount. The CIOMS VI Working Group recommends the following principles for this important objective:

- Individual case safety reports from studies should be as fully documented as possible.
- There should be diligent follow-up of each case, as needed.
- The reporter’s verbatim AE terms must be retained within all relevant databases.

Sponsors should avoid ‘excessive coding’ of events reported in serious adverse event cases. Each such report should contain only the minimum number of dictionary terms needed to ensure retrieval in the relevant clinical context(s). Conversely, sponsors should take great care not to ‘undercode’ events, namely assign codes that might downgrade the severity or importance of an event term or terms. Some companies and health authorities maintain a list of event terms that are always regarded as medically serious and important even if the specific case might not satisfy the criteria for serious in a regulatory sense (require expedited reporting, for example). Such ‘always serious’ events are used routinely to trigger

special attention and evaluation. Although such lists were originally created for post-marketing purposes, especially for spontaneous reports, they might be useful for pre-approval clinical research purposes.

Identification and Evaluation of Risk from Clinical Trial Data

The purpose of ongoing safety evaluation during drug development is to ensure that important safety signals are detected early and to gain a better understanding of the benefit–risk profile of the drug. Safety monitoring, evaluation and analysis should be performed in such a manner as not to compromise the integrity of the individual studies or the overall development programme. Study sponsor should be fully aware at every stage of development of the potential risks of the investigational product and the morbidities characteristic of the study population. They must also ensure that activities involved in the management of clinical trial safety data (e.g. data entry, edit checks, data queries, coding of adverse events using a standard dictionary) are undertaken with care and precision in order to ensure that the safety database is accurate and complete.

The working group recommended that frequent review of serious and special interest adverse events, as well as overall assessment of all AEs, regardless of seriousness, causality or expectedness, should be performed periodically:

- (1) ad hoc, for serious and special interest AEs;
- (2) routine, periodic, general review of all data, whose frequency will vary from trial to trial and from development programme to development programme and depend on many factors; and
- (3) reviews triggered by specific milestones established for a trial or a programme (e.g. numbers of completed patients, end-of-trial, end-of-program, preparation of integrated summary of safety, and a marketing application).

Aggregate safety data should be monitored and evaluated periodically during the course of the overall developmental programme, during each study, and at the end of every study to provide an ongoing appraisal of benefit–risk balance.

Statistical Analysis of Safety Data in Clinical Trials

Use of the most appropriate statistical techniques for analysis and display of the data are essential for placing the absolute and relative safety of a medicinal product in proper perspective. Early in drug development (Phase I and early Phase II trials), much of the assessment of safety depends on individual case assessment. However, as the database increases, aggregate analysis tends to become more important, and that is where statistics play a crucial role. The techniques and approaches to use of statistics for analysing safety data have not been developed as fully as they have for efficacy and it is not uncommon to find inappropriate or incomplete displays and analysis of adverse event data, even in refereed publications.

This chapter is not intended to be a manual for statistical analysis of safety data as the subject is much too broad and complex. However, it does highlight key points that need attention when considering analysis, and areas which the working group believed may not be adequately understood or appreciated.

Statistical approaches have application at several stages of clinical trials: protocol design, during a trial, for final analysis and writing of the trial report or publication, and when combining data across different trials. Professional statistical help is required and should be obtained at each of those stages. Statistical association (P-values or other measures) alone may or may not be of clinical value. In randomized trials they have great strength in testing causality but they inevitably have uncertainty. Examination of both statistical and clinical significance must involve a partnership.

The ability of a study to detect causal effects in the face of variation within and between individuals is dependent on sample size; the smaller or rarer an effect, the larger the sample size required, if any degree of certainty is to be given to the study conclusions. It is necessary to acknowledge when the data are insufficient to draw conclusions on safety, i.e. ‘absence of evidence is not evidence of absence’. In such situations, the use of descriptive methods and well-designed graphics will be helpful in this process. Finally, although this chapter concentrates on ways of graphically representing safety data, the recommendation is that the unwanted effects must always

be considered in the context of the benefits of the medicine.

Regulatory Reporting and Other Communication of Safety Information from Clinical Trials

This chapter makes a number of detailed recommendations on the expedited reporting process for clinical trial reports. More importantly and contrary to established regulations, CIOMS VI proposes that routine expedited case reporting by sponsors to investigators and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) be eliminated. Instead, sponsors should provide regular updates of the evolving benefit–risk profile and highlight important new safety information. Only significant new information, occasionally a single case report, that has implications for the conduct of the trial or warrants an immediate revision to the informed consent would be communicated on an expedited basis. More commonly, important new safety information would be communicated periodically, based on the assessment of accumulating, aggregate information.

For unapproved products, instead of sending individual expedited clinical trial case reports to investigators and IECs/IRBs, the CIOMS VI Working Group recommended periodic reporting. It was suggested that such reports include a line listing of unblinded clinical trial cases that were expedited to regulatory authorities since the last periodic report, a copy of the current DCSI along with an explanation of any changes, a statement if there are no changes, and a brief summary of the emerging safety profile. Although it is recommended that the default would be quarterly updates, there may be circumstances when either a more immediate or less frequent communication would be appropriate.

For approved products, the time frame for periodic reports to investigators and IECs/IRBs would depend on the extent to which new indications are being developed. For a product undergoing Phase III trials, continuation of the quarterly reports would be advisable. For well-established products, less frequent updates would be appropriate and, at some point, there should only be a need to update investigators and IECs/IRBs when there is significant new information to report. For Phase IV investigators and their

associated IECs/IRBs, communications of changes to the CCSI should be sufficient.

The working group proposed that there be a single Development Safety Update Report (DSUR) for submission to regulators on an annual basis, with a consistent format and content which were yet to be defined. Additional recommendations for the DSUR were taken up by the CIOMS VII working group (see CIOMS VII).

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor should issue a prompt notification to all parties, namely regulatory authorities, investigators, IECs/IRBs and, if relevant, Data and Safety Monitoring Boards (DSMBs). A significant safety issue could be defined as one that has a significant impact on the course of the clinical trial or programme (including the potential for suspension of the trial programme or amendments to protocols) or warrants immediate update of informed consent. DSMBs are most commonly employed for a single large clinical trial and are not usually charged with providing oversight of an entire clinical program. It would therefore be important to ensure that important new safety information is communicated to a DSMB even if the information did not originate from the DSMB-monitored study.

There was much discussion on whether the previously recommended concept and level of threshold for changes to the CCSI (CIOMS III/V report) should be applied to the DCSI and informed consent information. Although there was agreement on the concept, there was not agreement on the threshold. As reflected in Appendix 7 of the report, there was a body of opinion that fewer and less stringent criteria for including new ADR information in the DCSI be applied for events that might have a significant adverse outcome for the trial population. This opinion was not reflected in the main chapter.

The CIOMS VI report was published in 2005 (CIOMS, 2005).

CIOMS VII – THE FUTURE

The CIOMS VI working group proposed that there be a single Development Safety Update Report (DSUR) for submission to regulators on an annual basis, with

a consistent format and content which had yet to be defined. They strongly recommended that DSURs be based on an entire development programme and not per protocol. Consideration should be given to establishing a common international birth date which would be the date of first authorization to begin clinical trials anywhere in the world. The DCSI should be attached to the annual DSUR with an explanation of any changes since the last update, with any significant new safety information highlighted. Hence the CIOMS VII working group was formed to make recommendations on the format of the DSUR.

Progress on this and future CIOMS topics can be monitored on the CIOMS website (www.cioms.ch). The CIOMS VIII working group on data-mining had convened as this chapter went to press.

CONCLUSION

From the scope of work presented in this chapter it is very evident that the CIOMS working groups have made significant contributions to present-day pharmacovigilance practice, especially in their attempts towards achieving harmonisation. They have frequently focused on areas for simplification, clarification and harmonisation of practices on topics that are rarely or never addressed by regulations or guidelines. Much of the success of the working groups was due to the realisation of the vision of Zbigniew Bankowski, the Secretary General of CIOMS until his retirement at the end of 1999. This vision was that problems could best be solved by small working groups of constructive individuals gathered together to represent different aspects of a shared problem in an unofficial environment.

The work of safety surveillance and public health protection is never completed because regulations and requirements are constantly changing. Innovations and improvements will always be needed and, with finite pharmacovigilance resources in both industry and regulatory authorities, we must all do our outmost to maintain the vision that pharmacovigilance is about promoting public health and not bureaucracy.

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PEM in the UK

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BACKGROUND

As early as 1965, L.J. Witts wrote that ‘the final test of the safety of a drug is in fact its release for general use’. The recognition that not all hazards could be known before a drug was marketed and that spontaneous adverse drug reaction reporting systems may fail 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. The proposals included ‘Recorded Release’, ‘Registered Release’, ‘Retrospective Assessment of Drug Safety’ and a number of variants (Inman, 1978a).

One of the limitations of spontaneous reporting is that doctors may fail to identify and report illnesses which they do not suspect to be due to a drug. This realisation led to the development of systems based upon ‘event’ reporting in which the doctor did not need to diagnose or suspect the true cause but was asked merely to record events. To this thinking the distinguished statistician, D.J. Finney, made a fundamental contribution in a paper in 1965 in which an event was defined as ‘a particular untoward happening

experienced by a patient, undesirable either generally or in the context of his disease’ (Finney, 1965).

These ideas – published only 4 years after the original announcements of Lenz regarding thalidomide and congenital abnormalities (Lenz, 1961, 1962) – came together in the founding by W.H.W. Inman of prescription–event monitoring (PEM). The establishment of PEM at the University of Southampton in 1980 and Inman’s early experience with this technique have been recorded in publications (Inman, 1981a,b; Inman, Rawson and Wilton, 1981) which established that the key objective 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.

METHOD

PEM is a non-interventional, observational cohort form of post-marketing surveillance. It is non-interventional because nothing happens to interfere with the doctor’s decision regarding which drug to prescribe for each individual patient. Thus, the method provides ‘real-world’ clinical data involving neither inclusion nor exclusion criteria: the patients studied are those who receive the drug in everyday

medical practice. This ensures that the data are generalisable.

In the United Kingdom virtually all persons are registered with a general practitioner (GP) who provides primary health care and issues prescriptions (FP10s) for the medicines medically necessary. The patient takes the prescription to a pharmacist who dispenses the medication and then sends the FP10 to a central Prescription Pricing Division (PPD) which arranges the pharmacist's reimbursement. The Drug Safety Research Unit (DSRU) is, by virtue of a long-standing and confidential arrangement, provided with electronic copies of all those prescriptions issued nationally for the drugs being monitored by PEM. These arrangements continue for a collection period which allows exposure data to be collected for 20 000–30 000 patients. For each of these patients the DSRU prepares a computerised longitudinal record comprising, in date order, all of the prescriptions for the monitored drug. Thus, in PEM, the exposure data are national in scope throughout the collection period and unaffected by the kind of selection and exclusion criteria that characterise clinical trials. The exposure data are of drugs dispensed and provided to the patient but there is no method of measuring compliance or the use of non-prescription medication.

After an interval of 3-12 (usually 6) months from the first prescription for each individual patient the DSRU sends to the prescriber a 'green form' questionnaire seeking information on any events that may have occurred since the drug was first prescribed. An event is defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexplained 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.

Information which identifies the patient is deleted from the database when the green form is received from the doctor. The doctor enters any number or code used in the practice to identify the patient. This ensures that the clinical information received by the DSRU is anonymised. The practice code or number is used if follow-up information is sought from the doctor. In order to avoid placing an unreasonable demand on GPs no more than four green forms are sent to each doctor in any one month. The green form

PLEASE RETURN THIS HALF OF FORM				Ref:
Sex: _____ Age at start of treatment: _____		Was the drug effective? Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know <input type="checkbox"/>		
Your identification code for this patient* -----		Has the drug been stopped? Yes <input type="checkbox"/> No <input type="checkbox"/> Don't Know <input type="checkbox"/>		
Indication for prescribing		If 'Yes' reason for stopping		
Drug start date / / Dose mg/day		Drug stop date / /		
Date of last prescription / /				
Event Date	Dose mg/day	Events while taking this drug If none, please tick box	Event Date	Events after stopping this drug If none, please tick box
		<input type="checkbox"/>		<input type="checkbox"/>
IF YOUR PATIENT HAS DIED				
Certified date of death / / /				
Certified Cause of death: 1(a) _____ 1(b) _____				

Figure 24.1. Green form.

is illustrated in Figure 24.1, which shows the other information requested of the doctor.

The green form has been modified for certain studies with a small number of additional questions (with yes, no, don't know answers). These questions focus on issues specific to the drug under study, for example the green form for the PEM study on the NSAID meloxicam included questions about previous history of gastrointestinal conditions and intolerance to NSAIDs to identify possible confounding by indication.

General practitioners are not paid to fill in green forms. The arrangements allow good contact between the doctor and the DSRU and this facilitates the collection of any follow-up data that may be considered necessary by the research physicians monitoring each study and working within the DSRU. One of the strengths of PEM is follow-up with the GP or the health service to obtain further information from the doctor for a large number of reports. A list of reports for which additional information is sought is included in Table 24.1.

Over the 78 studies listed in Table 24.2, an average of 58% of the green forms sent out have been returned by the GPs to the DSRU. The cohort sizes, with an average of 10 613 patients, as given in Table 24.2, are derived from the mean 52% of returned green forms which provide clinically useful data.

PEM collects event data and does not ask the doctor to determine if any particular event is due to an adverse drug reaction (ADR). If, however, the doctor does consider the event to be an ADR or he has

Table 24.1. Reports for which additional information is sought.

- Medically important adverse events reported during pre-marketing development
- Medically important events reported during post-marketing in other countries (for products launched elsewhere before in the United Kingdom)
- Events considered to be possibly associated with the product during the prescription-event monitoring
- All pregnancies
- Any deaths for which the cause is not known or which may be related to the medication
- Reports of overdose and suicide

completed a yellow card (a spontaneous ADR report) regarding the event, then he is asked to indicate this on the green form.

Further details of the methodology of PEM, including the methods of data coding, computerisation and analysis, have been provided in a number of publica-

tions (Inman, 1978b; Freemantle *et al.*, 1997; Mann *et al.*, 1997).

Each PEM study starts as soon as possible after the new drug has been marketed in England. Each study aims to collect exposure and outcome data on approximately 10 000 patients. Some studies have included almost double that number and attempts are now being made, when PEM is an ideal method for studying the early experience with an important new drug, to maximise the size of the cohort. The drugs included in the system are (as advocated by the Second Grahame-Smith Working Party of the Committee on Safety of Medicines) 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 GP (Secretary of State, 1986; BMA, 1996). 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).

Table 24.2. List of 78 completed studies.

	Generic name	Drug name	Group	% returned	Cohort
1	Cisapride	Prepulsid	Antispasmodic	62.4	13 234
2	Femotidine	Pepcid	H ₂ -antagonist	51.8	9500
3	Nizatidine	Axid	H ₂ -antagonist	44.7	7782
4	Misoprostol	Cytotec	Prostaglandin analogue	67.3	13 775
5	Lansoprazole	Zoton	Proton pump inhibitor	51.0	17 329
6	Omeprazole	Losec	Proton pump inhibitor	62.4	16 204
7	Pantoprazole	Protium	Proton pump inhibitor	44.5	11 541
8	Betaxolol	Kerlone	Beta-blocker	54.7	1531
9	Doxazosin	Cardura	Alpha-blocker	60.1	8482
10	Enalapril	Innovace	ACE-inhibitor	68.3	15 361
11	Lisinopril	Zestril + Carace	ACE-inhibitor	63.5	12 438
12	Perindopril	Coversyl	ACE-inhibitor	53.4	9089
13	Ramipril	Tritace	ACE-inhibitor	47.3	1371
14	Irbesartan	Aprovel	Antihypertensive	59.4	14 397
15	Losartan	Cozaar	Antihypertensive	59.9	14 522
16	Valsartan	Diovan	Antihypertensive	54.7	12 881
17	Amlodipine	Istin	Ca-antagonist	58.7	12 969
18	Diltiazem	Tildiem	Ca-antagonist	67.3	10 112
19	Isradipine	Prescal	Ca-antagonist	51.3	3679
20	Mibepradil	Posicor	Ca-antagonist	54.1	3085
21	Nicardipine	Cardene	Ca-antagonist	62.6	10 910
22	Nicorandil	Ikorel	K-channel activator	58.3	13 620
23	Xamoterol	Corwin	Inotropic	68.7	5373
24	Fluvastatin	Lescol	Lipid-lowering	63.2	7542
25	Bambuterol	Bambec	Beta ₂ agonist	50.8	8098
26	Eformoterol	Foradil	Beta ₂ agonist	52.9	5777

(continued)

Table 24.2. *Continued.*

	Generic name	Drug name	Group	% returned	Cohort
27	Salmeterol	Serevent	Beta ₂ agonist	61.9	15 407
28	Nedocromil	Tilade	Asthma prophylaxis	68.1	12 294
29	Montelukast	Singulair	Leukotriene antagonist	53.6	15 612
30	Acrivastine	Semprex	Antihistamine	56.5	7863
31	Cetirizine	Zirtek	Antihistamine	57.4	9554
32	Fexofenadine	Telfast	Antihistamine	50.9	16 638
33	Loratadine	Clarityn	Antihistamine	50.7	9308
34	Zolpidem	Stilnoct	Hypnotic	49.0	13 460
35	Zopiclone	Zimovane	Hypnotic	54.8	11 543
36	Buspirone	Buspar	Anxiolytic	54.1	11 113
37	Olanzapine	Zyprexa	Antipsychotic	68.9	8858
38	Quetiapine	Seroquel	Antipsychotic	58.9	1725
39	Risperidone	Risperdal	Antipsychotic	64.7	7684
40	Sertindole	Serdolect	Antipsychotic	78.2	436
41	Moclobemide	Manerix	MAOI	58.8	10 835
42	Fluoxetine	Prozac	SSRI	58.4	12 692
43	Fluvoxamine	Faverin	SSRI	59.9	10 983
44	Paroxetine	Seroxat	SSRI	61.6	13 741
45	Sertraline	Lustral	SSRI	60.2	12 734
46	Mirtazapine	Zispin	Antidepressant	56.0	13 554
47	Nefazodone	Dutonin	Antidepressant	54.9	11 834
48	Venlafaxine	Efexor	Antidepressant	54.6	12 642
49	Tramadol	Zydol	Analgesic	55.8	10 532
50	Sumatriptan	Imigran	Antimigraine	70.8	14 928
51	Lamotrigine	Lamictal	Anti-epileptic	67.9	11 316
52	Vigabatrin	Sabril	Anti-epileptic	69.2	10 178
53	Gabapentin	Neurontin	Anti-epileptic	66.4	3100
54	Donepezil	Aricept	Alzheimer's treatment	58.9	1762
55	Cefixime	Suprax	Cephalosporin	39.6	11 250
56	Azithromycin	Zithromax	Macrolide	52.4	11 275
57	Ciprofloxacin	Ciproxin	Quinolone	60.0	11 477
58	Enoxacin	Comprecin	Quinolone	44.5	2790
59	Norfloxacin	Utinor	Quinolone	50.0	11 110
60	Oflloxacin	Tarivid	Quinolone	45.7	11 033
61	Fosfomycin	Monuril	Antibacterial	45.6	3363
62	Fluconazole	Diflucan	Antifungal	68.6	15 015
63	Itraconazole	Sporanox	Antifungal	63.5	13 645
64	Aciclovir	Zovirax	Antiviral	74.1	11 051
65	Famciclovir	Famvir	Antiviral	65.4	14 169
66	Valaciclovir	Valtrex	Antiviral	64.1	12 804
67	Acarbose	Glucobay	Antidiabetic	62.8	13 655
68	Troglitazone	Romozin	Antidiabetic	60.3	1344
69	Finasteride	Proscar	Prostate treatment	63.0	14 772
70	Alendronate	Fosamax	Biphosphonate	59.4	11 916
71	Tamsulosin	Flomax MR	Alpha-blocker	57.4	12 484
72	Terodiline	Terolin	Anticholinergic	69.6	12 444
73	Tolterodine	Detrusitol	Anticholinergic	59.0	14 526
74	Etodolac	Lodine	NSAID	49.9	9091
75	Meloxicam	Mobic	NSAID	52.0	19 087
76	Nabumetone	Relifex	NSAID	54.9	10 444
77	Rofecoxib	Vioxx	NSAID	38.9	15 268
78	Tenoxicam	Mobiflex	NSAID	44.5	10 882
			Mean response rate	57.9	10 613

In summary, the exposure data in PEM are derived from the prescriptions written by GPs attending the individual patients; the outcome data are derived from the green forms completed by those same GPs.

Within the DSRU each green form questionnaire is scanned into the system and the image is reviewed by a medical member of the DSRU staff so that important events can be investigated. In addition to important events (Table 24.1), pregnancies and deaths of uncertain cause are further investigated by the DSRU Research Fellows who can, with the permission of the GP, access the patient's life-time medical records, death certificates, etc.

Interim reports are written to summarise the data on each study with every 2500 patients entered into the database. These reports include a listing, by

month since the beginning of treatment, of all events reported. They are, if possible, discussed with the Product Licence holder so that reporting obligations to the regulatory bodies can be fulfilled. Wherever possible PEM is undertaken in a collaborative but always independent relationship with the drug originator. The methodology of PEM is summarised in Figure 24.2.

RESULTS

Data analysis in PEM utilises several approaches which combine the application of epidemiological methods with medical evaluation.

INCIDENCE DENSITIES

Since most adverse drug reactions are the so-called 'type A' reactions, which are caused by the pharmacological effects of the product, and commonly occur within a short period after exposure, comparing the rates of events occurring soon after exposure with subsequent periods provides a useful means to generate possible drug safety signals.

PEM provides a numerator (the number of reports) and a denominator (the number of patient-months or patient-weeks of exposure), both collected within a known time frame (the difference, for each patient, between the start and stop dates of the drug being monitored).

The incidence density (ID) for a given time period, t , for each of the event terms in the DSRU dictionary is calculated as follows:

$$ID_t = \frac{\text{number of events during treatment for period } t}{\text{number of patient-months (weeks) of treatment for period } t} \times 1000$$

The IDs per 1000 patient-months (or patient-weeks) of treatment are then ranked to give estimates of the 'real-world' frequency of reported events.

While events with higher incidence densities in the period after exposure compared with subsequent periods are considered safety signals for the product under study, such events may be due to the effects of a product taken before the drug under

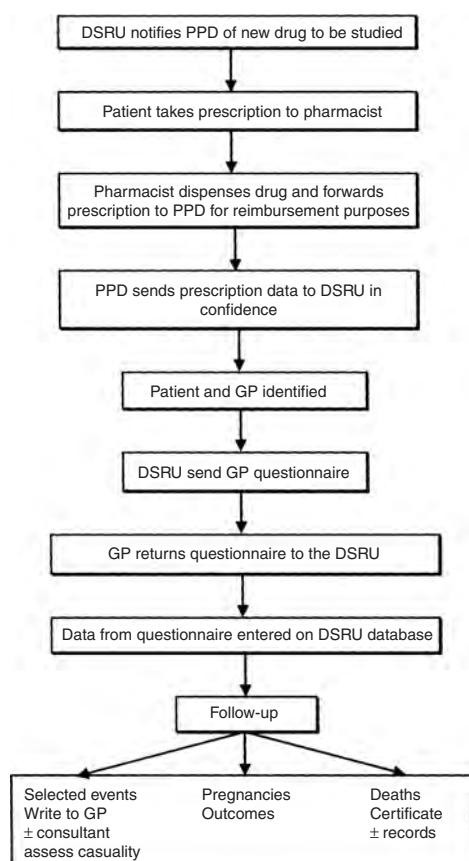


Figure 24.2. Prescription-event monitoring in England, DSRU = the Drug Safety Research Unit; PPD = Prescription Pricing Division.

study was started. For example, cough occurring soon after starting an angiotensin-II (A-II) receptor antagonist (e.g. losartan) may have been caused by an angiotensin-converting enzyme inhibitor taken before starting the A-II antagonist.

REASONS FOR STOPPING

The green form asks the doctor to specify the 'Reason for stopping' the drug being monitored if treatment was stopped. Thus, the ranked 'Reasons for stopping' (in terms of the number of reports of each event) is another source for generating signals and can be compared with the ranked IDs for the first month of therapy in each individual patient. As examples, data for the most frequently reported events with the two anti-epileptic drugs, lamotrigine and vigabatrin, are given in Table 24.3.

In general, there appears to be a high degree of correlation between these two sets of values. These values can be used to compare drugs within one therapeutic class: for example with anti-epileptic drugs it shows that rash is the most frequently reported event likely to be a drug side effect with lamotrigine, whereas rash is far less common with vigabatrin; similarly, 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.

GENERATION AND EXPLORATION OF SIGNALS

Signals are generated by an event having an unusually high ID or ranking in the list of 'Reasons for stopping' the drug being monitored or being considered medically important by the Research Fellow. While comparisons of incidence densities nearly always utilise the differences between the incidence density in the first month and subsequent months, it has been possible to use the difference between incidence densities in month 6 with months 1–5 in a 6-month study to generate signals for delayed adverse reactions such as gynaecomastia with finasteride (Wilton *et al.*, 1996), a product used for benign prostatic hypertrophy.

Many signals have been generated in PEM, examples include visual field defects in patients taking vigabatrin (Wilton *et al.*, 1999), gastrointestinal intolerance due to acarbose (Mackay *et al.*, 1997a), oesophageal reactions with alendronate (Mackay *et al.*, 1997b), aggression, agitation and abnormal dreams with donepezil (Dunn *et al.*, 2000), diarrhoea in the elderly with lansoprazole (Martin *et al.*, 2000), and serotonin syndrome with antidepressants (Mackay *et al.*, 1999).

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 judgement with appropriate systems for causal inference.

Medical evaluation of individual case reports and clusters of reports is an important part of PEM. Important safety signals have been generated in this way. In the PEM study of the antiepileptic 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 green 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. The follow-up information revealed an additional 29 cases of visual field defects which were considered by the ophthalmologist to be probably or possibly related to vigabatrin, giving an incidence of risk of 7.00 per 1000 patients (Wilton *et al.*, 1999). The follow-up exercise in the PEM study of vigabatrin contributed to the understanding of this important adverse reaction and provided a method to compute the reported rate of the adverse reaction in real clinical use which was not possible with spontaneous reporting or in clinical trials.

THE OUTCOME OF EXPOSED PREGNANCIES

All pregnancies reported during PEM studies are followed up by the medical and scientific staff of the DSRU in order to determine the outcome in those babies exposed during pregnancy to the drugs being monitored.

A review (Wilton *et al.*, 1997) showed that 2508 pregnancies have been followed up in 34 PEM studies. The study drug was known to have been dispensed during 904 of these pregnancies (839 during the first trimester and 65 during the second/third trimesters). The first trimester pregnancies produced 553 live births among which 20 (3.6%) abnormalities were reported. The findings are little different from the proportion of abnormalities reported in the general population in the United Kingdom. Thus, these observational data may be of value to those who need to advise pregnant women exposed to newly marketed medicines. The pregnancy database of PEM is expanding. Moreover, the DSRU is currently analysing the pregnancy exposure data with the application of comparative statistical methods between products in the PEM database or with external data, e.g. national statistics of congenital abnormalities, and the results will be published in due course.

LONG LATENCY ADVERSE REACTIONS

Delayed reactions can be investigated by sending out further green forms relating to those patients shown in the initial PEM survey to be receiving long-term medication. One such study has provided reassuring data on the safety of long-term use of lamotrigine in epilepsy (MacKay *et al.*, 1997c).

COMPARING DRUGS IN THE SAME THERAPEUTIC CLASS

The size of the PEM database (78 completed studies with a total of one million patients) and advances in information technology are providing increasing opportunities to compare the safety profiles of products in the same therapeutic class. In the last few years many comparative studies (Table 24.4) have been conducted using PEM data which contributed to the understanding of the safety of many products.

Comparisons in PEM have included the application of nested case-control methodology (Dunn

et al., 1999). Nested case-control design appears to have useful applications to PEM and will be applied increasingly in the future. Another method that is currently being developed for signal generation in PEM is the routine application of comparative reporting rates for reported events in PEM.

INVESTIGATION OF SAFETY SIGNALS FROM OTHER SOURCES

The DSRU monitors the literature and the World Wide Web for important drug safety signals generated elsewhere, particularly those that cause public health or regulatory concerns. The Unit also receives requests from regulatory authorities and manufacturers to investigate drug safety signals in the PEM database. Whenever possible the DSRU 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 is the 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 European Union 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 as well as deaths from other causes such as suicide. The report of the comparative analysis was considered to be a very important source of information for the regulatory decision on the matter.

Another example of a retrospective analysis of a PEM study is the analysis conducted on the association between selective serotonin re-uptake inhibitors (SSRIs) and bleeding, which showed a possible weak association (Layton *et al.*, 2001).

While such comparisons produce valuable additions to the understanding of the safety of medicines, it is important to emphasise that comparisons of independent cohorts are subject to bias and confounding, which must be taken into consideration in the analysis and evaluation process. However, the paucity of post-marketing 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 post-marketing safety study are taken into consideration but when its results are considered in relation to other studies that had been conducted on the same product.

COMPARISON WITH NATIONAL DATA

Where appropriate, comparisons are made between event rates in PEM studies and other data resources, e.g. national statistics. An example is the analysis of cardiovascular events of the PEM study on sildenafil (a product used for erectile dysfunction) (Shakir *et al.*, 2001). Reported deaths from myocardial infarction and ischaemic heart disease in users of sildenafil in the PEM study were found to be no higher than expected according to national mortality statistics. The precautions with regard to possible sources of bias and confounding also apply to external comparisons.

DISCUSSION

PEM is best regarded as a hypothesis-generating method of pharmacovigilance. However, provided appropriate care is taken, the kind of hypotheses it provides can be further explored, or tested, by validation of selected cases, the study of age- and sex-adjusted relative risks, comparing products in the same therapeutic class, comparing reported events with national statistics, and conducting nested case-control studies. Hypothesis-testing methods, such as randomised controlled clinical trials, can only be satisfactorily undertaken when a hypothesis is already available.

The disadvantages and limitation of PEM, like those of most of the available techniques of pharmacovigilance, are however real. They include the following:

1. An average of only 58% of the green forms sent out are returned and an average of only 52% contain clinically useful data. This is significantly higher than the reporting rate in the yellow card and similar schemes (Martin *et al.*, 1998; Wilton *et al.*, 1998) but could conceal biases as it cannot be established in each PEM study whether the patients

whose doctors return the green forms are in any way different from those whose doctors fail to complete and return the questionnaire. We already know (MacKay, 1998) that the responding and non-responding GPs differ very little in the distribution of ages in which they became principals or in their geographical distribution. Recently, second green forms were sent to doctors who did not return the first green form, the data will be analysed to see whether there are differences in the safety profile between these patients and those reported initially.

2. PEM does not yet extend into hospital monitoring, although pilot studies have been conducted. Thus, for drugs started in hospital it is important to follow-up reports of interest in order to identify the first prescriptions because a 'survivor bias' can operate for patients who both started and stopped a drug under hospital care and 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 into hospital practice.
3. PEM data include confounders, for example the highest value for ID, with the anti-epileptic drugs lamotrigine and vigabatrin for convulsions. Medical evaluation and relating the various findings in PEM to each other is an essential part of the analysis. 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. It is a further limitation that statistical comparisons between drugs need to be undertaken with great care. Each PEM study begins as soon as the drug is launched and the 'trade-off' is between capturing the real-world and generalisable data from PEM and randomisation in clinical trials, which have many logistical and even ethical difficulties as well as limited external validity caused by exclusion criteria and other restrictions.
5. While one of the strengths of PEM is that it collects dispensed rather than prescribed data,

compliance is not examined routinely in PEM studies. However, it is possible, if necessary, to monitor repeated dispensing for the same patient as an indicator of compliance.

In essence, PEM can be as good but can be no better than the clinical case notes of the GPs or their precision in completing event forms for their patients.

The advantages of PEM are:

1. It is non-interventional and thereby minimises the selection biases that occur when the study design interferes with the doctor's choice of drug for the individual patient.
2. It is national in scale and the cohort comprises all patients given the drug immediately after its launch into general practice. In Europe it is the only database that can identify cohorts of more than 10 000 patients for newly introduced medicines soon after launch.
3. The system prompts all prescribers who automatically receive a green form for each patient prescribed the drug being monitored. It is probably this prompting function that is responsible for the success of the method: 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.
4. Because the data are concerned with events, the system could detect side effects which none of the doctors has 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 for, as most reactions resemble fairly common clinical events, avoiding the doctor having to decide on causation may well encourage reporting.
5. The system allows direct contact between the doctors working in the DSRU and GPs so that follow-up surveillance of individual cases or deaths and all pregnancies is facilitated.
6. PEM can explore the possibility of long-latency adverse reactions and cohorts can be tagged on the NHS Central Register so that very long-term or lifetime follow-up can be undertaken.
7. Additional advantages accrue from the increasing size of the PEM database which has been built up since 1984. The database now contains information on 78 completed PEM studies and one 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.

Future plans include hospital monitoring, establishing registries of iatrogenic diseases, monitoring by community pharmacists, monitoring the safety of herbal products, and the establishment of an investigational unit in which the mechanisms of some of the uncommon ADRs identified by PEM can be explored by pharmacological and pharmacogenetic techniques.

CONCLUSION

Prescription-event monitoring (PEM) is a valuable and well-established method of hypothesis-generating pharmacovigilance. Its use since 1984 has produced a substantial database which itself forms an important research tool. PEM has found its own place in pharmacovigilance and is at its best in monitoring drugs receiving widespread, long-term GP use. The method lends itself to validation of individual case reports and allows the data to be explored by well-established epidemiological and clinical research techniques.

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PEM in New Zealand

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INTRODUCTION

In New Zealand (NZ), prescription-event monitoring (PEM) methodology is the main tool of the Intensive Medicines Monitoring Programme (IMMP), a national unit that performs proactive post-marketing surveillance on selected medicines. As outlined in Chapter 24, PEM studies are prospective observational cohort studies, in which cohorts are established from prescription data and adverse events are solicited from prescribers using follow-up questionnaires. This chapter describes how the IMMP has developed and enhanced PEM in NZ and discusses some of the differences to PEM in the United Kingdom.

BACKGROUND

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 post-marketing surveillance programme. 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 programme, which commenced in 1977, was called the 'Intensified Adverse Drug Reaction Reporting Scheme' and was aimed at selected new drugs. 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 drugs selected for study, this intensified reporting was an attempt to change

* Retired.

the nature of reporting from that of suspected adverse reactions of recognizable clinical significance, to that of reporting all adverse events of any type or severity and without any judgement on causality. Thus 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 or incidence 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 programme (Coulter and McQueen, 1982), it was decided to send questionnaires to the prescribers after the drugs had been on the market 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 patients were no longer having their drug dispensed and specific questionnaires were then sent out asking why treatment had ceased. The use of these two questionnaires was the first endeavour at what has since been called PEM (Inman, 1981b), and the first publication resulting from the use of this methodology was the report and 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 Intensive Medicines Monitoring Programme.

THE INTENSIVE MEDICINES MONITORING PROGRAMME AS PART OF NEW ZEALAND PHARMACOVIGILANCE

The IMMP operates within the NZ Pharmacovigilance Centre (NZPhvC), which also incorporates the national spontaneous reporting programme – the

Centre for Adverse Reactions Monitoring (CARM). The NZPhvC is located in the Department of Preventive and Social Medicine at the University of Otago. Most of the activities of the NZPhvC are undertaken under contract to the Ministry of Health, which provides the majority of the funding for the Centre. Both programmes in the NZPhvC (IMMP and CARM) report to the Ministry of Health's medicines regulatory body (Medsafe) and its expert advisory group the Medicines Adverse Reactions Committee (MARC). This illustrates some differences to the UK PEM scheme, which is not a government funded unit and does not report directly to the medicines regulatory body or its committees. In addition, because the IMMP operates within the national pharmacovigilance centre, all spontaneous reports for monitored medicines are entered into the IMMP databases, which enhances the identification of adverse events (see *IDENTIFICATION OF EVENTS*).

SELECTION OF MEDICINES FOR MONITORING

In NZ, drug applications submitted for licensing are considered by the Medicines Assessment Advisory Committee (MAAC), which is advisory to the Ministry of Health. The MAAC has traditionally made the recommendations for which drugs should be monitored. For each drug recommended, the Director of the IMMP 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 panel gave priority to monitoring those drugs where the conditions in Table 25.1 applied.

At the time of writing, no new medicines are being recommended for monitoring by the IMMP. One reason for this is the planned merger of the NZ and Australian medicines regulatory bodies and their advisory committees in 2007. Proposals for how the new Joint Tasman Agency will monitor the safety of new medicines is currently under development and is anticipated that the IMMP will continue to perform targeted post-marketing studies on selected medicines.

Table 25.1. 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 drugs 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

OVERVIEW OF INTENSIVE MEDICINES MONITORING PROGRAMME METHODOLOGY

The core methodology of the IMMP – prospective observational cohort studies on selected medicines – remains very similar, and reviews of the IMMP methods have been published (Coulter, 1998, 2000; Clark and Harrison-Woolrych, 2006). Essentially, exposure data are obtained by establishing cohorts of patients prescribed 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 programme in the world, the IMMP methodology has developed considerably and has become much more comprehensive. 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 cohorts are established using identifiable patients from prescription records supplied by community and hospital pharmacies throughout NZ. All pharmacies in NZ maintain electronic prescription records and computer software programs flag IMMP medicines. Thus printouts of all prescriptions dispensed for IMMP medicines can be produced, and these are sent (Freepost) to the IMMP every 4 months on request.

In NZ to date, it has been necessary to use dispensing pharmacies as the source of medicine usage. In the UK, the Drug Safety Research Unit obtains the prescription data from a central source, the Prescription Pricing Division (Chapter 24). There is no equivalent database in NZ – there are centralized

records of subsidized medicines, but 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.

Pharmacists' provision of data to the IMMP is voluntary and unpaid, although the NZ Pharmaceutical Council's Code of Ethics requires pharmacists to participate in the programme. Compliance with returning the prescription reports has always been extremely high (currently greater than 90%), and the direct relationships established with pharmacists are valuable in providing additional prescribing information and further reports of adverse events. Many pharmacists also provide professional input by commenting on usage trends, which alert to problems of tolerance, inefficacy, medication error, misuse or abuse.

DURATION OF PRESCRIPTION DATA COLLECTION

All prescriptions for the monitored medicine during the period of monitoring (historical mean 58 months) are recorded, providing a prescribing history for each patient for as long as treatment continues. This is another difference to the UK system of PEM, where medicines are usually monitored for an average time of 6 months after first prescription (Chapter 24). 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 post-marketing phase of a drug frequently differ from later use.

COHORT SIZE

The desirable size for a cohort is around 10 000 patients (Inman, 1981a). For 22 medicines where monitoring was completed, 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 ever subsidized, 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. Prescription 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 the medicine.

Table 25.2. Monitoring studies for medicines in same class or for same indication.

Class of medicine	Medicine	Monitoring commenced	Monitoring completed	Number of patients
Antidepressants	Mianserin	April 1983	February 1988	10 899
	Fluoxetine	February 1989	February 1993	6 616
	Moclobemide	August 1990	April 1996	17 351
	Nefazodone	December 1998	November 2002	5 348
Peptic ulcer medicines	Cimetidine	November 1977	August 1981	10 526
	Omeprazole	August 1990	January 1997	22 050
Beta-agonists	Salmeterol	March 1992	December 2000	9 975
	Eformoterol	March 1992	December 2000	1 604
Calcium channel blockers	Perhexiline maleate	April 1977	August 1981	5 052
	Nifedipine	October 1980	February 1985	10 575
Beta-blockers	Acebutolol	April 1977	March 1980	2 019
	Atenolol	April 1977	March 1980	2 837
	Metoprolol	April 1977	March 1980	9 719
	Labetalol	November 1977	March 1980	3 143
ACE inhibitors	Captopril	April 1981	December 1986	16 342
	Enalapril	June 1984	January 1989	25 686
Lipid lowerers	Lisinopril	February 1988	April 1991	12 132
	Bezafibrate	February 1989	March 1994	10 226
	Gemfibrozil	February 1989	March 1994	4 541
	Simvastatin	February 1989	March 1994	7 588
Dopaminergic agents	Pravastatin	August 1991	February 1996	1 271
	Tolcapone	April 1999	March 2004	492
Cox II inhibitors	Entacapone	December 2000	March 2004	53
	Celecoxib	December 2000	November 2001	32 630
	Rofecoxib	December 2000	November 2001	26 666
	Etoricoxib	February 2003	March 2004	11 886
IUDs	Parecoxib	April 2003	July 2004	364
	Valdecoxib	April 2003	July 2004	7457
	Multiload	July 1991	July 1999	16 128
	Mirena	March 1998	March 2005	11 492
Atypical antipsychotics	Olanzapine	April 1999	Continues	7234 ^a
	Quetiapine	April 1999	Continues	3851 ^a
	Clozapine	December 2000	Continues	2826 ^a
	Risperidone	December 2000	Continues	14917 ^a

^a Patient numbers as at 30 June 2005.

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 (Table 25.2). Having comparators has obvious advantages, but unlike a clinical trial, there are often confounders that can make interpretation of differences difficult (Beggs *et al.*, 1999). Concurrent monitoring is valuable as it reduces the likelihood of potential confounding factors affecting the analyses and interpretation of results.

Monitoring rofecoxib and celecoxib during the same time allowed a comparison of the incidence of thrombotic cardiovascular events with each medicine (Harrison-Woolrych *et al.*, 2005). The IMMP is currently monitoring four atypical antipsychotic medicines, which will allow useful comparisons to be made across this class of drugs. 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 the demands made of practitioners.

PRESCRIPTION DATA

The data elements normally captured from the prescription information are summarized in Table 25.3. There may be variations on the type of data captured for particular medicines.

The continuous prescription records obtained by the IMMP are very useful for studying how specific medicines are used. For medicines not continually administered, it is possible to identify how many courses of treatment patients have and how long each course is. Recently, patterns of use of the weight reduction medicine sibutramine have been examined. The majority of the cohorts (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. Of the 2093 patients (12% of the cohort) who received more than one course of sibutramine, the mean duration between courses was 9 and 10 months, suggesting seasonal use of this medicine in NZ.

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 25.3). However, in NZ, an increasing proportion of patients have a unique National Health Identification (NHI) number. Currently, the IMMP is able to identify the NHI number for at least 80% of patients (over 90% for the COX II inhibitor cohorts). This not only assists in checking each patient's identification but also gives the potential for record linkage to national morbidity and mortality databases (see *DATA LINKAGE*).

Table 25.3. Data elements captured from prescription information.

Data element	Details recorded in IMMP databases
Patient details	First and last names, address, date of birth, NHI number
Prescribing doctor	Name and specific worksite address Type of doctor (GP or specialist)
Dispensing pharmacy	Name and worksite address
Drug 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)
Concomitant therapy	Not usually recorded from prescription data If required, this information is sought by specific follow-up questionnaire

ENHANCING PRESCRIPTION DATA CAPTURE

As described above, prescription records are received mostly as hard copy directly from individual pharmacies (currently 927 pharmacies) around NZ. Prescription and patient records are then entered into the computer database manually. This has resulted in very accurate and high-quality data but has often taken considerable time and resource – especially for larger cohorts.

Electronic capture of the prescription data (as done in the UK PEM scheme) has been considered by the IMMP in the past, but has not proved possible for various reasons including the lack of a complete centralised database of all prescriptions (see above) and insufficient resource. However, there have recently been proposals to include NHI numbers on all prescriptions and this may ultimately enable the IMMP to establish electronic capture of prescription data. It would be a great enhancement to PEM in NZ be able to establish cohorts quickly – and perhaps not just for new medicines – when safety issues arise. Therefore, the IMMP is currently reviewing its methods of data collection again, with the aim of moving towards a less paper-based system. However, there are obviously costs associated with such enhancements, and funding for the IMMP has been under threat in recent times (Herxheimer, 2004). Development of the IMMP systems will therefore depend on securing adequate funding to allow enhancements to be made whilst protecting the currently high standard of data collection.

IDENTIFICATION OF EVENTS

DEFINITION

The IMMP definition of an event is similar to that used in PEM in the UK (Chapter 24) – any new clinical experience since the patient started the medicine, whether the event is thought to be drug related. This definition incorporates several possible clinical outcomes which are summarized in Table 25.4.

INTENSIVE METHODOLOGY FOR IDENTIFYING EVENTS

The IMMP methodology is unique in that events in patients taking the monitored medicines are identified

Table 25.4. IMMP definition of an event.

-
- | |
|--|
| Any new clinical experience since the patient started the medicine including <ul style="list-style-type: none"> – All new, clinical events, including common and minor ones – Adverse changes in a pre-existing condition – Abnormally changed laboratory values – Unexpected failure of therapeutic effect – Any possible interactions – Accidents – Pregnancies – All deaths |
|--|
-

from several different 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 other pharmacy data and also from data linkage to national morbidity and mortality databases. This intensive methodology for identifying adverse events is described in this section.

FOLLOW-UP QUESTIONNAIRES

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 may be another prescribing doctor, including specialists. Doctors are asked to record all new clinical events (Table 25.4) 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 given to facilitate record searching). For drugs used intermittently or if there is no follow-up information in the notes, the doctor (or practice nurse) may contact the patient directly to obtain the information required.

The compliance rate for returning IMMP questionnaires has always been very high (greater than 80% for many medicines) and is currently around 70%. This average response rate is higher than that normally obtained in the UK PEM programme and may be related to several factors, including the high spontaneous reporting rate observed in the NZ

(Olsson, 1999). Doctors are not paid for completing the questionnaires, but they are now able to claim Continuing Medical Education (CME) points for completed forms.

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 intrauterine devices (IUDs) included questions about pregnancies and for sibutramine included questions on body mass index (BMI). Some questionnaires (e.g. for antipsychotic medicines) have sought information on indication for use of the medicine and concurrent medications. All questionnaires request information on the cessation of therapy and reasons for stopping treatment.

SUPPLEMENTARY QUESTIONNAIRES

It is sometimes necessary to obtain additional information to that obtained from the standard questionnaires described above. Examples include

- Baseline and serial liver function tests for tolcapone.
- Asthma severity questionnaire for salmeterol and eformoterol.
- Results of endoscopy checks for omeprazole.
- Questions about previous history of peptic ulcer disease for the COX II inhibitors.

If pregnancies are reported on the standard questionnaires (questions are incorporated for women of child-bearing age), then further information is sought regarding the outcome of the pregnancy. For reported deaths, further information on the cause of death and possible relationship with the medicine is sought by further questionnaires and also by linkage to mortality databases (see *DATA LINKAGE*).

DUPLICATE PRESCRIPTIONS

During the 1980s, the IMMP developed duplicate prescription pads to enhance event reporting. In particular, regions of NZ (covering about 25% of the population) personalized prescription pads were given to GPs, private specialists and hospitals (printed with the name of the hospital). Doctors gave the original and 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). This is because on duplicate prescription forms prescribers are asked to record any adverse events at the time of the consultation (Coulter, 1998) thus increasing the number of event reports received by the IMMP. The IMMP prescription pads have now 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.

INTENSIFIED SPONTANEOUS REPORTING

Spontaneous reports sent to the NZ Pharmacovigilance Centre currently comprise about 12% of the total reports received for IMMP medicines. These 'yellow card' reports may come from health professionals, patients/carers or pharmaceutical companies. They are often of great value as they highlight a specific clinical concern and may 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 Ministry of Health publication *Prescriber Update* and in the *MIMS Catalogue* (the latter is linked to most patient management systems). In addition, drug companies are required to state that their medicine is being monitored by IMMP in all company product information, and visiting company representative are asked to remind doctors. The inclusion of a medicine in the programme 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 programme (CARM) is

much valued as both programmes benefit from working together in the same national pharmacovigilance unit. This is a key difference to the UK PEM scheme, which operates entirely separately to the UK spontaneous reporting scheme.

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 databases. This has proved very useful for identifying which patients have died whilst taking a monitored medicine, and additional information is routinely sought on the cause of death. In addition to enabling the identification of events that may not be picked up from other sources, data linkage also offers great opportunity for other pharmacoepidemiology studies of patients in the IMMP cohorts (see *SPECIFIC STUDIES USING INTENSIVE MEDICINES MONITORING PROGRAMME DATA*).

PROCESSING OF EVENTS

CLINICAL REVIEW OF REPORTS

All events are assessed by a physician using the same process as for reviewing ADR reports in the spontaneous reporting programme. A ‘relationship’ is established between the drug and the event following the protocol for causality assessment recommended by the World Health Organisation Collaborating Centre for International Drug Monitoring (Meyboom and Royer, 1992). The 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). The hierarchy has five levels, and events can be sorted at each level into their clinically related groupings or individually. There are approximately 3000 event terms in the dictionary.

DRUG-EVENT RELATIONSHIP ASSESSMENT

Each drug-event relationship is coded as one of the following: definite, probable, possible, unlikely or unclassified. These assessments are based mainly on duration to onset of the event and the response to withdrawal and/or re-challenge. They are not regarded as ‘causality’ assessments and are made without prejudice. Judgements on causality for many of the events can only come later when epidemiological evidence using aggregated IMMP and other available data can be considered along with biases and confounders and pharmacological plausibility. With this background thinking, and to facilitate further evaluation, the assessed events are divided into two categories: those events with a relationship of certain, probable or possible are classified as ‘reactions’ and those with a relationship of unlikely are called ‘incidents’ (because they are likely to be incidental to the use of the drug and represent the background noise of the condition being treated or community morbidity). These two groups are then evaluated for signals of previously unidentified adverse reactions. This is largely undertaken by observation of the nature and pattern of events being reported, examining comparative rates controlled for age, gender, indication and severity of disease as appropriate and differences in profiles. Signals arising from this process may be investigated further by special studies.

INCIDENTS AS CONTROLS

Unless the incident group contains unrecognized adverse reactions, it should represent the background noise, and this should be generally similar for drugs of similar indication. If the incident rates are similar for comparator drugs, then it can be assumed that reporting bias is not present. If there are statistically significant differences between the incident profiles of comparator drugs, then this may be because of the presence of an unrecognized adverse reaction or confounding, e.g. by indication or reporting bias. Any such differences are therefore investigated.

Incidents are also used as within-drug controls for characterizing adverse reactions. The variables associated with, respectively, the reactions and incidents for a drug and also the patient characteristics are compared, and should there be differences these may indicate risk factors – e.g. a gender or dose difference – for the

reaction under study. An example of the use of incidents as within-drug controls is as follows. The rates of adverse reactions were higher in women than men for moclobemide [relative risk (RR) 1.7; 95% confidence interval (95% CI) 1.4–2.0] and fluoxetine (RR 1.7; 95% CI 1.3–2.2). There was no significant gender difference seen in the incident rates. It would appear therefore that the gender difference seen for the reactions is a true risk factor and not because of reporting bias.

For these two drugs, which were monitored concurrently, the incidents were also used as between-drug controls. The reaction rate for fluoxetine was 50% higher than that for moclobemide (RR 1.5; 95% CI 1.2–1.7). There was no significant difference between the incident rates, suggesting an absence of reporting bias and strengthening the finding of greater risk with fluoxetine (Coulter, 1996).

PRIVACY AND ETHICAL CONSIDERATIONS

The processes and practices of the IMMP have been set up to comply with the NZ Health Information Privacy Code, and the Privacy Commissioner has been advised of the purpose and methodology of the programme (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 all staff in all aspects of confidentiality.

Regarding patient consent for involvement in the programme, 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 also provides information leaflets that doctors may give to patients. 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.

Ethics Committee approval is not sought for routine monitoring of medicines in the IMMP as the programme is longstanding and has regularly been scrutinized without objection. 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 PEM IN NEW ZEALAND

SIGNAL IDENTIFICATION

There are several key elements to successful identification of previously unrecognized adverse reactions in the IMMP. These have been reviewed recently (Clark and Harrison-Woolrych, 2006) and include (a) the intensive methodology used to obtain events from multiple sources (see above), (b) the high quality and completeness of reports received by the IMMP and (c) the evaluation of every event report by at least one clinical assessor. 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. In addition, analyses of ‘incidents’ – as outlined above – contributes to the process at a later stage of monitoring.

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 reporter), other databases including the WHO-UMC international spontaneous reporting database, pharmaceutical companies, medicine regulatory bodies and the published literature. Using these methods, the IMMP has had some success in signal identification, as outlined in this section.

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* (Table 25.5). 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.

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 anaemia (Edwards and Coulter, 1989), mianserin and agranulocytosis (Coulter and Edwards, 1990), the intestinal effects of captopril (Edwards, Coulter and Macintosh, 1992), psoriasis with ACE inhibitors (Coulter and Pillans, 1993) and fluoxetine and hyponatraemia (Pillans and Coulter, 1994).

RECENTLY IDENTIFIED SIGNALS

Signals published in the international literature during the last 11 years (from 1995 to 2006) 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, Clark and Savage, 2003), psoriasis associated with rofecoxib use (Clark and Coulter, 2003), the activation of pain by sumatriptan (Coulter *et al.*, 2003), nose bleeds associated with risperidone (Harrison-Woolrych and Clark, 2004), amnesia associated with sibutramine (Clark and Harrison-Woolrych, 2004), QT interval prolongation associated with sibutramine (Harrison-Woolrych *et al.*, 2006) and cardiac dysrhythmias with COX II inhibitors (Savage, Coulter and Harrison-Woolrych, 2005).

Table 25.5. Titles of articles in *Prescriber Update* (1994–2004).

Visual disturbances with COX-2 inhibitors (2004)
IMMP studies of the Multiload intrauterine device (2003)
Atypical antipsychotics may cause hypertension (2003)
Cox-2 inhibitors and hepatotoxicity (2003)
Omeprazole may elevate clozapine levels (2002)
Acute psychiatric reactions with COX-2 inhibitors (2002)
Cerebrovascular events with sumatriptan (2002)
Adverse respiratory reactions to long-acting beta-agonists (1999)
Top 10 adverse events to sumatriptan in the IMMP (1998)
Top 10 adverse reactions with Multiload Cu375 in the IMMP (1997)
Top 10 adverse reactions to omeprazole in the IMMP (1997)
Interactions with fluoxetine and other SSRIs (1997)
Top 10 adverse reactions to fluoxetine in the IMMP (1996)
Top 10 adverse reactions to moclobemide in the IMMP (1996)
Sumatriptan in the media (1996)
Interactions with moclobemide and serotonergic antidepressants (1996)
Omeprazole and bacterial overgrowth in the gut (1995)
Selective serotonin reuptake inhibitors and hyponatraemia (1994)
Chest pain and sumatriptan in the IMMP (1994)

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 incidence or prevalence of specific adverse reactions and may also investigate risk factors for these reactions. Following a cluster of reports of nocturnal enuresis (bed wetting) associated with the atypical antipsychotic medicine clozapine, the IMMP is now further investigating this signal. Cohorts of patients taking clozapine, olanzapine, quetiapine or risperidone during 2003 have been established, and follow-up questionnaires with additional specific questions about bed wetting have been 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 an embarrassing problem which is unlikely to be spontaneously reported. This study will enable calculation of the prevalence of enuresis in patients taking clozapine (and identify risk factors for this adverse event) and will allow comparison with three other atypical antipsychotics.

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 felt that if there was any general trend to tolerance, then mean usage per patient over time would increase.

The prescription data were therefore analysed, 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 25.6 over a period of eight intervals, and an increase was demonstrated at each interval. The first interval was omitted because

Table 25.6. 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

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, DM, presentation at 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) and the outcome (events) data. The analyses performed on the exposure data are summarized in Table 25.7.

Table 25.7. Analyses performed on exposure data.

Analyses performed	Comments
Age and gender distribution of cohort	Presented in tabular and graphical formats
Regional distribution	Prescribing 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 also calculated
Prescribing patterns	Courses and cycles of treatment examined with mean and median durations
Indication for treatment	For medicines with more than one indication

ANALYSES OF OUTCOME DATA

The main outcome analysed is adverse events whilst the patient is taking the medicine (and for a feasible period after stopping). There are however additional endpoints analysed – e.g., reasons for the cessation of therapy and failure of therapeutic response.

- *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 visual 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, which presents the events in the context of the whole reaction.
- *Table of reports:* This is a listing by report and shows all the events associated with each report, e.g. 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 reactions, incidents and all events, respectively.
- *Incidence of adverse reactions:* This provides a listing of all events assessed as reactions, 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.
- *Reporting rates:* For each drug monitored, rates per 1000 patients are calculated for the numbers of (a) reports, (b) all events, (c) reactions and (d) incidents, respectively, in total and by gender. The overall reaction and incident rates are useful

for comparing subgroups and for between-drug comparisons, but in contrast to rates for individual events, do not provide a specific measure of risk because some patients have several events associated with the one report.

THE IMPORTANCE OF REPORTING RATES

The profiles of adverse events for a drug are different at high- and low-reporting rates. At specific rates of reporting, some events are more likely to be reported than others and, equally important, some are less likely to be reported. The IMMP provides a unique opportunity for comparing the rates of IMMP (intensified) spontaneous reporting of specific events with the rates from using PEM questionnaires. Angioedema/urticaria, extrapyramidal effects and blood dyscrasias were as likely to be reported spontaneously as with PEM. Conversely, cardiac dysrhythmias, dry mouth, dyspepsia, constipation, death and events suggesting immunological disorders were, by comparison, very unlikely to be reported spontaneously. Other events ranged between these two extremes. It needs to be emphasized that this refers to IMMP ‘intensified’ spontaneous reporting, which has a higher rate of reporting than the standard spontaneous reporting programme in NZ. It follows therefore that studies on specific drugs are not comparable unless the reporting rates are similar. Similarly, rates of reporting may provide a guide as to what types of reactions may have been missed.

SPECIFIC STUDIES USING INTENSIVE MEDICINES MONITORING PROGRAMME DATA

In addition to the routine data analysis performed for every monitored medicine, the cohort and event databases of the IMMP are increasingly being used for specific pharmacoepidemiology studies. Some examples of studies that have been performed are discussed in this section.

STUDIES OF INTRA-UTERINE DEVICES

The IMMP has performed unique post-marketing safety studies on IUDs and has effectively adapted

PEM methodology for this purpose (Zhou, Harrison-Woolrych and Coulter, 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 gynaecologists if this was more appropriate.

For Multiload Cu375, in addition to the routine IMMP reporting (Coulter, 1997), 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, Ashton and Coulter, 2002). This study, which is thought to be the largest study of IUD insertion published to date, also identified nulliparity and experience of the inserting doctor as risk factors for inserting problems.

The second Multiload Cu375 study investigated the incidence of uterine perforation with this device (Harrison-Woolrych, Ashton and Coulter, 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 Cu 375 device and the levonorgestrel IUD Mirena (Harrison-Woolrych, Ashton and Coulter, 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 now widely used in NZ and many other countries for contraception (and menorrhagia) and comparative studies of this kind are of great value in assisting women and their doctors to make appropriate choices (Harrison-Woolrych, 2003).

STUDIES IN SPECIAL POPULATIONS

Using similar methodology to the UK PEM scheme, the IMMP routinely collects information on pregnancies in women taking the monitored medicines. All pregnancies are followed up to determine outcome for the mother and baby. In the IUD studies, information was collected on both inadvertent pregnancies and planned pregnancies after device removal.

Paediatric use of atypical antipsychotic medicines has been a recent focus of interest for the IMMP. A population of children (defined as age 15 years or under) has been identified from the IMMP cohorts, and specific follow-up questionnaires have been sent to child/adolescent psychiatrists and/or the children's GPs. This study is seeking information primarily on adverse events in children but also on indication for use, the duration of treatment and reasons for stopping the medication. Data on the safety of medicines in children are often very limited, and frequently pre-licensing trials do not include a paediatric population, so post-marketing studies of this type are very important.

DATA-LINKAGE STUDIES

Earlier in this chapter, we explained how the NHI number of every patient in the IMMP cohorts can be linked to national morbidity and mortality databases to perform record linkage studies. Generally, this type of pharmacoepidemiology study is most useful for studying deaths and more serious events, which result in hospital admission (GP consultations are not recorded in the NZHIS databases), and NZ is an ideal country in which to perform such studies.

The IMMP is currently developing a data-linkage approach to perform studies on the four atypical antipsychotic medicines – clozapine, olanzapine, quetiapine and risperidone. Having these four cohorts established for the same time gives the potential to perform comparative studies. Routine IMMP follow-up of patients on these medicines (via their doctor) has proved very difficult, and response rates have been significantly lower than for other medicines. Using record-linkage methodology allows a higher proportion of patients to be followed up, often in a more time-efficient manner. Information obtained on clinical events from national databases can subsequently

be checked or supplemented with further detail from patients' doctors.

There are limitations to data-linkage studies – e.g. usually less detailed information will be obtained than from IMMP follow-up questionnaires, information on risk factors for events is frequently not available and only events resulting in hospital admission or death are recorded. However, for the investigation of specific events, e.g. ectopic pregnancy in Mirena users or sudden cardiac death in patients taking sibutramine, data-linkage methodology may be extremely useful.

PHARMACOGENETIC STUDIES

The ability to identify individuals who are susceptible to ADRs has the potential to reduce the personal and population costs of drug-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 has been 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 discusses some future directions for linking pharmacoepidemiology studies with pharmacogenetic investigations.

COMMUNICATING RESULTS OF INTENSIVE MEDICINES MONITORING PROGRAMME STUDIES

A high priority for the IMMP is provision and feedback of information to prescribers and patients. Every spontaneous report submitted to the IMMP receives a detailed individual reply that includes (anonymized) information from the IMMP databases. Similarly, information is provided in response to telephone or other enquiries on a daily basis. In addition, summaries of IMMP work on particular medicines are regularly provided to individual doctors or those

working in a specialist area – e.g. a summary of work on the Mirena IUD was e-mailed to all family planning clinics in NZ via the Family Planning Association network.

Reports of IMMP data and studies are regularly provided to the Ministry of Health (Medsafe) and the MARC, with summaries of these reports published in the MARC minutes. IMMP reports may raise new signals or other issues for consideration or might provide reassuring data on emerging issues. The IMMP also provides reports for information to the NZ licensing committee (MAAC) and – with the agreement of the NZ Ministry – will provide information to other national committees or other international regulatory authorities on request. As NZ is a small country, collaboration in pharmacovigilance with other countries is valuable, and data may be pooled and expertise shared.

CONCLUSIONS

PEM in NZ, like PEM in the UK, is a valuable method of post-marketing surveillance. The methodology of PEM is particularly useful for the calculation of rates of adverse events, as exposure is defined from prescription data. This information is of great value to patients and doctors when evaluating the benefits and harms 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 pre-marketing clinical trials.

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. The symbiotic relationship of the IMMP with the national spontaneous reporting programme has enhanced signal identification in NZ.

Once cohorts are 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.

There is much potential to further enhance the methodology of the IMMP. Electronic capture of prescription data may enable cohorts to be established in a shorter time, although this would require additional funding to set up. There is also scope to investigate different methods for identifying events, and this is already in progress with the record-linkage studies that have been initiated. In the future, it is hoped that the IMMP will be able to continue to develop and enhance these methodologies.

Internationally there is scope for PEM methodology to be used much more widely, and pooled information from several centres would provide added value. Countries struggling to obtain a 'worthwhile' number of reports from their spontaneous reporting programmes could switch resources to PEM studies of a few selected drugs. Countries with a large population who feel unable to mount a national scheme could use the method regionally.

In recent times, medicines regulatory authorities worldwide have announced that all new medicine applications will require a post-marketing pharmacovigilance plan to be submitted at the time of first evaluation (<http://www.fda.gov/cder/guidance/6355fnl.htm>). In Australasia – where plans for pharmacovigilance in the new Joint Tasman Agency are currently under discussion – it is possible that this proposal will also be adopted. The IMMP, using the methods described in this chapter, has much to offer in performing targeted post-marketing surveillance studies in this new environment. Although NZ has a population of only 4 million people, the IMMP has produced results that have made a significant contribution to pharmacovigilance worldwide. 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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MEMO in the United Kingdom

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INTRODUCTION

The Medicines Monitoring Unit (MEMO) is a University-based organisation that has access to data generated within the UK National Health Service (NHS). MEMO uses record-linkage techniques to carry out studies to detect and quantify adverse effects of drugs in the community. Currently, MEMO utilises data from the Tayside region of Scotland, which is geographically compact and serves over 400 000 patients. A computerised record of all patients registered with a general practitioner and inpatient hospital morbidity and mortality data are available to MEMO and form the backbone of the record-linkage system.

Although MEMO was originally set up for pharmacoepidemiologic research and this is still the main focus of its research activities, recent advances mean that studies in outcomes research, general epidemiology and health economics are also possible.

DESCRIPTION OF THE DATABASE

Every person who is registered with a General Practitioner (GP) in Scotland is allocated a 10-digit

unique patient identifying number called a Community Health Index (CHI) number. The CHI database contains additional demographic information such as patient's address (including postal code), GP registered with, and date of death (if applicable). For practical purposes, the entire Tayside population is registered with a GP and thus appears in the central computerised records of the Community Health Master Patient Index. Once patients are allocated a CHI number it is never re-allocated so record-linkage of medical data over a large number of years is possible.

The CHI number is used as the patient identifier for all healthcare activities in primary and secondary care in Tayside. The patient-specific number allows for efficient linkage of records of patient activity and outcome.

PRESCRIPTION DRUG DATA

After a patient receives a prescription from his/her doctor, the patient takes it to the community pharmacy where it is dispensed. Dispensed prescriptions are then sent to the Pharmacy Practice Division

(PPD) of the Information and Statistics Division of the Common Services Agency to obtain reimbursement and dispensing fees. After paying the pharmacists and dealing with any appeals, PPD sends the cashed prescription forms to MEMO. GP prescribing information is captured by MEMO by a unique menu-driven computer system, which links the prescribing information with the CHI number database (Figure 26.1). Using this system, it is possible to allocate the CHI number from the patient details on the prescription.

All items from the prescription are entered and stored on a database for research purposes. The date the prescription was written as well as the GP that prescribed the medication is recorded. The drug prescribed is entered via a 'drop-down menu' to ensure product availability and to avoid miscoding of preparation and spelling errors.

Both generic and proprietary names are used so the ability to differentiate between product types is available. The total amount of drug dispensed is also

entered together with the dosing instructions, thus allowing the duration of any prescription to be calculated. Community prescribing data have been entered for selected medications from January 1989 (notably non-steroidal anti-inflammatory drugs, ulcer healing drugs, lipid-lowering drugs and hormone replacement therapy) and all prescribed medications from January 1993. MEMO now has records of 30 million prescriptions dispensed in Tayside up to 2006.

HOSPITAL DATA

Since 1961, all hospitals in Scotland have been required to compile and return coded information on all acute inpatient admissions, forming the basis of the Scottish Morbidity Record 1 (SMR1), which contains administrative, demographic and diagnostic information. In Tayside this is coded by medical clerks before being entered onto computer and subjected to quality control. The data are then sent to the Information and Statistics Division (ISD) of the Common Services Agency of the National Health Service. Each SMR1 record has one principal and five other diagnostic fields coded according to the International Classification of Diseases 9th Revision (ICD9) (World Health Organisation, 1977). In 1996, the NHS introduced the 10th Revision of the ICD codes (World Health Organisation, 1992). There is also one main operation or procedure field and three others coded according to the Office of Population and Census Surveys 4th Revision (OPCS4) classification (HMSO, 1990). In Tayside, there are approximately 63 000 hospital discharges per year available as a CHI number-specific record. MEMO holds historical SMR1 data from 1980 allowing for a past medical history of hospitalisation for a condition to be controlled (Figure 26.1).

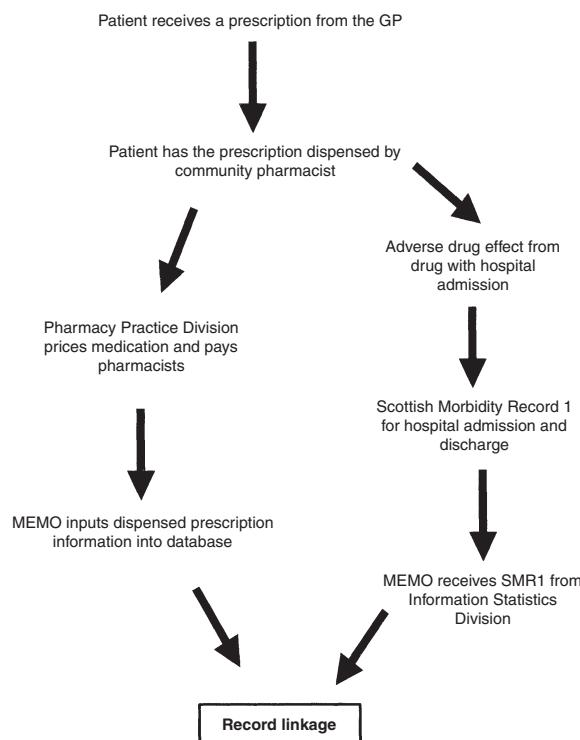


Figure 26.1. Schematic of record-linkage of data.

OTHER IN-HOSPITAL AND OUTCOME DATA SETS

Any healthcare data set that is indexed by the CHI number can be linked to MEMO's record-linkage database, including other Scottish Morbidity Record returns supplied by the ISD. In MEMO, commonly used data sets are the cancer registration

database (SMR6), child development records, maternity records (SMR2), psychiatric records (SMR4) and neonatal discharges (SMR11).

RECORD-LINKAGE OF OTHER DATABASES

Most of primary and secondary care use the CHI number as the patient identifier; however, if data do not have CHI numbers, these can be allocated from patient demographic details, such as name, date of birth and postcode. MEMO can identify the correct CHI number for a very high proportion of patients in the database. This is the same method as is employed to allocate CHI numbers to prescription data. MEMO has constructed a database of 100 000 endoscopy and colonoscopy procedures, and, in collaboration with Tayside Police, subjects involved in 22 000 road traffic accidents in Tayside using this allocation procedure.

CLINICAL LABORATORY DATA

Clinical laboratory investigations for the Tayside region since 1989 are held on a computerised archive in the Department of Biochemical Medicine in Ninewells Hospital. The database has CHI-specific biochemical, haematology, microbiology, virology and serology laboratory results and reports. CHI-specific results from all pathology investigations since 1990 for Tayside are electronically stored in MEMO. These data can be record-linked to the MEMO database to complete the clinical characteristics of disease or hospital admission.

PRIMARY CARE DATA

Progressively more GPs are using computerised systems to aid in patient management, although at present they are not available to MEMO for record-linkage. However, it is possible to abstract written records in primary care manually and research nurses in MEMO have been granted access to primary care records for specific studies (Morris *et al.*, 1997a; Evans *et al.*, 1998).

OTHER INFORMATION

Since all patients and their addresses are known, including postcode, and information is available from the decennial census regarding the relative deprivation levels of postcode areas, the so-called Carstairs deprivation score can be used as a relatively crude indicator of the socioeconomic status of patients (Carstairs, 1990; Evans *et al.*, 1997a). The deprivation category component variables are the percentage of people in a postcode sector with no car, the percentage living in overcrowded housing, the percentage with the household head in semi- or unskilled occupations, and the percentage of men unemployed.

Details of all deaths in Tayside since 1989 are electronically recorded through a copy of the General Registers Office – Death Certification Database and held within MEMO. The date and underlying cause of death can be identified and linked to the MEMO database using the CHI number of the patient.

CURRENT AREAS OF INVESTIGATION

DRUG SAFETY RESEARCH

Numerous drug safety studies have been completed in MEMO. For example, the cohort study design has been used to evaluate the risk profile of non-steroidal anti-inflammatory drugs (NSAIDs). Although the increased risk of upper gastrointestinal complications associated with NSAID use is well established (Hawkey, 1990), the large number of study subjects and the additional information available in MEMO have allowed more detailed investigations. For example, a cohort study among 78 191 patients newly exposed to NSAIDs and 78 207 unexposed comparators showed that there was an increased risk only among patients without a history of upper gastrointestinal events (McMahon *et al.*, 1997). Another study in 50 000 subjects investigated the risk with duration of use, and found that it remained constant with continuous exposure (MacDonald *et al.*, 1997) in contrast to previous findings (Carson *et al.*, 1987).

The case-control method is an efficient study design requiring fewer subjects than cohort studies. This is an important consideration when a study involves validating information by checking the original medical notes of patients. The case-control

design has been used in a range of studies investigating the adverse effect profile of topical NSAIDs. These studies found that oral NSAIDs, but not topical NSAIDs, are implicated in hospitalisation for upper gastrointestinal haemorrhage and perforation (Evans *et al.*, 1995b), acute renal failure (Evans *et al.*, 1995a) and acute colitis (Evans *et al.*, 1997b), but that they are unlikely to be associated with acute appendicitis (Evans *et al.*, 1997c).

The case–crossover design was employed in a study examining the risks of road traffic accidents associated with benzodiazepine use (Barbone *et al.*, 1998). This design is suitable for the evaluation of transient risks, and because cases are used as their own controls, problems of confounding can be dealt with neatly.

DRUG UTILISATION RESEARCH

MEMO is able to produce detailed drug utilisation data, broken down by age, sex, date, day of week prescribed, prescriber, generic or proprietary dispensing, co-prescribing, acute prescribing and/or repeat prescribing, dose and duration. One important dimension is the audit of GP prescribing in the population, although GP-specific data are analysed anonymously and individual GPs are never identified. For example, one study identified rare instances of potentially hazardous co-prescribing of β -antagonists and β -agonists to patients in Tayside likely to have asthma or chronic obstructive airways disease, by linking the dispensed prescribing database to hospital admission records (Hayes *et al.*, 1996). The processing of prescribing data according to the demographic characteristics of prescribing GPs has also yielded some useful insights into the characteristics of ‘good’ prescribers. For example, a difference in the prescribing of antibiotics was seen between GP registrar training and non-training practices (Steinke *et al.*, 2000a).

VARIATION IN PRESCRIBING AND MEDICATION COMPLIANCE

Prescribing may vary by patient factors that are independent of need or disease severity. For example, the variation of use of hormone replacement therapy by socio-economic status independent of need

(Evans *et al.*, 1997a). Compliance to labelled medication direction or therapy is a related issue. By assessing how patients collect dispensed medication, in terms of numbers of prescriptions dispensed and intervals between them, and linking to outcome data sets, patient compliance or non-compliance to medication can be studied. For example, a study in diabetes showed that adolescents in Tayside who have ‘brittle’ diabetes are often non-compliant with insulin (Morris *et al.*, 1997b).

PHARMACOECONOMICS AND HEALTH RESOURCE USE

Pharmacoepidemiology studies often have a pharmacoeconomic analysis ‘attached’ to the protocol. Both methods have specific objectives that are clearly defined and apparently independent. Pharmacoeconomic analyses have become more widely used over the past 10 years. Their primary use is for selecting more efficient drugs; in other words, those exhibiting a better relationship between acquisition cost and therapeutic effects and/or economic benefits. Pharmacoeconomic studies use the tools of clinical pharmacology, epidemiology and economics to obtain data on the effects (beneficial or harmful) of drugs and the costs of treatment alternatives.

MEMO has the ability to identify the drug, type of medication (either generic or proprietary), strength, amount and directions for use and therefore can accurately cost the medication for cost analyses. For example, a comparison of the use and cost of self-monitoring reagent strips and patterns of drug use by type 1 and type 2 diabetics was investigated by Evans *et al.* (1999, 2000). Both studies found a difference between the diabetes type and the cost of medication and health resource use.

CHRONIC DISEASES EPIDEMIOLOGY AND AUDIT

Diabetes Audit and Research in Tayside, Scotland (DARTS)

The MEMO/DARTS collaboration is a joint initiative of the Department of Medicine and MEMO at the University of Dundee, together with the Diabetes Units at three Tayside Health Care Trusts (Ninewells

Hospital and Medical School, Dundee; Perth Royal Infirmary and Stracathro Hospital, Brechin) and all Tayside GPs with an interest in diabetes care. They have combined their expertise to create the Diabetes Audit and Research in Tayside, Scotland (DARTS) initiative (Morris *et al.*, 1997a). It has been in operation since 1995, continually developing and gathering data from the population base of Tayside.

The MEMO/DARTS collaboration has used electronic record-linkage of information to create a robust clinical information system of all patients with type 1 and type 2 diabetes in Tayside whether they attend primary or secondary care. The DARTS database has information from many different sources including: patients attending hospital diabetes clinics, dispensed prescriptions for diabetes-related medication and monitoring equipment, patients discharged from hospital, patients attending a community-based mobile diabetic eye screening facility, glycosylated haemoglobin and plasma glucose results from the regional biochemistry database, and information collected from case records of patients in every general practice in Tayside. The register has been used for pharmaco-epidemiologic research (Morris *et al.*, 1997b,c).

Epidemiology of Liver Disease in Tayside (ELDIT)

The Epidemiology of Liver Disease in Tayside (ELDIT) study group has registered and validated a group of patients with potential and definite liver disease in Tayside for research purposes only. This disease register has a range of liver diseases that affect the whole organ including viral hepatitis (A, B and C) (Steinke *et al.*, 2000b), autoimmune hepatitis, alcoholic liver disease (Steinke *et al.*, 2000c), primary biliary cirrhosis and hepatocellular carcinoma (Weston *et al.*, 2000) and complications of liver disease like ascites. The ascertainment of liver disease by electronic record-linkage was maximised because of the unique integration of multiple sources of data to create a patient-specific information system. The specificity of virology, immunology and biochemistry tests increases the completeness of the data. Accurate incidence and prevalence rates of liver disease and its complications are used to ensure that hepatology services run effectively and efficiently.

Heart-disease, Evidence-based Audit and Research in Tayside, Scotland (HEARTS)

The latest addition to MEMO's disease management databases is the HEARTS database of cardiovascular disease in Tayside. This is a regional collaborative effort to support improvements in clinical care, education and research in cardiovascular disease and to provide GPs with information that will be useful for audit and clinical governance purposes. The database contains information on high-risk patient populations like those who have suffered a myocardial infarction (MI) and those who have undergone coronary angioplasty or artery bypass grafting (CABG). The database includes a variety of other cardiovascular diseases. For example, those with angina pectoris, peripheral vascular disease, ischaemic stroke, cardiac failure, hypertension and those undergoing primary prevention for cardiovascular disease. The aims of HEARTS are to identify and determine the risk factors of cardiovascular disease from a population base and to evaluate and determine whether medications are optimised in these patients. This information is fed back in various ways to GP practices in an effort to support them in improving care. HEARTS also provides high quality epidemiological data for research, understanding and care of similar patients and their families.

CONFIDENTIALITY AND ETHICS IN MEMO

Studies in MEMO use highly confidential, although anonymised, medical data. MEMO has an agreement with the Local Medical Committee of the British Medical Association never to divulge person-specific or GP-specific data, unless it is to a doctor requesting information on one of his or her own patients. All staff in MEMO sign confidentiality agreements and all databases are registered for research purposes with the Data Protection Officer. All studies in MEMO use de-identified data. The anonymisation process uses a randomly selected number mapped to the CHI number. The random number then becomes the link between databases. The Data Protection Officer is the only person that holds the mapping key. Ethics committees and Caldicott Guardians must approve study protocols before each study begins. Approved studies are logged in MEMO and may be audited

by Caldicott Guardians at anytime. Any changes to a study protocol require resubmission to the ethics and Caldicott Guardians for approval of the change. As data protection and ethical issues continue to evolve, MEMO will ensure that it meets the standards in both these areas (Data Protection Act, 1998).

STRENGTHS

PATIENT IDENTIFICATION

One of the greatest advantages with using data from Tayside is the unique patient identifier. This allows for relative ease of record-linkage and generation of comparator groups from the population. Selection of patients for both cohort and case-control studies is efficient.

POPULATION-BASED DATA

MEMO is regularly supplied with updated copies of the Community Health Master Patient Index from the Tayside Health Board, and uses this to track the population of patients alive and resident in Tayside to define study populations for drug safety studies. Such population-based data allow the calculation of incidence rates, excess risk and attributable risk.

DRUG EXPOSURE DATA

The data captured at MEMO represent prescriptions that have been dispensed at a pharmacy and so primary non-compliance is eliminated. In a study carried out to assess the extent of primary non-compliance in Tayside, a large family practice (11 500 patients) wrote all prescriptions in duplicate (carbon copy) form over a 3-month period (Beardon *et al.*, 1993). The copies were sent to MEMO. The original top-copy forms that were redeemed by the patients at community pharmacies were also returned to MEMO by PPD. Duplicate forms for which no original was present represented the prescriptions that were not redeemed.

A further advantage of Tayside is that there is currently no structure to inhibit the prescribing of newly marketed drugs. Thus, studies of new agents that penetrate the market at a high rate are possible.

ACCESSIBILITY TO MEDICAL RECORDS

A major strength of MEMO is the ability to examine original hospital records where necessary. Several studies validating the computerised diagnostic data with the case records have been carried out, with variable results depending on the criteria used (Kohli and Knill-Jones, 1992; Park, McCabe and Russell, 1992; Pears *et al.*, 1992). Within the National Health Service, such case record searching for the purposes of drug safety evaluation is ethically permissible once Medical Ethics Committee approval from the Caldicott Guardians has been obtained (HMSO, 1992).

WEAKNESSES

The current population of Tayside is approximately 400 000 people and is comparatively small, even for the study of commonly prescribed drugs. However, drug exposure data in Tayside are only available from 1989 and cover only a limited set of drugs until January 1993 from when all dispensed prescriptions have been collected. Scottish doctors are conservative prescribers of new drugs, so new agents tend to penetrate the market a few years after their launch. This limits the ability to study new chemical entities, arguably the most important and interesting drug group to study. Offsetting these disadvantages, the profile of certain diseases, for example cardiovascular disease, is higher in Scotland than in other populations and consequently the prescribing of drugs used in the prevention and treatment of these diseases is proportionately higher.

Another weakness, but one that is common to many drug safety databases, is the inability to capture directly exposure to over-the-counter drugs or drugs prescribed in hospital. Perhaps more importantly, the diagnostic indication for prescribing is not available to the researcher. In some cases, the indication for drug use may be clear; for example, glyceryl trinitrate is used primarily for angina. However, difficulties arise when a drug has more than one indication for use, leading to misclassification of exposure or outcome. For example, beta adreceptor-blocking drugs can be given for indications varying from anxiety to hypertrophic cardiomyopathy. This may be a potential source of error called confounding-by-indication that

is difficult to adjust for in pharmacoepidemiologic research if the information is not available.

MEMO cannot contact patients directly to elicit information on possible confounding factors. However, with the Ethical Committee's approval GPs can do this in a collaborative manner. Primary care and hospital records can also be checked and some data on smoking and alcohol can be retrieved from them, although the quality does vary (Evans *et al.*, 1998). This is also a method to identify outpatient diagnoses, which are not available electronically for record-linkage in MEMO. MEMO is therefore currently best suited for the study of serious drug toxicity that requires hospital admission.

One of the criticisms levelled at record-linkage studies is the inaccuracy of computerised medical diagnoses. The discharge diagnoses for SMR1 are abstracted from the clinical discharge summaries by specially trained coding clerks. These clerks on occasions have to interpret the 'soft diagnoses', such as symptoms, for which no cause can be found. In addition, non-standard terminology may be employed to describe an illness, for example eponymous terms, and so the coding of diagnoses may be imprecise. Computerised algorithms exist to detect and reject the most glaring errors, but errors of interpretation persist within any database. Several validation studies of the accuracy of hospital discharge data in Scotland have been performed comparing the coded diagnoses with diagnoses inferred by one or more senior doctors who have reviewed the original case records (Kohli and Knill-Jones, 1992; Park, McCabe and Russell, 1992; Pears *et al.*, 1992). The most pertinent of those studies carried out on Tayside data found 18% of internal medicine diagnoses to be clinically unacceptable (Pears *et al.*, 1992). Since the publication of this study, steps have been taken, mainly for resource management reasons, to improve the diagnostic accuracy of computerised data by involving clinicians in quality control. This initiative has substantially improved the diagnostic accuracy of records.

FUTURE DEVELOPMENTS IN MEMO

Dispensed prescribing data collection in MEMO is labour-intensive and expensive. The automated capture of computerised dispensed prescribing data

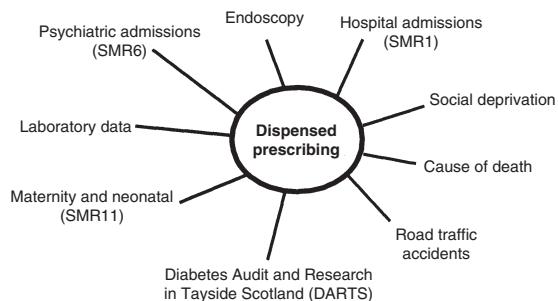


Figure 26.2. Data available to MEMO for record-linking.

has been investigated in five test pharmacies, a method that could eventually become Tayside wide or Scottish wide (McGilchrist and MacDonald, 1996). Of 200 000 prescription items from which data were collected using this methodology, a comparison with a sample of duplicate data collected by MEMO in the usual way showed that there was agreement for 98% of the items.

CONCLUSION

In conclusion, MEMO is a comprehensive record-linkage system that can be used for the detection and quantification of serious drug toxicity, outcomes research and pharmacoeconomic studies. The realisation of disease management also strengthens the capabilities of MEMO. Figure 26.2 summarises the record-linked data sets that are available in MEMO.

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The General Practice Research Database: Now and the Future

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INTRODUCTION

The General Practice Research Database (GPRD) is the world's largest computerised database of well-validated longitudinal patient records collected through the universal primary care system operated within the UK National Health Service (NHS). Almost all inhabitants are registered with a single general practice. Hospitals are required to inform general practitioners (GPs) of any significant medical events that occur in their patients. Long-term care of chronic conditions is typically managed by GPs. As a consequence, patients' medical records as managed by the GPs contain longitudinal information on all significant medical events and prescribing. They are essentially the lifelong record for each patient and include the key secondary care information as well as laboratory, other investigations and details of all medications prescribed within general practice. These GP records contain unique information for research.

The GPRD contains the anonymised patient medical records from GPs who use the Vision IT system from InPractice System Ltd (INPS) and who allow the

data to be exported from their clinical system to the GPRD. Only practices that meet continuous quality standards are included in the GPRD. At present, data are collected from over three million active patients throughout the United Kingdom, representing approximately 5% of the UK population. Longitudinally, it now includes twelve million ever-registered patients. The total amount of follow-up in the GPRD is as of 2006 over 46 million patient-years.

HISTORICAL OVERVIEW

The full history of the GPRD, since its creation in 1987, has been well documented elsewhere (Lawson, Sherman and Hollowell, 1998; Wood and Coulson, 2001). Since 2000, the database has been managed by the Medicines and Healthcare Products Regulatory Agency (MHRA) under its remit to safeguard public health. It is used within the Agency 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 United Kingdom) may be tested in the GPRD. Such hypothesis testing is in GPRD conducted not only by the MHRA but by pharmaceutical companies, academics and other regulators.

Given the importance of the GPRD to public health, the MHRA has made an extensive investment in staff and information technology required to store and obtain access to the data. The MHRA developed the Full Feature GPRD that has now been available for over 5 years. It provides world-wide users with online access to a data warehouse. It was developed as not every researcher has access to the large data storage capabilities required to house the full data set or the experience of using powerful data manipulation and analysis tools as available in SAS or STATA. Researchers can access, through the Full Feature GPRD data warehouse, anonymised patient records alongside markers relating to the quality of the data, which are set during the data loading process. These markers include

- (i) the acceptable patient flag, which relates to the internal consistency of key patient data including age, gender and registration status, and
- (ii) the practice up to standard date, which defines the first date at which the practice to which the patient is registered met the GPRD-derived minimum standards for data recording quality (Wood and Martinez, 2004).

In addition to the quality markers, a variety of other parameters, which increase the research utility of the data, are calculated during the data-loading process. Owing to the rapid increase in size of the GPRD data set and the volume of queries being run across the Web system, the GPRD has recently become available in a variety of other formats. This includes flat files for large subsets of the GPRD that can be loaded into statistical software packages.

CHARACTERISTICS OF GENERAL PRACTICE RESEARCH DATABASE 2005

Table 27.1 lists the main characteristics of the GPRD in 2005. It should be recognised 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 GPRD more valid:

- Demographics, including the patient's age and sex.
- Medical diagnosis, including free-text comments.
- All prescriptions and immunisations 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 GPRD 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 that 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 GPRD 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. Data from the practice records are submitted to and analysed by the Quality Management and Analysis System (QMAS), a national IT system, that supports the QOF payment process. Achievement is measured against indicators in four domains; most importantly, the clinical

Table 27.1. Summary of key characteristics of GPRD 2005.

Data source	UK general practice computer system containing detailed data on primary care activities as well as laboratory and hospitalisation data
Size	Three million active patients, twelve million ever-registered patients
Geographic cover	Good samples of United Kingdom. Representative of UK age, sex and socio-economic class
Access to data and/or research	Through a variety of means, online, flat file or data cubes for own research use. GPRD has a large in-house team of epidemiologists and statisticians
Quality of data	GP data are entered into GPRD only after meeting data quality checks
Longitudinal nature	Data back as far as 1987 for some practices
Standard information in GPRD	Registration file, drug prescribing, primary care diagnosis, laboratory data, immunisations, hospital discharge and referral summaries, death data and lifestyle factors. Most of this information is coded
Coding of data	Read clinical terms are currently used for coding of medical data. This has been matched to the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The Multilex dictionary is used for coding prescription information and is linked to anatomical therapeutic chemical classification (ATC) codes
Additional information on request	Anonymised free-text data as entered in the medical records, possibility to seek additional information from the GP
Governance	Not for profit, ISAC, central ethics approval
Users	World-wide regulatory authorities, pharmaceutical industry, academics and public health departments

domain, which focuses on a range of indicators in 11 key disease areas. 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 GPRD 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 500 GPRD-based peer-reviewed publications, nearly 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 GPRD. A large study recently examined the validity of the computerized diagnoses of autism in the GPRD. Anonymised copies of all relevant available clinical reports, including GP's 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 GPRD is high (Fombonne *et al.*, 2004). Another study compared the distribution of the cause of death in GPRD to national mortality statistics and concluded that they were broadly similar. This provides further evidence that the GPRD population is broadly representative of the general population (Shah and Martinez, 2004).

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 compared the risk of non-fatal 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 non-fatal self-harm in adults prescribed SSRIs was greater than in those prescribed tricyclic antidepressants (Martinez *et al.*, 2005).

Most of the drug safety research in the GPRD has concerned the estimation of relative rates, i.e. 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, whereas 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 GPRD, 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 was found that a woman aged 65 years with rheumatoid arthritis, low body mass index (BMI) 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 individualised long-term probabilities can help to better quantify the risks and benefits associated with a treatment.

FUTURE DEVELOPMENTS IN THE UK NATIONAL HEALTH SERVICE

The UK government has initiated a large programme called the National Programme for IT (NPfIT) that is being implemented by an Agency called "Connecting for Health" (CfH). This programme is designed to change the IT systems of the NHS in England to foster seamless and improved care delivery. The implications for the GPRD of NPfIT and similar programmes in other parts of the United Kingdom are immense and are only beneficial to the utility of GPRD in pharmacovigilance and in the wider field of pharmacoepidemiology. Traditionally, a patient's medical record was stored on PC/server systems within the general practices. The future model is one in which the IT infrastructure is more centralised. This enables more rapid changes and updates to systems, coding

changes and drug dictionaries as well as providing high-level IT service to all practices regardless of size or location. The main objective is to allow seamless health care with a patient medical record being available appropriately across the health service. Thus, the GPRD will be obtaining data through improved and more simplified methods. The huge challenge for the GPRD will be the data size. The estimate of the size of the GPRD in 5 years is about 5 terabytes (5×10^{12} bytes); a pile of printed A4 pages 20 km in height. Within 10 years, GRID computing is expected to have become the standard for storing and analysing huge databases. In GRID computing, the original data sets do not leave their original server, but special middleware interrogates each server and downloads only data that are specifically needed or it may even run without actually downloading the data. 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 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.

CURRENT AND FUTURE DEVELOPMENTS IN GENERAL PRACTICE RESEARCH DATABASE

The data in the GPRD is a person-level data set with the linkage to other information currently undertaken within the primary care system by the GP and his staff. This is, in many ways, the ideal situation as the GP, or other primary care healthcare professionals, do the disease coding at the time of consultation. Increasingly, the information within the UK NHS is being communicated electronically using the NHS number unique for each patient. Table 27.2 lists the major changes in GPRD data collection that are happening. Laboratories are now sending biochemistry results electronically to the GP, and this information can be loaded electronically into the GP medical records. Over the years 2002–05, the amount of biochemistry data in the GPRD has increased three fold due to increases in the number of tests undertaken, the fact that tests are grouped for common requirements

Table 27.2. Developments in data collection in GPRD.

	Pre-2003	2003–06	2007–
Primary care diagnosis	Coded by GP	Coded by GP	Coded by GP and algorithms
Symptoms	Coded by GP	Coded by GP	Coded by GP
Laboratory data (biochemistry)	Manual data entry following telephone call or letter	Drag and drop from email	Automated data entry through NHS number
Hospitalisations	Manual data entry of discharge letter	Email of discharge letter	Automated data entry through NHS number
Microbiology	Manual data entry following telephone call or letter	Drag and drop from email	Automated data entry through NHS number
Hospital clinics	Manual data entry of hospital letter	Email/letter	Automated data entry through NHS number
Social care	Very little	Email/letter	Automated data entry through NHS number
Prescriptions in surgery	Prescriptions issued through GP system	Prescriptions issued through GP system	Prescriptions issued through GP system
Prescriptions dispensed by pharmacy	None	None	Full pharmacy – GP links through NHS number
Death data	Manual data entry of GP cause of death plus some coroners reports	Manual data entry of GP cause of death plus some coroners reports	Record linkage to national death certificates
Extended hospital records, procedures, drugs and number of bed days	Very little	Very little	Record linkage to Hospital Episode Statistics
Socio-economic	Practice level	Practice level	Small area level
Other geographic variable	Practice level only	Practice level only	Small area level
Other NHS or research data sets	Not possible	Not possible	Through trusted third party and NHS number

even when only one result was requested and automatic recording of these data (with better recording of results within normal reference ranges). Figure 27.1 shows the number of laboratory results as recorded in the GPRD over calendar year. It is likely that the introduction of the QOF has also directly impacted on the recording of tests in the GPRD. The framework focuses on key disease areas such as diabetes, hypertension and asthma; it is expected that specific tests are conducted (and the results recorded in the electronic record) in patients with diagnoses in these key disease areas. For instance, diabetic patients are expected to have a record of HbA1c or equivalent in the previous 15 months. Recording of HbA1c in 2004 was 13% higher than in 2003; the requirement under QOF to measure and record HbA1c levels for diabetic patients makes it likely that the increase in recording is not simply because of the general increase in

recording of test results in patient records resulting from the electronic transmission of test results.

The quality of GPRD recording of lifestyle factors such as weight, BMI, smoking and alcohol use is continuously improving and is not as reported by Ilkanoff *et al.* (2005) a limitation to using GPRD. The reason is that NHS has undertaken initiatives to improve data recording in GP practices and has linked quality standards in care and data recording to practice reimbursement. The GPRD currently only records prescriptions as written by the GP, but due to NHS IT initiatives, data from pharmacies on dispensed drugs may also become available over the coming years.

As of 2007, the GPRD will be using a trusted third party to enable record linkage to other NHS data sets. This linkage is planned for practice-level socio-economic class and complete death certificate information. It will be done at regular intervals and available to all researchers. Other linkages will only

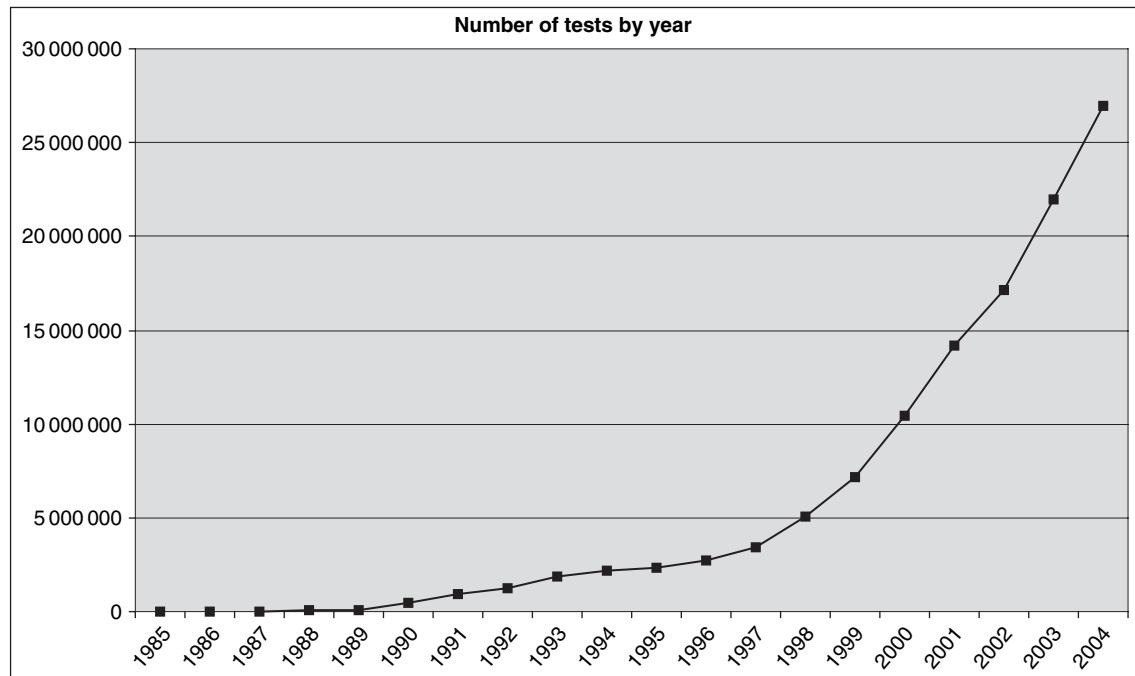


Figure 27.1. Number of all laboratory tests as recorded in GPRD.

Note: The increase is due to four factors – more tests being undertaken, a greater range of tests, greater recording of tests results in the normal range and the effect of tests being undertaken in groups even when a single test was requested.

be available subsequent to ethics and scientific protocol approval and only for that specific study as these linkages bring additional requirements for governance and data privacy. Detailed information on hospitalisations (including main procedures and number of bed days) may also become available.

The following programmes have been developed to allow even better use of the GPRD:

- **Risk-management programmes:** 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 GPRD Group has developed the Risk Management Knowledge and Tracking programme, which allow the monitoring of outcomes in drug users and importantly the key background information required for case assessment.
- **Surveillance programmes:** Patients prescribed a drug can be followed for selected outcomes. Further information (including hospitalisation 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.
- **Randomised 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 randomise patients 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 randomisation 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.

Current research governance guidance is to separate the scientific and ethical elements of protocol review, and the GPRD Group is currently working to implement new plans that will put its research governance arrangements on a robust footing with regard to current best practice. From March 2006, the Independent Scientific Advisory Committee (ISAC) for MHRA database research will be responsible for the scientific review of protocols for research using GPRD data. Members of this independent committee are appointed following a formal recruitment exercise run by the NHS Appointments Commission. The committee membership includes expert epidemiologists and statisticians as well as GPs and a lay member. Whilst the committee's remit with regard to protocols is confined to the scientific aspects of the proposed research, it will have the ability to refer protocols for further ethical review by an NHS Research Ethics Committee (REC) where the proposed research is not covered by the existing ethics approval.

STRENGTHS AND WEAKNESSES OF THE GENERAL PRACTICE RESEARCH DATABASE

The inherent strengths in the GPRD stem mainly from the NHS system of health care delivery, which essentially provides single UK cradle to grave healthcare delivery. General practitioners are the central health care providers in the United Kingdom, and thus, GPs have longitudinal medical records for their patients. The data subjects included in GPRD 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 GPRD 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 computerised information and to collect prospective data and samples is an additional major strength of this data set. The planned external record linkages will further enhance the utility of the

database. The GPRD is now used by several regulatory authorities and numerous pharmaceutical companies and as of the end of 2005 is available through a collaboration with the Medical Research Council (MRC) to UK academics.

Some of the traditional weaknesses of the GPRD 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 massive IT changes in the UK NHS. Drag and drop data entry into a patients record is now becoming the norm for laboratory data as well as hospitalisations. In the future, it will become fully automated.

A limitation of the GPRD, 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 standardised manner. Another challenge is for researchers to understand the complexity of this data set and to take into account the huge variability of patient characteristics and drug use. Association is not causation, and simplification of analysis can mean complication of result.

CONCLUSION

The GPRD is a widely used resource for studies in drug safety and pharmacoepidemiology. The GPRD is maintained and developed by the MHRA. The challenge is that analyses of GPRD data require a deep understanding of both the GPRD and the UK health care system. For example, there have been major changes in the reporting and collection of some laboratory data. Collaboration with researchers who understand the GPRD and the UK health care system may be helpful.

The GPRD is used by researchers internationally in academia, the pharmaceutical industry, the NHS and UK Government Departments for research in areas such as disease epidemiology, drug/vaccine utilisation and safety, pharmacoeconomics and resource utilisation. Its value in pharmacoepidemiology is highlighted by its ongoing use by drug regulatory authorities – namely the US Food and Drugs Administration (FDA) as well as the Post Licensing Division of the MHRA. Over 500 papers have been published

in peer-reviewed journals testifying to the quality of the data. A bibliography can be found on the GPRD website (www.gprd.com).

General Practice Research Database is indebted to the GPs who contribute the data from their clinical system; INPS, the supplier of the Vision software computer system, used by contributing GPs; and the members of the Scientific Ethical Advisory Group (SEAG) and the recent replacement group ISAC who give necessary oversight to the research conducted in GPRD.

In conclusion, GPRD is highly valuable for studies in drug safety and pharmacoepidemiology. Future developments will enable even higher standards of data collections and access to other data sets. The challenge is not only to further improve the granularity of information available in GPRD but also to enhance our methods for analysing these data.

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Overview of North American Databases

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INTRODUCTION

Large electronic databases can often meet the need for a cost-effective and efficient means of conducting surveillance after a new drug is marketed, and to establish baseline data prior to marketing. 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, Faich and Tilson, 2005). Large databases are often needed to address acute and serious regulatory, commercial and public health crises. Post-marketing studies of drug effects must generally include at least 10 000 exposed persons 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 (GPRD) in the UK (Gelfand, Margolis and Dattani, 2005), do not exist yet in North America. The resulting databases of health insurance claims are inherently different from medical record databases (Strom, 2005). Health insurance in the United States is

typically obtained through one's place of employment, and does not always include coverage for prescription drugs. The instability of this system is 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. However, strategies have been developed for selecting stable populations within a specific database and for addressing compliance, such as examining patterns of refills for chronically used medications. Most of the US health care programmes described in this chapter are employee-based, but may offer coverage to Medicaid and Medicare recipients as well, providing some representation of the elderly and the economically disadvantaged in its databases.

Beyond the employer-based health insurance programmes are the US Medicaid programme, which provides medical care, including prescription drug coverage, for economically disadvantaged and disabled persons, and the Medicare programme, which provides health care to persons aged 65 and older. The latter is now undergoing changes to include a prescription drug programme. In contrast to the variety of health care systems for selected eligible subsets

of populations in the United States, Saskatchewan, a province in Canada, provides a publicly funded health system for all of its 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 per patient 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 pre-marketing testing. 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 include interim diagnoses and recurrent or chronic, as opposed to acute, events. Information on potential confounders, such as smoking and alcohol consumption, and such information as time of menarche and menopause, 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 and useful for assessing compliance with the medication regimen as well as for obtaining information on other factors that may relate to drug effects. Information on drugs taken intermittently for symptom relief, over-the-counter drugs 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, Strom and Poole, 2005), 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 post-marketing surveillance.

In the following sections we will discuss the databases associated with four major US health plans, one Canadian health plan, a unique consortium of health plans created to meet the needs of the research communities, and a special-purpose database.

GROUP HEALTH COOPERATIVE OF PUGET SOUND

Group Health Cooperative of Puget Sound (GHC) is a health maintenance organization (HMO), established in 1947, which provides health care on a prepaid basis to approximately 562 000 persons in Washington State, located in the northwestern corner of the United States (Saunders, Davis and Stergachis, 2005). Three-quarters of these enrollees receive all their care at Group Health facilities. A fifth of the total number of 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 58 500 Medicare, 30 000 Medicaid and 18 000 Washington Basic Health Plan recipients, thereby expanding its membership to include elderly and low-income residents (Saunders, Davis and Stergachis, 2005).

GHC offers comprehensive health care coverage for outpatient care, inpatient services, emergency care, mental health services, and prescribed drugs, although the latter are not provided to Medicare enrollees new to GHC since 1993. 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.

The socio-demographic profile of GHC enrollees is generally comparable to that of the population of the Seattle-Tacoma area, with the GHC enrollees somewhat better educated. The median income of both groups is similar, although the GHC membership is less representative of the highest income category.

Multiple database files exist, and date from varying time-points. The current enrollment file consists of some 562 000 individuals; historical files contain records for some 2 million persons enrolled in GHC at any time since 1980 (Saunders, Davis and Stergachis, 2005). 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 currently 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 (DRG) 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 MRI and CT 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 SEER (Cancer Surveillance, Epidemiology and End Results) 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 13 SEER population-based registries in the United States (see <http://seer.cancer.gov/AboutSEER.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 (see section on Vaccine Safety Datalink (VSD) later in this chapter), 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 is estimated to be approximately 15% per year (Saunders, Davis and Stergachis, 2005). Since Group Health has been in existence for more than 50 years, a subset of enrollees can be identified whose tenure spans decades.

The GHC databases have been widely used for pharmacoepidemiologic research (Saunders, Davis and Stergachis, 2005), and GHC contributes to the HMO Research Network (see section below). Limitations to the GHC databases include its 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; loss of drug coverage for its Medicare enrollees; 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.

KAISER PERMANENTE MEDICAL CARE PROGRAM

The Kaiser Permanente Medical Care Program is the largest and one of the oldest pre-paid group model health care systems in the United States (Selby *et al.*, 2005). With more than eight million members in nine states, the programme is divided into eight administrative regions, seven of which have their own research centers. Each research center operates as a distinct entity, using only its own regional databases. The two oldest research centres, 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). Both centres have made major contributions to pharmacoepidemiology, including developing strategies for dealing with methodological 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 (Selby *et al.*, 2005). Four of the Kaiser HMOs participate in the HMO Research Network (see below).

KAISER PERMANENTE NORTHERN CALIFORNIA

Kaiser Permanente's largest and oldest regional entity is in Northern California, and now serves approximately 3.1 million enrollees in a 14-county area that includes the Oakland–San Francisco Bay and Sacramento metropolitan areas (Selby *et al.*, 2005). About 30% of the population in the area covered by this region of Kaiser Permanente is enrolled, mainly through employment; 13% receive some Medicare coverage, bringing the proportion of members 65 and older close to the proportion in the general population (Selby *et al.*, 2005). 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 under-representation 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 programme for relatively long periods of time. 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 15 million prescriptions per year. Information on each prescription is entered into the database prior to its being

dispensed, and includes patient and prescribing physician identification numbers, drug name, National Drug Code (NDC), dose, therapeutic class, date dispensed and prescription cost. Nearly all prescriptions are captured for the 94% of members who have the drug benefit (Selby *et al.*, 2005).

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.

KAISER PERMANENTE NORTHWEST

Kaiser Permanente Northwest (KPNW) serves over 440 000 members, approximately 25% of the population of the membership area, which includes the Portland (Oregon)–Vancouver (Washington) metropolitan area (Selby *et al.*, 2005). The distribution of the membership by age, race and gender proportionately reflects that of the population of the Portland–Vancouver area. 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. Most of the members are covered by a prepaid drug benefit; for the less than 10% without the drug benefit, prescriptions are provided at or below prevailing community charges.

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 code, 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 more than 900 000 KPNW members (Selby *et al.*, 2005). Spin-offs of subsets of these files can make these data accessible for research purposes.

EpicCare® has served as the prototype for HealthConnect®, which is currently being implemented across the Kaiser Permanente Program. This new program collects information not currently collected 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. This information will allow 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. A genetics registry of more than 5 million members of the Northwest Division and the Northern and Southern California regions was begun in 1986, with Hawaii joining this registry in 1992.

The KPNW Center for Health Research also maintains multiple databases that provide data on outpatient utilization, information on health status and behaviours 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 Center for Disease Control and Prevention (CDC) (see below).

The KPNW membership mostly reflects the population of the area it serves, although again the poor and the very wealthy are under-represented. The membership is relatively stable after one year; the median length of enrollment retention is more than 5 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.

UNITEDHEALTH GROUP

UnitedHealth Group provides a continuum of health care and specialty services to more than 16 million members throughout the United States through HMOs, point-of-service arrangements, preferred provider organizations, managed indemnity programmes, Medicare and Medicaid managed care programmes and senior and retiree insurance programmes (Shatin, Rawson and Stergachis, 2005). 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. Unique member identifiers allow for tracking across enrollment periods, so that a member can be followed through disenrollment and re-enrollment. Participating providers include 3300 hospitals and more than 400 000 physicians (Shatin, Rawson and Stergachis, 2005).

The 11 UnitedHealth Group-affiliated health plans in the research databases are geographically diverse, with plans in the Northeastern, Southeastern, Midwestern and Western regions of the United States. These databases were begun in 1990, with 3.8 million members and 2.8 million member-years, representing commercial, Medicaid, and Medicare recipients (Shatin, Rawson and Stergachis, 2005). 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 under-represented in other databases as well, since most UnitedHealth members are enrolled in employment-based plans.

The research databases are compiled from 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. Claim forms must be submitted by a health care 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, and enable 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 Group has no data on drugs that cost less than the copayment amount, and inconsistent data on those eligible for Medicare, as noted above. 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.

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.*, 2005). 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 programmes for specific groups of persons who do not qualify for federally supported programs. Services provided by the states under the federal Medicaid programme 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 health care services, Medicaid functions as a payer

for eligible services provided by participating physicians, hospitals and pharmacies. Of the US population 16%, or 51 million persons, received health care services through Medicaid in 2002, serving as the largest health insurance programme in the United States (Iglehart, 2003). 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. These are the populations that are often under-represented in randomized trials.

The Medicaid programme is administered by the Centers for Medicare and Medicaid Services (CMS), which has established a mechanism for researchers for obtaining 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 (MSIS) are also available. Support for the process of obtaining files and technical assistance in the use of the data is 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 a commercial data vendor, a common source of Medicaid data in the past (Hennessy *et al.*, 2005).

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 programme 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. NDC Codes 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 programmes), 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 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. More than 10 states have over a million Medicaid recipients each; prescriptions for the top medication dispensed numbered 9.3 million prescriptions (for albuterol) for the total Medicaid programme in 2001. Far down the list, ranked at number 50, were prescriptions for trimethoprim/sulfamethoxazole, accounting for 2.4 million prescriptions (Hennessy *et al.*, 2005).

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, environmental exposures, illicit drug use, alcohol use, occupation, family history and use of over-the-counter drugs.

The International Classification of Disease Ninth Revision – Clinical Modification (ICD-9-CM) is the coding scheme for diagnoses. 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. Although a mechanism exists through the recently implemented Health Insurance Portability and Accountability Act (HIPAA) for requesting hospital records of specific patients without patient contact, the willingness of hospitals to use this mechanism has yet to be gauged. Studies where primary record confirmation is less important are those which focus on drug-to-drug relationships, or studies which can use drugs or procedures as markers of diagnoses.

HEALTH DATABASES IN SASKATCHEWAN

Saskatchewan is a province in western Canada with a stable population of about 1 million people, or about 3.2% 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 9% 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 2004, more than 3500 drug products were listed (Downey *et al.*, 2005). The drug database contains information from September 1975, with an 18-month hiatus in 1987–88 when data were incomplete. The database includes patient, prescriber, pharmacy and cost information. Drug information includes pharmacologic-therapeutic classification, using the

AHFS classification system, active ingredient, generic and brand names, strength and dosage form, drug manufacturer, 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. Approximately 8.4 million prescription claims were processed by the drug plan in fiscal year 2002–03 (Downey *et al.*, 2005).

Data from hospitalizations, including day surgeries, include up to three discharge diagnoses (ICD-9 codes), up to three procedures, an accident code (ICD-9 external cause 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. In 2001–02 there were approximately 140 000 inpatient separations (discharges, transfers or deaths) of adults and children (Downey *et al.*, 2005).

Physician services data are obtained from claims, and include diagnoses (three-digit ICD-9 codes) 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 given only to support the claim for payment, and only one three-digit ICD-9 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 are only available in patient records or through direct patient contact.

HMO RESEARCH NETWORK

The HMO Research Network is a consortium of 14 health plans that collaborate to perform public domain research. Each of these health plans has linkable automated pharmacy, claims and membership data, and so are capable of identifying important safety problems within a reasonable time following the marketing of many new drugs. Some also have automated medical records and laboratory data. Ten of the Network plans, with a total population of almost 11 million, have been funded by the US government as a Center for Research and Education in Therapeutics (CERTs), bolstering their efforts to create and maintain the infrastructure needed to support research and education in therapeutics, including the standardization of data, provision of central programming support and mapping of drugs to a standard formulary (Chan *et al.*, 2005). The HMOs participating in this effort are Harvard Pilgrim Health Care, which leads the CERTs, GHC of Washington State and Northern Idaho, Health Partners Research Foundation in Minnesota, Meyers Primary Care Institute/Fallon Healthcare System in central Massachusetts, Lovelace Health System in New Mexico, UnitedHealthcare, with health plans in several states, and four of the Kaiser Permanente HMOs: Kaiser Permanente Northern California, KPNW, Kaiser Permanente Georgia and Kaiser Permanente Colorado. Outside of the CERTs and also part of the collaboration are four additional plans: the Henry Ford Health System – Health Alliance Plan in Michigan, Kaiser Permanente Hawaii, Kaiser Permanente Southern California and Scott and White Memorial Hospital in Texas. These remain separate

data resources, however, and each HMO can elect to participate, or not, in any given study.

The populations involved are ethnically and geographically diverse; the CERTs HMO Research Network represents approximately 4% of the US population. Membership in the respective health plans remains relatively stable, with annual turnover rates between 10% and 15%. Retention rates tend to be higher among patients with chronic diseases.

With the advent of confidentiality requirements stipulated under HIPAA, each participating health plan prepares its own data, stripping them of any patient identifiers while preserving the link between the unique number assigned to each patient and the plan identifier within that plan's locked file. All dates are converted to age at a certain event (diagnosis, hospitalization, etc.) to further preserve the patient's identity. Datasets are prepared and tailored for each protocol. Once formulated and de-identified, they are forwarded to the Channing Laboratory at Harvard for analysis. When necessary for confirmation of diagnoses or obtaining information on confounders, medical records can be retrieved at the participating sites.

VACCINE SAFETY DATALINK: A SPECIAL PURPOSE DATABASE

In order to identify rare vaccine adverse events, the CDC funded the Vaccine Safety Datalink (VSD), a large database that brings together computerized information on immunizations, medical outcomes and potential confounders. The VSD has been used to evaluate hypotheses from the medical literature, from the VAERS, from changes in immunization schedules, and from the introduction of new vaccines. Beginning in 1991, CDC joined with four HMOs, GHC, KPNW, Kaiser Permanente Northern California and Kaiser Permanente Southern California, all in the western part of the United States. Up to ten HMOs have been utilized for specific studies (DeStefano, 2001), capitalizing on the efficiencies offered by HMOs for population-based health research. Initially focusing on children up to 6 years of age, the database now includes adolescents and adults as well, and totals to approximately 6 million members (DeStefano, 2001). Information on all vaccinations given within the HMO study population, either routinely or for special

indications, is computerized, including the vaccine type, date of vaccination, concurrent vaccinations, the manufacturer and lot number and site of vaccination. Outcome data are collected from various sources at each site, such as hospitalizations, emergency department visits and outpatient clinic visits. To preserve patient confidentiality, each site assigns unique study identifiers to its data before shipping to the CDC annually for merging and analysis (Chen *et al.*, 1997).

Quality control studies have shown high levels of agreement between computerized data and paper medical records. A quality control analysis of three of the HMOs comparing the automated database with paper records for common childhood vaccines showed that from 83% to 99% of the automated records were present in the paper records, and from 82% to 98% of the paper records were present in the automated database (Mullooly *et al.*, 1999).

WEIGHING IN

Selecting an appropriate database for the investigation of drug effects warrants consideration of multiple factors. Once it has been determined that a specific drug or set of drugs under investigation is on the formulary, the relative size of the prospective databases may be an important consideration, as the process of evaluating the occurrence of rare effects requires large numbers of users of the drug(s) in question. UnitedHealth and Medicaid offer the largest databases, although UnitedHealth is not population-based. GHC is the smallest of these North American databases, but it contains information on inpatient drug exposures. The combined HMO Research Network is an important new option for large-scale post-marketing drug studies.

Saskatchewan contains a stable, representative, population-based database, in which loss to follow-up is minimal, making it more desirable for studying outcomes that have a delayed effect. Among the US databases, Kaiser is the most stable, with 3% loss a year after the first 2 years of enrollment. Compared to the total populations in the areas they serve, the members of GHC, Kaiser and UnitedHealth are disproportionately employed. Medicaid recipients over-represent the poor and disabled.

Drug data vary in their completeness across the databases. Medicaid data would be the most complete, as the formularies are the least restrictive, and Medicaid patients are unlikely to purchase drugs outside of the insurance plan, as they are economically disadvantaged individuals who can obtain them without charge through Medicaid. Saskatchewan drug data are likely to be complete, if the drug is on the formulary. GHC is missing drug data on Medicare patients, that is, the elderly. Kaiser and UnitedHealth lack pharmacy benefits for 6%–7% of their populations, and Medicare drug benefits vary depending on the specific plan, so pharmacy files may be incomplete in this age range. Most health plans lack the means of assessing drugs purchased that cost less than the plan's copay, or drugs purchased prior to the patient's meeting the annual deductible (e.g., HMOs) or after the patient has reached the drug benefit limit. This is not a problem for Medicaid data.

Outpatient diagnosis data are available for the described health plans, but are limited in Saskatchewan to only one code per visit, and only three digits of the five-digit ICD9-CM code are used.

Access to medical records is often crucial for verifying diagnoses, characterizing the severity of a diagnosis, and for obtaining data on important potential confounding variables not found in the computerized data. This access has been possible with all these databases, but is no longer feasible in Medicaid for reasons of confidentiality; other databases that rely on claims may begin to suffer from the same problems. The HMO Network has been resourceful in meeting the HIPAA requirements, and can draw on the relative strengths of the participating entities as needed for specific studies. Essential requirements for their studies are carefully designed and well-coordinated planning in the preparation of the individual datasets by each participating entity.

None of these databases can assess the use of over-the-counter drugs, complementary/alternative therapies or physician or other professional samples. Patient compliance has not been directly measurable, although the benefit of a claims database compared with use of physician records is knowing that not only was a prescription written by the physician, it was also dispensed by the pharmacist. Prescriptions that are renewed suggest that the patient was indeed taking the

drug. The extent of use of drugs taken intermittently for symptom relief is difficult to assess.

Of course, much of this will likely change over the next few years, as US Medicare begins paying for drugs for the elderly for the first time. On one hand, this represents the potential for the largest database yet created, if available to researchers. On the other hand, it may create huge gaps in the other databases. This will need to be watched closely as the programme evolves.

The growing adoption of electronic medical record systems in the US 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 with the UK GPRD (Gelfand, Margolis and Dattani, 2005). Systems must be established to monitor the quality of data entry by health care 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 would be a rich complement to claims data for future pharmacoepidemiologic research.

CONCLUSION

Electronic databases are useful in hypothesis testing of signals from pharmacovigilance as well as drug safety surveillance. The speed with which data can be accessed and the relatively low cost of their use make these databases excellent resources.

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Other Databases in Europe for the Analytic Evaluation of Drug Effects

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INTRODUCTION

A systematic review of the abstracts presented at the 16th and 21st International Conference on Pharmacoepidemiology in 2000 and 2005, respectively, showed that the majority (53% and 51%) of submitted European pharmacoepidemiological studies were conducted by means of automated general practitioner (GP), pharmacy or insurance data (Table 29.1). Little has changed between 2000 and 2005. The United Kingdom ranked highest in number in 2000, basically because of the wide use of the General Practice Research Database (GPRD) within the United Kingdom itself. In 2005, the majority of GPRD-based abstracts comes from outside the United Kingdom. Twenty-five abstracts were based on data from the GPRD, eight from the United States, nine from the United Kingdom, five from the Netherlands and three from Spain. The UK databases will not be further discussed in this chapter as they are covered elsewhere in this book.

In the ranking of abstracts that were based on automated databases, the first positions were taken by Denmark, The Netherlands and Italy, which were consistent in 2000 and 2005. Spain ranked high in 2005 because of the use of the GPRD by the Spanish Center for Pharmacoepidemiology (CEIFE). A Spanish general practice database is being established in collaboration with CEIFE (www.bifap.es), but validation processes are on its way.

The Netherlands is well known for the PHARMO Record Linkage System (www.pharmo.nl) and the Integrated Primary Care Information (IPCI) (www.ipci.nl) GPRD. Other dispensing databases (Interaction) are occurring, but little information is available on them so far. In addition, there are fixed cohort studies that are linked to pharmacy data (e.g. Rotterdam study) and have proven useful for pharmacoepidemiological research, but ad hoc studies fall outside the scope of this chapter. Pharmacoepidemiology in the Netherlands is strong because of the availability of various academic training and doctoral programmes, the organization of health care and

Table 29.1. Sources for European abstracts presented at the 16th International Conference for Pharmaco-epidemiology.

Country	Number of abstracts	Percentage based on automated sources (within country)	Drug utilization		Adverse or beneficial effects of drugs	
			Number of ad hoc studies	Number of studies with automated sources	Number of ad hoc studies	Number of studies with automated sources
Scotland	9	78		4	1	4
The United Kingdom	44	73	2	9	10	23
The Netherlands	28	71	3	9	5	11
Denmark	10	70		6	2	2
Italy	5	60	1	2	1	1
Hungary	2	50	1	1		
Norway	4	50	2	2		
Sweden	6	50	1	1	2	2
Spain	15	33	5	5		
Germany	14	21	4	3	7	
France	17	6	6	1	10	
Belgium	2	0	2			
Portugal	2	0	2			
Switzerland	2	0			2	
Total	160	53.8	29 (18.1%)	43 (26.9%)	45 (28.1%)	43 (26.9%)

Automated sources include GP records, record linkage systems, insurance claims data or drug sales data.

the availability of high-quality data (Leufkens and Urquhart, 2005).

Denmark is well known for its regional and national dispensing databases that can be linked to other national registries such as the cancer, mortality and hospitalization registry. Initially only Jutland and Funen county had prescription databases, but since 2003 the national prescription database can be used and linked to other registries at Statistics Denmark. This creates the unique possibility to study an entire country and provides a strong backbone for pharmacoepidemiologic research in Denmark.

The Italian story is quite different. In 2000, the Italian studies were mostly based on claims databases that are compiled for National Health Service (NHS) payments (regional or local). Nowadays access to regional databases is complicated because of privacy legislations. Local databases are sometimes used for pharmacoepidemiological studies, but not all have the same structure and quality, combination of these databases at a local level may provide opportunities in the future. Since 2000, a general practice database (former name Health Search) and paediatricians' medical record database (PEDIANET) have

gained importance in the field of pharmacoepidemiology. Both of these databases will be discussed.

The results from the abstract review underline that national differences in the organization and reimbursement of health care have a major impact on the possibility to conduct pharmacoepidemiologic research (Leufkens and Urquhart, 2005). The countries with the highest numbers of abstracts are flourishing because of specific features of the systems for health care delivery and the presence of (pharmaco)epidemiologists. Italy has many databases that are suitable for pharmacoepidemiological research, but the output is limited so far because of the scarcity of academic (pharmaco)epidemiology programmes.

This chapter describes general practice and record linkage databases from the Netherlands, Italy and Denmark, which have yielded peer-reviewed pharmacoepidemiological papers during the period 1990 and 2005. Since the quality of databases depends on the health care systems they are embedded in, a summary of the major health care characteristics will be provided for each of these countries. Table 29.2 provides a systematic overview of the characteristics of the databases.

Table 29.2. Characteristics of multi-purpose automated databases in Italy, The Netherlands and Denmark.

Characteristics	Italy		The Netherlands		Denmark
	Pedianet	Health Search	IPCI	PHARMO	OPED/PDNJ/ National database
Current source population	160 000 children	800 000	700 000	2 000 000	>2 million together OPED/PDNJ/5.2 million national database
Demographics					
Unique identifier for linking of files	Yes	Yes	Yes		
Registration date	Yes	Yes	Yes	No (based on first prescription)	Yes
Date of transferring out	Yes	Yes	Yes	No (based on last prescription)	Yes
Date of death	Yes	Doubtful	Yes	No	Yes
Insurance type	Yes	NHS and private	Yes	Yes	NHS only
Date of birth	Yes	Yes	Yes	Yes	Yes
Gender	Yes	Yes	Yes	Yes	Yes
Race	Yes	No	No	No	No
Socio-economic status	No	No	Yes	No	Yes
Prescriptions					
Unique product code	Yes (MINSAN)	Yes (MINSAN)	Yes (HPK)	Yes (HPK)	Yes (Varenummeret)
ATC code	Yes	Yes	Yes	Yes	Yes
Date of Rx	Yes	Yes	Yes	Yes	Yes
Quantity	Yes	Yes	Yes	Yes	Yes
Dosing regimen	Yes (50%)	No	Yes	Yes	No
Indication	Yes	No (derived from date)	Yes	No	No
In-patient use of drugs	No	No	No	No	Not yet
Prescription drugs	Yes (independent of reimbursement)	Yes (only reimbursed)			
OTC drugs	No	No	Not validly	No	No
Outcomes					
Symptoms	Yes	Yes	Yes (free text/ICPC)	No	No
Out-patient diagnoses	Yes (ICD-9)	Yes	Yes (ICPC)	No	No
Hospitalizations	Yes	Yes (ICD-9)	Yes	Yes	Yes (OPED not routinely)
Outpatient specialist care	Yes	Yes	Yes	No	No
Values of laboratory measurements	Yes	Yes	Yes	In subset only	No (partially in PDNJ)

(continued)

Table 29.2. *Continued.*

Characteristics	Italy		The Netherlands		Denmark
	Pedianet	Health Search	IPCI	PHARMO	OPED/PDNJ/ National database
Costs	Only resource use	Only resource use	Only resource use	Yes (drugs/ hospitalization/ inpatient procedures)	Yes (drugs/ hospitalization)
Potential confounding factors					
Smoking	–	Yes	Yes	No	No
BMI	Yes	Yes	Yes (incomplete)	No	No
Cardiovascular risk profile	Yes	Yes	Yes (incomplete)	No	No
Indication	Yes	Yes	Yes	No	No
Access					
Raw data	Yes (at site)	Yes at SIMG/Segedim	Yes (at Erasmus University)	Yes (in PHARMO Institute)	Yes at Statistics Denmark
Original medical charts	Yes	Yes	Yes (discharge letters)	Yes (discharge letters)	No
Additional data collection from patient	Yes (possibility to insert software modules for prospective data collection)	Yes	Yes	No	No
Contact person/site	Carlo Giaquinto (carlog@unipd.it) and www.pedianet.it	Carlo Niccolai (niccolai. carlo@ simg.it and www.simg.it)	m.sturkenboom@ erasmusmc.nl and www.ipci.nl	ron.herings@ pharmo.nl and www.pharmo.nl	Jesper Hallas/David Gaist (OPED) (www.sdu.dk/health/research/units/clinpharm.php)/ Sørensen (PDNJ) (www.clin-epi.dk)

MINSAN codes are collected but are not provided as raw data.

THE NETHERLANDS

GENERAL PRACTICE SYSTEM

The Dutch system of health care is based on GPs who practice in the community but not in the hospital, referring ambulatory patients to specialists for outpatient or inpatient care. Specialists report their findings to the GP, who acts as a gatekeeper. Approximately 90% of the patients' presenting problems are addressed by the GP

(van der Lei *et al.*, 1993; Leufkens and Urquhart, 2005) time staff physicians who are specialists of various kinds provide hospital care. Medical care, including prescription drugs, is paid for by various insurers, which provide a basic service to all citizens. Patients can only be registered with one GP but are free to change, which happens infrequently and nearly always because the patient moves out of the area. When a patient transfers, so does the record. More than 75% of the patients will visit their GP at least once per year (van der

Lei *et al.*, 1993). The high degree of computerization of GPs has given rise to the birth of several GP networks; most of them are connected to one of the seven University Centres. One of the largest research-oriented GP databases is the IPCI database, which has been created with the specific purpose to conduct pharmacoepidemiological studies (van der Lei *et al.*, 1993; Vlug *et al.*, 1999).

INTEGRATED PRIMARY CARE INFORMATION

In 1992, the IPCI Project was started by the Department of Medical Informatics of the Erasmus University Medical School, initially in collaboration with Intercontinental Medical Statistics (IMS). In 1998, IMS stepped out, and since then the database was run independently by the department of Medical Informatics in collaboration with the Pharmacoepidemiology Unit. Integrated Primary Care Information is a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs throughout the Netherlands that voluntarily chose to supply data to the database (Vlug *et al.*, 1999). General practitioners only receive a minimal reimbursement for their data and control usage of their data, through the Steering Committee and through the possibility to withdraw data for specific studies. The collaborating GPs are comparable to other Dutch GPs regarding age and gender.

As of January 2005, there are 120 practices belonging to more than 150 GPs that have provided data to the database. The first practice was recruited into the IPCI project in 1994. Practices have therefore been supplying data for varying periods. The database contains information on more than 700 000 patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of registered patients. Turnover occurs as patients move and transfer to new practices. The records of 'transferred out' patients remain on the database and are available for retrospective study with the appropriate time. As of December 2005, there were 400 000 active patients registered with the collaborating GPs, 49% was male and 57% was insured through the Sickfund, and the mean age was 38 years. In 2006, the IPCI database is expected to grow to cover a population of 1 million active subjects. This is achieved by extending data retrieval to GPs with other GP information systems than the original ELIAS system alone. Data

are downloaded on a monthly basis, and the information is sent to the gatekeeper who anonymizes all information before further access is provided.

The database contains anonymous patient identifiers, demographics and eligibility dates (date of birth, sex, patient identification, insurance, date of registration and transferring out and date of death), notes (subjective and assessment text), symptoms, signs, prescriptions, and indications for therapy, physical findings, referrals, hospitalizations and laboratory values. All data are directly entered into a computer during the consultation hour where it is stored (see Figure 29.1 for database structure). The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text that is available as raw data (Lamberts and Wood, 1987). Prescription data such as product name, quantity dispensed, dosage regimens, strength and indication are entered into the computer to produce printed prescriptions (Vlug *et al.*, 1999). The National Database of drugs, maintained by the Z-index, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO (de Smet, 1988).

Access to original medical records (discharge letters of hospitals) and administration of questionnaires to GPs is possible through the gatekeeper but only after approval of the IPCI Steering Committee. Data accumulated in the IPCI database have proven to be of high quality and suitable for epidemiological and pharmacoepidemiological research (Vlug *et al.*, 1999). Data can be used for research purposes, but because of the privacy issues related to the presence of clinical notes access is possible only at the Erasmus University Medical Centre and after approval of the Steering Committee.

The database has been used for studies on disease occurrence (Eland *et al.*, 2001, 2002; Verhamme *et al.*, 2002; Straus *et al.*, 2004a; van Soest *et al.*, 2005) and drug utilization such as the change in prescriptions of terbinafine following a highly debated press campaign ('t Jong *et al.*, 2004) or appropriate prescribing in the elderly (van der Hooft *et al.*, 2005); adherence and persistence with treatment ranging from gastropreservation (Sturkenboom *et al.*, 2003a,b), antihypertensives, lipid lowering drugs,

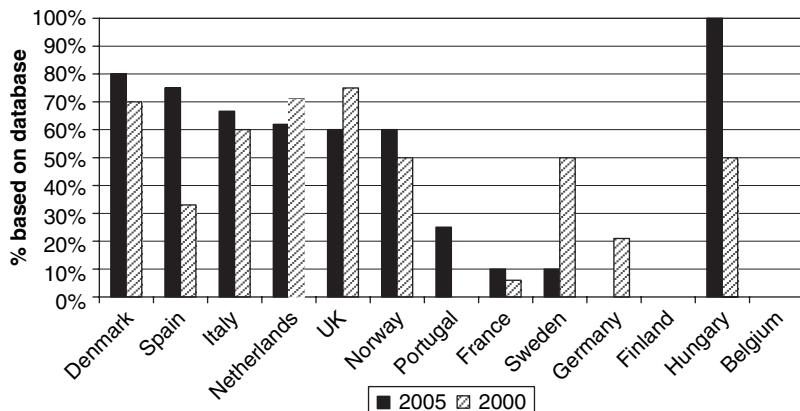


Figure 29.1. Percentage of epidemiological abstracts that were based on multipurpose automated database in 2000 and 2005 per country.

antidepressants and respiratory drugs and the association between adherence and treatment outcomes; effectiveness of drugs and vaccinations (Voordouw *et al.*, 2003, 2004; Dieleman *et al.*, 2005); and last but not the least, a variety of adverse drug reactions (Visser *et al.*, 1996; van der Linden *et al.*, 1998, 1999; Straus *et al.*, 2004b, 2005). For a complete updated list of publications, we refer to the website (www.ipci.nl).

Special features of the database comprise the possibility to conduct randomized database studies with naturalistic follow-up (Mosis, 2005a,b), pharmacogenetic studies and the possibility to return to patients and ask for additional information, such as reasons for non-compliance, quality of life and blood samples.

COMPUTERIZATION OF THE DUTCH COMMUNITY PHARMACY SYSTEM

Computerization of outpatient pharmacy records in the Netherlands is almost universal and so is (because of the patient's habit to frequent only one pharmacy) the compilation of longitudinal prescription drug histories. Although computerization has started for administrative (reimbursement) purposes, medication surveillance and computerized stock holding and ordering have become important incentives for optimal registration of drug dispensing. Computerized medication surveillance tracks change in dosages of chronic medications, correct dosing (especially

for elderly and children), contra-indications (deducted from previously prescribed medications) and interactions between concomitant medications. In case of 'abnormal' situations, a signal will be generated that needs to be verified by the pharmacist (Herings, 1993; Leufkens and Urquhart, 2005).

All information stored in pharmacy computers, independent of the employed software or hardware, is primarily based on the information written on a prescription order by a GP, dentist or specialist. The information that should be stated on this order is legally regulated and has to comprise the prescribed product, the date of prescription, name and residence of prescriber, a patient identifier (name) and the daily dose regimen. For reimbursement purposes, the amount dispensed is also available on each prescription (Herings, 1993).

The longitudinal data collection in pharmacies, the completeness of data and the fact that all prescription drugs are recorded (independent of reimbursement) make these data a useful source for pharmacoepidemiological research. They have served for national cohort tracking in case of drug alerts after which outcome data may be either linked or collected by ad hoc methods (Visser *et al.*, 1996). The PHARMO database is based on pharmacy data and is unique in the Netherlands for its record linkage with national hospitalization registries and recently in subsets also with inpatient pharmacy data, laboratory, cancer and pathology registries (www.pharmo.nl).

PHARMO

The PHARMO record linkage system was developed in the early 1990s by Herings and Stricker. It now includes the drug-dispensing records from community pharmacies and hospital discharge records of about 2 million community-dwelling inhabitants of 30 medium-sized cities in the Netherlands (www.pharmo.nl). Until 2006, patients in the Netherlands did not have a unique identifier. Therefore, the underlying source population is not exactly known, but it has been estimated by using information for each city from the Bureau of Statistics (CBS). Patients that are registered within the pharmacy files are regarded as non-residents and eliminated from the patient registers if they did not have recorded a family practitioner residential in one of the cities. Patients are assumed to be present in the source population between the first and last encounter in the pharmacy. For all residents, the drug-dispensing histories are linked on a yearly basis to the national hospital discharge records of the same patient, using a probabilistic algorithm, based on characteristics such as date of birth, gender and a code for the GP since no unique patient identifier was present until 2006. Validation of the initial database in 1993 (nine cities) showed that these registries are linked with a sensitivity and specificity exceeding 95%, which is comparable with record linkage systems based on unique personal identifiers (Herings, 1993).

The computerized drug-dispensing histories contain outpatient prescription data concerning the dispensed drug, type of prescriber, dispensing date, dispensed amount, prescribed dose regimens and the legend duration (prescription length). The hospital records include detailed information concerning the primary and secondary diagnoses, procedures and dates of hospital admission and discharge. All diagnoses are coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). Recently, PHARMO RLS has been linked to national pathology data and a regional cancer registry. For subsets of the database linkage with in-hospital drug use and outpatient laboratory data as well as primary care data are also available. Five years ago, the PHARMO record linkage system has been transferred from the Department of Pharmacoepidemiology and Therapeutics at Utrecht University to the PHARMO research institute.

The database has been used by the Department of Pharmacoepidemiology at Utrecht University and the PHARMO Institute for studies on drug utilization, persistence with treatment, economic impact and adverse drug reactions. For a complete updated list of publications that were based on PHARMO RLS data, the website can be inspected (www.pharmo.nl).

The impact of recent policy changes on the Dutch health care structure and quality of data in claims databases is unclear. The Dutch health care system is moving ahead in the direction of more market forces, freedom of choice by patients and more emphasis on cost containment and efficiency (Leufkens and Urquhart, 2005). The recording of diagnoses in the national registry of discharge diagnosis will change because of the introduction of a Diagnosis-Related Group (DRG) system, but the strong actuarial basis of the GP will continue. A national electronic patient record should exist by 2007 with the use of a unique national patient identifier. This identifier might facilitate record linkage, but its introduction will reinforce privacy legislations that may actually negatively impact on the possibility to conduct record linkage studies.

DENMARK

COMPUTERIZATION OF DANISH PHARMACIES

Similar to the Netherlands, GPs in Denmark act as gatekeeper to second line health care and provide most of the medical care. The majority (97%) of citizens are assigned a GP, who generate 90% of the prescriptions. Although initiatives have been taken to create GP databases, the most important source for pharmacoepidemiological studies in Denmark to date constitute data from the Danish pharmacies that became increasingly computerized in the 1990s and have allowed for the establishment of regional and national prescription registries (Gaist *et al.*, 1997). As part of its tax funded health care for all inhabitants, the Danish NHS provides medical attendance free of charge and reimburses 50% of all expenditure on a wide range of prescribed medicines independently of the presenters income and employment status. Measured in defined daily doses, 73% of all medication sold in Denmark in 1996 was on prescription (Gaist *et al.*, 1997).

The Danish NHS is divided into 16 sections. Each community pharmacy collects data on all prescription drugs and forwards data on reimbursable medicines to their local NHS section on a monthly basis. These data form the basis for the two prescription registries, the Odense University Pharmaco-epidemiological Database (OPED) and the Pharmaco-epidemiological Prescription Database of North Jutland (PDNJ) (Sorensen and Larsen, 1994; Gaist *et al.*, 1997). Publications from these databases are numerous and can be obtained from the departmental websites.

A third prescription register was established in 1995, the Register of Drug Statistics (RDS) at the Medicines Division of the National Board of Health, that collects information on all pharmacy transactions of prescribed drugs independent of reimbursement status and covers the entire population of 5.2 million inhabitants. Since 2003, study-specific access to these data is available through National Board of Health.

Denmark has a long tradition in registration; church files were established in 1645, and in 1968 the Danish Civil Registration System was established. This civil registration system, which is updated daily, is used in all registries and comprises the civil registration number (CRN), civil status, CRN of father/mother/children, death data, immigration and emigration. These data allow for exact assessment of follow-up time of all citizens. Other nationwide registries in Denmark are the hospital discharge registry, the cancer registry, birth registry, mortality files and the social registries.

PREScription DATABASE OF NORTH JUTLAND, ODENSE UNIVERSITY PHARMACO-EPIDEMIOLoGICAL DATABASE AND THE NATIONAL DATABASE

The OPED database covers the county of Funen (population approximately 470 000) persons, and PDNJ covers the county of Jutland and other (approximately 1.6 million persons) and together they cover a representative sample of 40% of the Danish population (Nielsen *et al.*, 1996; Gaist *et al.*, 1997). Dispensing claims data that are collected in the systems comprise a unique patient identifier, the CRN, that allows longitudinal tracking of the patient through

different layers of the health care system, the date of dispensing, the product code (unique for brand, quantity and formulation) and ATC code. The computerized drug-dispensing histories contain data concerning the dispensed drug, type of prescriber, dispensing date and dispensed amount. The prescribed dosing regimen (and therefore legend duration) is not recorded in the systems. Over-the-counter medication and non-reimbursed drugs (such as sedatives, hypnotics, oral contraceptives and laxatives) or in-hospital drugs use are not registered. Population data are obtained from the Central Registration System every 6 months to track migration or date of death. Completeness of reimbursed dispensed drugs has proven to be good (Gaist *et al.*, 1997).

Prescription data have been linked to local, regional and national hospitalization discharge data, cancer registries, psychiatric registry, death and birth registries for specific projects through the CRN in the PDNJ database (Nielsen *et al.*, 1999; Olesen *et al.*, 1999; Thrane and Sorensen, 1999; Dalton *et al.*, 2000; Fonager *et al.*, 2000; Larsen *et al.*, 2000; Sorensen *et al.*, 2000). For a more recent list of publications, the website 'www.clin-epi.dk' should be visited.

Almost all the OPED studies are based on prescription data only (Gaist, 1999; Bjerrum and Bergman, 2000). Odense University Pharmaco-Epidemiological Database and Prescription Database of North Jutland are public institution research registries. Data can be accessed upon approval of a protocol by the Steering Committees.

Data from the national prescription database can be linked to the hospital discharge registry, the cancer registry, birth registry, mortality files and social registries on the basis of the CRN. The Danish hospital discharge registry comprises data on 99.4% of all discharges from Danish hospitals and includes the CRN code, dates of admission and discharge, the surgical procedures performed and up to 20 diagnoses classified according to the ICD-10 classification of diseases (Andersen *et al.*, 1999). Access can be obtained for specific projects, but all analyses must be done in Statistics Denmark or by modem. Statistics Denmark links the registries and deletes the CRN. As there is no access to the CRN, paper records validation is not possible. Currently, the procedure for getting access to the data might take up to 6 months and is project related.

ITALY

HEALTH CARE

Similar to the Netherlands and the United Kingdom, GPs in Italy act as gatekeeper to second line health care and provide most of the medical care. Contrary to the Netherlands, however, feedback from specialists or hospitals to GPs is organized through the patient. In 2000, a GP database called the Health Search database (HSD) was set up by the Italian College of General Practitioners. In 2004, the database was sold to the market research company Segedim that also owns THIN and THALES, but research can still be conducted.

Italy is rather unique in having a specific paediatric primary care system for children between 0 and 14 years of age. A minority of children are cared for by family physicians (mostly those 10 years and older), whereas there are almost 7000 paediatricians throughout the country associated with the NHS that gives a flat fee for service per registered child to the paediatrician. Inscription in the National Health system is compulsory for residents; thus, every child at birth is referred to as a paediatrician associated with the NHS. All consultations, prescriptions and examinations that are prescribed by the paediatrician are free of charge to the patient; thus, there are no economic constraints to attend medical care (Fornaro *et al.*, 1999). This unique feature of Italian health care has resulted in the initiation of the PEDIANET database in 1999.

As part of its tax funded health care for residents, the Italian NHS provides medical attendance and prescribed medicines. Typically, new and more expensive drugs are preferred in Italy even when effective, safe and less expensive alternatives are available. Prescribers had to face a highly dynamic pharmaceutical market in which 30% of substances (among the 300 most sold) changed every 5 years before the Drug Reform Act. After the Drug Reform Act in 1994, the reimbursement status of drugs is categorized in three groups: class A drugs are reimbursed completely, class B drugs require a small patient fee dependent on age and exemption status and class C drugs are not reimbursed at all (Rolle *et al.*, 1995). An example of class C drugs is sedatives.

Health care is organized by regional and local health agencies (USSL) that use the local and regional health care information systems (SISR) for planning

of resource utilization. Historically, the most important source for pharmacoepidemiological studies in Italy have been the SISR that accumulate data on all births, deaths, claims of dispensed drugs, hospitalizations and procedures that are reimbursed by the NHS through their local health units (Caffari and Raschetti, 1991; Menniti-Ippolito *et al.*, 1998; Degli Esposti *et al.*, 1999). The SISR of the Friuli-Venezia-Giulia (FVG) region in the north-east of Italy has been used most frequently for the conduct of pharmacoepidemiological research (Rossi *et al.*, 1991; Simon *et al.*, 1994; García-Rodríguez *et al.*, 1998; Castellsague *et al.*, 1999).

Access to regional SISR databases and especially original hospital records has become more complicated with the European privacy legislations for external organizations. Access to original hospital records for validation purposes is not possible anymore. Local databases are more and more being used for the conduct of epidemiological studies; an example is the database in Ravenna that is commercially exploited (Degli Esposti *et al.*, 1999). The future will learn whether access to (combined) local databases through key persons may be easier than formal access to regional databases.

PEDIANET

Since 1999, the Società Servizi Telematici (So.Se.Te.) based in Padova is developing a national database, called PEDIANET, which currently collects the clinical, demographic and prescription data for approximately 180 000 children that have provided informed consent and who are under the care of any of the 105 primary care paediatricians (GP) that currently provide data to the database.

Data are generated during routine patient care with the software JB 95® and are stored in different files, which can be linked through a unique (anonymous) numerical identifier. The identification file contains information on the demographic data of the child and the eligibility status (registration status, date of registration and date of death). The prescription file contains information on all drugs (date of prescription, ATC code, product, quantity, dosing regimen, legend duration, indication and reimbursement status) and vaccinations that are prescribed by the paediatricians. Reasons for contact and diagnoses (free text or coded

by the ICD-9 system) are collected in the medical file. In addition, the database contains information on referrals to specialists, procedures, hospitalizations, medical examinations, health status (according to the Guidelines of Health Supervision of the American Academy of Paediatrics) and centile diagrams.

The database is suitable for both retrospective inspection of routinely collected data and for prospective data collection (outcomes and indirect costs of disease) (Menniti-Ippolito *et al.*, 2000; Nicolosi *et al.*, 2003; Sturkenboom *et al.*, 2005a). Data access is possible after approval of the protocol by the Scientific Board.

HEALTH SEARCH DATABASE

The HSD was set up by the Italian College of General Practitioners in 1998 (Cricelli *et al.*, 2003) and is a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs throughout Italy, who voluntarily chose to supply data to the database and to follow courses on data entry/collection. The HSD currently contains information from over 561 GPs who cover a total source population of about 800 000 persons since 2001. Each GP undergoes formal training for data entry and uses standard software to record data. Data are subject to a range of quality checks. Any variations within agreed ranges are investigated and submitted to each participating GP. Physicians who fail to meet standard quality criteria are not considered for epidemiological studies. Currently, 320 GPs with a representative population (around 500 000) are judged up to a standard, and their data can be used for scientific research.

The database contains identification information (age, sex, patient identification and GP registration information), which is linked to prescription information, clinical events and diagnoses, hospital admission and causes of death. All diagnoses are coded according to the ICD-9-CM. Drug names are coded according to the ATC classification.

Studies on disease prevalence and incidence as well as drug utilization and adherence have been conducted (Cricelli *et al.*, 2003; Filippi *et al.*, 2003a,b; 2004a,b; 2005a–c; Mazzaglia *et al.*, 2003; Sturkenboom *et al.*, 2005b; Galatti *et al.*, 2006).

GENERAL CONSIDERATIONS

The use of automated data for the conduct of observational epidemiological research has been heavily discussed in the past and will continue to be discussed even more so if researchers are using the same or similar data. A good example are the conflicting results of two studies on the risk of venous thromboembolism in women using third-generation oral contraceptives that were both conducted in the GPRD (Farmer *et al.*, 2000; Kaye *et al.*, 2000). Despite the controversies that may arise between persons with conflicting interest (researchers, producers, prescribers and patients), there is no doubt that the use of automated linkage or GP data has proven its value in pharmacoepidemiology. The exploitation of the GPRD by the MHRA, the sublicensing of the GPRD to different research groups and companies and the interest of various regulatory agencies such as the EMEA in the use of automated databases clearly demonstrate the need for longitudinal medical databases to anticipate, evaluate and assess the use, the cost, the positive and adverse effects of drugs.

Large automated databases have given us the opportunity to study the rare and common effects of (in)frequently used drugs. Good examples are the studies conducted with the PDNJ database on the teratogenic effects of specific drugs (Nielsen *et al.*, 1999, 2001; Sorensen *et al.*, 1999, 2000; Thulstrup *et al.*, 1999; Fonager *et al.*, 2000; Larsen *et al.*, 2000). Owing to the tax funded health care structures in many European countries, it is possible to conduct population-based studies that do not suffer from potential socio-economic selection biases that may occur with the health maintenance organization databases in the United States. In addition, the longitudinal prospective collection of routine care data eliminates recall errors that have plagued so many ad hoc case-control studies in the past.

Challenges remain the validation of outcomes, misclassification of exposure and the adequate control of confounding by indication, severity and contraindication. The extent of these potential problems depends on the type of database. Record linkage databases such as PHARMO, FVG, OPED, PDNJ and also MEMO usually contain only data on hospitalizations and (reimbursed) drug use. Important confounding factors such as the indication of drug use, body mass index (BMI), smoking, family history and minor

medical problems cannot easily be assessed and adjusted for. The validation of outcomes with original charts has become more difficult due to the current privacy regulations.

General practitioners databases like IPCI, Health Search and PEDIANET and more famously GPRD and Mediplus have fewer disadvantages than record linkage systems due to both the nature of the data and the fact that data are collected directly from the individual health care provider. The latter simplifies not only the access to original data but also the inclusion of project-specific modules in the software. In these databases, it would be possible to conduct randomized database studies as was recently attempted in the IPCI database (Mosis *et al.*, 2005a,b). Randomized database studies may bridge the gap between randomized trials and observational studies and deal with confounding by indication.

The unification of Europe and the increased computerization of health care are promising future perspectives. Initiatives have been taken to further link hospitalization and pharmacy claims data to GP records, and we may soon expect databases also in other countries (Sweden and Spain). Now that we move from data scarcity to an era of data abundance, it will be possible to choose a database that is tailored for the research question at hand. Table 29.2 may offer an aid in comparing the available databases. As researchers, we may want to unite forces. Effort should be put on the organization of multi-national database studies that have advantages in size but also in variability of drug use, allowing for the full evaluation of drug- and dose-specific risks and comparisons between countries. One such attempt is the pharmacoepidemiological studies as part of the TEDDY project, an EU network of excellence aiming at drug development for the young (www.teddynoe.org). In this network, GPRD, Mediplus, IPCI and PEDIANET data are combined to assess drug safety issues in children.

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Surveillance for Medical Devices – USA

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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 has a US market valued at more than \$75 billion as of 2002 and consists of approximately 8000 medical device firms, more than 80% of whom have fewer than 50 employees (Gallivan, 1997; US Department of Commerce, 2004).

The agency'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 (Food and Drug Administration,

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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 agency 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 non-binding 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), 720 (92%) 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 [*i.e.* 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 re-use 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 (and risk assessment) 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, assessments of identified potential patient risks. 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 and risk assessment are: (1) identification of previously unknown or not well-characterized adverse events/product problems (‘signals’); (2) identification and characterization of sub-groups at risk; (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 agency to achieve these goals are: (1) adverse event/product problem reporting [through the Medical Device Reporting (MDR) system and MEDWatch, PMA conditions of approval, the pilot 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

MDR and MEDWatch

The FDA monitors postmarket device-related adverse events/product problems (AEs), 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 as per 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 adverse events by user facilities (hospitals, nursing homes, ambulatory surgical facilities, outpatient diagnostic and treatment facilities, ambulance services, and health care 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; formerly Medical Product Surveillance Network), 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 slightly more than 1 million reports and currently averages approximately 200 000 per year, with mandatory reports accounting for about 98% 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 agency-wide standard operating procedures;
- pre-designated high priority reports are reviewed within 24 hours of receipt and include, among others, reports of pediatric death, exsanguination, explosion/fire, or anaphylaxis;
- other individual reports (account for about 24% of all reports) are reviewed within 5–15 workdays of receipt;
- autoscreen reports (account for about 12%) are those that are computer-screened (by pre-designated 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 64%) 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 is being 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 sub-group-specific (e.g. pediatric use). Complicating the selection of appropriate denominator data are the myriad types of devices (e.g. single-use disposables to multi-component durable medical equipment) and the inherent difficulties in assessing potential population exposure (e.g. factoring in multiple uses, average shelf-life, component replacement).

A staff, predominantly of nurses, 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 and include:

- 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.
- Recommending internal expert safety meetings. These may lead to public notifications, recommendations for additional postmarket study, or meetings with the company to explore issues further.
- Alerting regulatory authorities outside the United States through the international vigilance program (see below).

Other internal uses of the AE data are widespread and include: 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.

A recent example of reports of AEs typifies the system in action. In June 2002, the agency 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 US in July 2002. Other manufacturers, however, notified the agency of additional cases of meningitis, principally in children. A nationwide collaborative investigation was begun by the agency 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 compared to children in the general population, and those with positioners had over four times the risk of developing meningitis compared to recipients of other cochlear implant types (Reefhuis *et al.*, 2003). Throughout this process, the agency posted periodic updated public health notifications on its website to keep the public informed (Food and Drug Administration, 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 (Center for Disease Control and Prevention, 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 under-reported – 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 under-reporting and lack of 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 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 pre-specified 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.

Supplementing this reporting system are PMA conditions of approval (applies to Class III devices). All products with approved PMAs have conditions of approval, one of those being the submission of information on AEs outside the MDR regulatory requirements [Title 21 CFR Part 814.82 (a)(9)]. Examples of this include labeled AEs occurring with unexpected severity or frequency. This requirement helps the agency cast a wider ‘safety net’ in its surveillance of AEs.

MEDICAL DEVICE SAFETY NETWORK (MEDSUN)

Although user facility reporting was mandated in 1990, it accounted for only 3% of all reports in 1999. Furthermore, only about 2000 reports came from hospitals in 1999, representing about 800 hospitals out of a universe of about 7000. Likewise, only 90 reports came from nursing homes, representing 50 nursing homes out of a universe of about 12 000. This lack of mandatory institutional reporting has many root causes (some alluded to above under weaknesses of AE reporting), but basically reflects a lack of educational outreach coupled with a lack of enforcement (with both tied to inadequate resources). 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, FDA has been collecting data about problems with the use of medical devices from a sample of hospitals and nursing homes via MedSun. By mid-2005, this interactive Internet-based reporting program expanded to approximately 350 healthcare institutions (mostly hospitals) nationwide. The program’s principal objective is 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); clinical engineering audioconferences; device safety exchanges (highlighting best safety practices and safety solutions); and surveys on high-profile safety concerns.

INTERNATIONAL VIGILANCE REPORTING

The reach of AE surveillance was augmented and truly became global under the auspices of the Global Harmonization Task Force (GHTF) established in 1992. The GHTF was established to respond to the increasing need for international harmonization in the regulation of medical devices (www.ghtf.org). The GHTF is a voluntary international consortium of public health officials, responsible for administering national medical device regulatory systems, and representatives from regulated industry. The task force acts as a vehicle for convergence in regulatory practices related to ensuring the safety, effectiveness and quality of medical devices and promoting technological innovation as well as facilitating international trade. This is principally accomplished through publication and dissemination of harmonized guidance documents on basic regulatory practices.

One of the four GHTF study groups is charged with reviewing current adverse event reporting, post-market surveillance and other forms of vigilance for medical devices, and performing an analysis of different requirements with a view to harmonizing data collection and reporting systems. A process for the global exchange of vigilance reports between National Competent Authorities (NCAs) has been established. Standardized reports on potentially high risk issues for which action is to be taken (even if investigations are incomplete) are submitted electronically to a shared listserver. 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, all public health notifications, and special public health concerns (e.g. high index of preventability or particularly vulnerable populations). Currently, the program exchanges approximately 150 reports per year.

GLOBAL MEDICAL DEVICE NOMENCLATURE

Part of the information requirements for the vigilance exchange program includes the official name of the device that is the subject of the vigilance report. Only since 2001 has the medical device community had an official international source for such names, the Global Medical Device Nomenclature (GMDN). 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). Currently, version 3 of the GMDN has 8000 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, fibreoptic. It is meant for use by regulatory agencies, but has the potential for wider applications (e.g. inventory control or marketing) and may eventually be incorporated into administrative and healthcare databases that could be used for public health purposes. When compared with the National Drug Classification coding system, however, the GMDN is more limited in that it does not at present include model-specific information, or other potentially useful data such as material composition, component parts, or size.

MANDATED POSTMARKET STUDIES

Another ‘tool’ that the FDA uses to achieve its surveillance and risk assessment goals are 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).

In addition to the PMA authority for Class III products, the agency may, under Section 522, impose postmarket study requirements on certain devices. The latter provision, originally mandated in 1990 under SMDA, allows the agency, under its discretion and for good reason, to order a manufacturer of a class II or class III device to conduct a post-market study if the device: (1) is intended to be implanted in the human body for more than one year; (2) is life-sustaining or life-supporting (and used outside a device user facility); or (3) 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 agreed to by the firm). The FDA recently issued a regulation clearly specifying, among other items, the requirements for a study plan, conduct, and follow-up (Title 21 CFR Part 822).

The FDA has issued guidance on criteria used in considering order issuance as well as possible study approaches (October, 1998; www.fda.gov/cdrh/postsurv/index.html). Briefly, the criteria include: the public health issue must be important; other postmarket mechanisms cannot effectively address the issue; the study must be practicable (i.e. feasible, timely, not cost-prohibitive); and the issue is of high priority. The possible study approaches vary widely (designed to capture the most practical, least burdensome

approach to produce a scientifically sound answer) and include: a detailed review of complaint history and the literature; non-clinical testing of the device; telephone or mail follow-up of a patient sample; use of registries; observational studies; and, rarely, randomized controlled trials.

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.

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, Hutter and Bushar, 1998). The FDA issued a public health correspondence (FDA Talk Paper) on the results and their reassuring implications (Food and Drug Administration, 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 sub-groups at risk, test hypotheses, and evaluate device performance and use. The epidemiology program serves a vital postmarket function at the agency and works to inform Center and agency 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, as of 2005, the program has been given oversight of post-approval studies (i.e. those as a condition of approval of PMA products). It is now the program's responsibility to help design, implement, track, and oversee completion of these studies of high-risk devices. 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 databases (e.g. the National Inpatient Sample to evaluate in-hospital mortality associated with heart valve replacement; Astor *et al.*, 2000) and develops device-specific supplements to nation-wide surveys (e.g. US National Mortality Followback Survey to assess characteristics of persons receiving pacemakers in their final year of life; Hefflin, 1998). In addition, the program explores new means of surveillance [e.g. through a nation-wide surveillance network of emergency departments operated by the US Consumer Products Safety Commission (CPSC); Hefflin, Gross and Schroeder, 2004], explores methods of active surveillance (in a large tertiary hospital; Samore *et al.*, 2004), develops and expands existing device registries (e.g. exploring device safety using the American College of Cardiology National Cardiovascular Data Registry; Tavris *et al.*, 2004), reviews and assesses observational literature (e.g. studies of cellular phones and their relation to brain cancer), and conducts applied research (e.g. breast implants and rupture rates) (Brown *et al.*, 2000).

The ability of drug or device epidemiologists within the agency 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 postmarket 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 agency'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, a new and not fully understood technology, the program undertook a collaborative effort with investigators who oversee the Society of Thoracic Surgeons 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. The epidemiology program was also involved in assessing the public health impact of the only marketed continuous glucose monitoring system in the US (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 complexity of devices and the varied environments in which they are used, multiple approaches to detecting and assessing their potential safety and/or effectiveness are warranted. FDA has recognized this need and has strived to enhance existing mechanisms and develop new approaches to build an integrated system for postmarket surveillance and risk assessment that will help manage the risks of medical devices in as effective a way as possible given limited resources.

The agency 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 risk assessment must be used in concert with other agency 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. Increasing use will be made of effective means of report triage (e.g. auto-screen and summary reporting), so that more resources can be devoted to detecting unknown problems. Reports will be increasingly submitted electronically, eventually by the device industry as a whole, allowing for more efficient and error-free processing. A revamping of the coding thesaurus, allowing for more complete and sophisticated coding of both patient and device outcomes, will aid problem detection. Datamining, already in use by our drug colleagues, is being explored as an analytic aid in identifying potential signals of public health problems among the ever-burgeoning number of reports of device-related AEs. And lastly, the MDR system will continue to become even more international as device nomenclature is standardized and the exchange of vigilance reports grows.

MedSun will be of ever-increasing importance as it expands, and consolidates, its network of health-care facilities across the US. By working closely with these facilities, MedSun aims to: (1) significantly reduce barriers to reporting; (2) emphasize error

prevention, risk mitigation, and risk communication; and (3) enhance each institution's culture of safety. In addition to enhanced passive surveillance, MedSun will provide the means to conduct active surveillance in these institutions via real-time queries/surveys or targeted studies of important potential device problems. Given certain issues, denominator data may also be obtained – a significant contribution given the problems previously noted with reliable numerator and denominator data.

Other efforts are also underway to expand FDA's approaches to active surveillance. Based on the initial work (Hefflin *et al.*, 2004), FDA continues to collaborate with the CPSC in the use of its National Electronic Injury Surveillance System to help define the public health burden of device-related injury and, ultimately, to help identify or refine signals of potential device problems. The agency is also collaborating with the Center for Medicare and Medicaid Services (CMS), as well as other agencies, in the exploratory use of Medicare data to assess the frequency of designated device-related complications in the elderly. Lastly, based on initial findings (Samore *et al.*, 2004), various methodological approaches to active surveillance, including direct observation of intensive care unit staff performance, are continuing to be explored in a collaborative effort with a major tertiary care facility.

Aside from the significant additions to surveillance as noted above, the future system will rely more and more on formal studies to address potential safety/effectiveness issues or to refine our understanding of those issues. Recently, a new emphasis has been placed on agency-mandated post-approval studies as a condition of approval for high risk devices, and their oversight has been moved from pre- to post-market staff. These studies will increasingly address important postmarket device issues using effective observational study methodology. The public will be informed of the status of these studies and interventions (aside from changes to the product labeling) will be considered based on study findings. In concert with this effort, and although limited to date, targeted use of the Section 522 authority will continue to be made. Both of these efforts are designed to help the agency strike the right pre-/postmarket balance in terms of the information needed to assure reasonable safety and effectiveness prior to marketing, and continued product safety and effectiveness in the 'real world.'

In the future, the agency will increasingly use other sources of data to address important device issues. National registries, maintained by professional societies, have become an increasingly important means to address short-term safety issues. Previously cited have been recent examples of use of such registries to address complications with hemostasis devices (Tavris *et al.*, 2004) and operative mortality associated with transmyocardial revascularization (Peterson *et al.*, 2004). Importantly, CMS has recently based reimbursement for use of selected breakthrough technologies (e.g. left-ventricular assist devices and carotid stents) on the contingency that entities who wish to be reimbursed must enter patient outcome data into nation-wide registries. FDA is working with CMS, and others, to help develop these registries. FDA is also further exploring the use of national Medicare claims data with CMS and academic researchers to assess its potential utility as a means to address postmarket device issues.

Finally, FDA is making significant efforts to address more fundamental 'information infrastructure' issues related to lack of and/or poor documentation of device-related AEs in medical records, as well as lack of device-specific identifiers in major healthcare datasources (as alluded to previously). The former is well known and is related to multiple causes. The agency will be conducting a series of 'think-tank' workshops to develop possible solutions that may be pilot tested. Other efforts, in parallel with further development of the GMDN, will explore refinement and use of electronic systems, such as bar coding radiofrequency tagging, to link more specific device information to healthcare records. Success in these two fundamental endeavors would markedly advance the ability of the agency, and healthcare researchers, to conduct effective postmarket surveillance and risk assessment.

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, which 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 man or other animals; or
 (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man 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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Pharmacovigilance and Risk Management in Japan

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INTRODUCTION

Pharmacovigilance in Japan has traditionally been characterized by a small number of spontaneous reports of suspected adverse drug reactions (ADRs). Recently, however, there has been a dramatic increase in the number of ADRs following the implementation of complex post-approval safety procedures. For example, the drug company has long had the legal duty to conduct the ‘Drug Use Investigations’ (DUIs), which involves physicians registering thousands of patients treated with newly launched products to monitor and report any suspected ADRs (Tanaka *et al.*, 2002). In the last decade, however, a rapid improvement of the spontaneous reporting system (SRS) took place and the role of the DUIs has been changed. The change will be further accelerated by the recent implementation of the international guideline on the pharmacovigilance planning for which agreement has been reached at the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

(ICH). In this article, some of the other new trends associated with the recent amendment of Pharmaceutical Affairs Law (PAL) as well as the current status and future problems for risk management in Japan will be described.

SPONTANEOUS REPORTING SYSTEM (SRS) IN JAPAN

The Japanese SRS was created in 1967. In the early developing stage of Japanese SRS, the reports were sent from dozens of ‘designated medical institutions’ to the Ministry of Health and Welfare (MHW, renamed the Ministry of Health, Labour and Welfare, MHLW in 2000). Since 1984, reports were also sent from ‘designated pharmacies.’ For the first few years after implementation of the SRS, the annual number of ADR reports was only in the hundreds. However, with the increase in the number of ‘designated medical institutions’ and ‘designated pharmacies,’ the number of ADR reports steadily increased to reach around

1500 per annum by the early 1990s (Table 31.1.). After a further expansion of the system in 1997, the MHW (MHLW) received around 5000 reports per annum from health professionals in all of the medical institutions and all of the pharmacies. Following the

recent amendment of the PAL in 2002, doctors, dentists, pharmacists and other health professionals now have 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 (Pharmaceutical affairs law, enforcement ordinance and enforcement regulations, 2003).

Since 1967, the MHW has received ADR reports sent *via* drug companies as well as reports directly from the doctors. However, until 1979 the annual number of reports was less than 500. In 1979 the ministerial ordinance 'Enforcement Regulations on the Pharmaceutical Affairs Law' (Article 62-2) made drug companies duty bound to send the ADR reports to the MHW. Thereafter the number of ADR reports gradually increased until the late 1980s when the increase accelerated significantly. The number of domestic reports per annum exceeded 17 000 in 1997 when the duty of the drug companies to send the ADR reports to the regulatory body was clearly stipulated in PAL (Article 77-4-2), and ICH-E2A guideline and its expedited reporting criteria were implemented for the approved drugs. The number of ADR reports has consistently been around 25 000 per annum over the 3-year period since 2002 (Table 31.1.). Electronic submission of safety reports with E2B/M2 format has been mandatory since October 27 in 2003. At the start, in 2003, 25% of submitted reports were via electronic data interchange (EDI); however, the fraction of EDI was increased to 83% being employed by 73 companies in August 2005.

AMENDMENT OF PHARMACEUTICAL AFFAIRS LAW (PAL) IN 2002

In addition to the legal duty of the health professionals to report an ADR, many other changes were made in the 2002 amendment of PAL. The 2002 amendment of PAL has important implications concerning the status of pharmacovigilance in Japan from 2002 to the present time and beyond (possibly until around 2010). The 2002 amendment of PAL is characterized by (1) the enhancement of post-marketing safety measures (detailed in the next section) and (2) the introduction of new regulations to further ensure the safety of biological products. Because strict regulation

Table 31.1. The number of spontaneous reports sent to the Spontaneous Reporting System in Japan.

Fiscal year	From companies	From health professionals
1966	—*	3
1967	—*	44
1968	—*	595
1969	—*	293
1970	—*	200
1971	—*	338
1972	—*	271
1973	—*	360
1974	—*	285
1975	—*	336
1976	—*	416
1977	—*	456
1978	—*	530
1979	—*	712
1980	388	669
1981	383	816
1982	455	822
1983	751	766
1984	1072	767
1985	1183	803
1986	1562	890
1987	1669	854
1988	1672	1025
1989	2357	1332
1990	2523	1374
1991	3823	1451
1992	6540	1667
1993	8440	1505
1994	12 980	1615
1995	14 288	1859
1996	16 831	1914
1997	17 504	3730
1998	18 466	4882
1999	20 031	5502
2000	22 326	5297
2001	22 451	4094
2002	24 221	4195
2003	28 004	5399
2004	25 142	4594

*A small number of reports sent to the SRS is not shown

of biological products was an urgent social requirement in the late 1990s, the 2002 amendment gave it top priority. In the 1990s it became clear that many hemophiliacs with HIV infection contracted the virus from plasma products prepared in the 1980s. The occurrence of many of these cases might have been prevented by stricter regulation of blood products. Indeed, a senior official in the MHW was arrested in 1996 because of nonfeasance of preventive measures against the spread of the HIV infection. Similarly, many patients suffering from hepatitis C contracted the virus from blood and plasma preparations made around 1980. Many of these cases might also have been prevented by better regulatory measures, including restriction of the widespread superfluous use of blood and plasma preparations particularly up until the mid-1980s in Japan. 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.

Another important feature of the 2002 PAL amendment included (3) the introduction of a marketing authorization holder (MAH) license by which it is no longer required to possess manufacturing facilities to market drugs in Japan. Associated with the 2002 PAL amendment, (4) the Pharmaceutical and Medical Device Agency (PMDA) was established in April 2004 under Law of the incorporated administrative agency – Pharmaceutical and Medical Devices Agency enacted in December 2002.

ENHANCEMENT OF POST-MARKETING SAFETY MEASURES

In this section, the regulations in the 2002 PAL amendment of drug companies are detailed. Since 1971, Japan has adopted a system for the 're-examination' and 're-evaluation' of marketed drugs. The 're-examination' system involves a reassessment of the usefulness of all new drugs after a fixed period of time (6 years for usual products, 10 years for orphan drugs) following the first approval. Unless the results of the 're-examination' indicate that the product has no major problem, the manufacturer (currently, MAH) is no longer allowed to market the product. On the other hand, the quality, efficacy

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 're-examination' system has been further systemized where the basic plan of post-marketing studies is required to be submitted at the stage of the approval of the new products. The result of the post-marketing study has been also requested to be included in Periodic Safety Update Report (PSUR) in line with the implementation of ICH-E2C guideline (on PSUR) in April 1997. As an additional regulation, Early-Phase Post-marketing Vigilance (EPPV) has been introduced in 2001 that is unique to Japan. According to this regulation, the MAHs are required to repeatedly explain the appropriate use of the new drug to health professionals, collect information on serious ADRs through intensive monitoring for spontaneous reports, and keep a record of the vigilance for the first 6 months after launch.

The details for these regulations, including those for the EPPV, were given in the 'Good Post-Marketing Surveillance Practice' (GPMSP), first made as a notice in 1994 and then promulgated as a ministerial ordinance in 1997. The GPMSP covered the regulations on EPPV, ADR reports and risk communication as well as those on the investigational studies conducted by the drug companies. Following the 2002 PAL amendment, in 2004 the GPMSP was divided into two ministerial ordinances of 'Good Vigilance Practice' (GVP) for the regulations of the ADR reports and risk communication, and 'Good Postmarketing Study Practice' (GPSP) for the regulations of the investigational studies.

GOOD VIGILANCE PRACTICE (GVP) AND ADR REPORTS VIA COMPANIES

According to the GVP and 'Good Quality Practice' (GQP), which represents the license rules that MAH must follow, the 'general manufacturing & marketing supervisor' in the MAH should appoint a 'quality assurance supervisor' and 'pharmacovigilance supervisor.' The pharmacovigilance supervisor controls all the safety issues in the safety control management department and should be independent from the sales department. The pharmacovigilance supervisor has the responsibility for collecting and analysing safety

information, planning and execution of measures to ensure safety, planning and execution of the EPPV, audit, training/education of relevant staff, and preparation of Standard Operating Procedures (SOPs) for these activities.

According to the 2002 PAL amendment, the definition and standards for expedited reporting of post-approval ADR reporting 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. Before April 2005, the drug company had to submit domestic report of 'moderate' unexpected reactions (where 'moderate' was defined as intermediate between 'serious' and 'mild') within 30 calendar days from the first receipt of the case report. In addition, prior to April 2005 all domestic reports of the expected serious reactions should also be submitted within 30 calendar days. However, since 1 April 2005, non-serious reactions have been excluded from those requiring the expedited reporting, though they should be included in the periodic report of unexpected and non-serious ADRs. Under the new regulations, when the MAH is aware that a domestic case has experienced an expected and fatal ADR, the reaction should be reported within 15 calendar days. 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. All the expected and unexpected serious cases of infection due to the use of any kind of drug should be reported within 15 calendar days and non-serious unexpected domestic cases of infections should be also reported within 15 calendar days. The MAH should also meet the research report requirement (including papers published in scientific journals and meetings) as well as the requirement to report on the safety measures taken in the foreign countries.

GOOD POSTMARKETING STUDY PRACTICE (GPSP) 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 with DUI and

followed up usually for up to 6 months, depending on its usual administration term. Until 2000, it was mandatory to apply the results of the DUI when the product was assessed in the 're-examination.' The predecessor of 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 7180 188 patients or an average of 8215 (range 37–111 810) patients per study were monitored (Tanaka *et al.*, 2002). Although the methodological requirements for the 'Side Effect Investigation' and DUI, including the number of patients being monitored, have altered many times, 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 associated with the 'GPMSP' enacted as a ministerial ordinance in 1997, the target number of patients to monitor 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 3000 in order to detect, with 95% confidence, unknown ADRs with the 0.1% or more of the frequency' (Safety Division, Drug Affairs Bureau, 1997). Until recently, the number of spontaneous domestic reports of ADRs was small and the DUI was thought to complement the SRS. However, in the amendment of the 'GPMSP' in 2000 the DUI was no longer a uniform requirement and was only carried out in certain cases, according to the characteristics of the drug. The MHLW explained that one of the reasons for this change in the regulation was the increase in the number of spontaneous reports *via* drug companies together with the increase in the size of clinical trials (Pharmaceutical and Food Safety Bureau, 2000).

In November 2004, an agreement between the EU, US and Japan was reached for the guideline of 'Pharmacovigilance planning (PVP)' (also known as the 'E2E guideline') in the ICH (E2E Pharmacovigilance Planning, 2004). The 'ICH harmonised tripartite guideline' was incorporated into Japanese regulation rules as the notice issued from the MHLW in September 2005. According to the notice, the basic plan of post-marketing studies should be prepared according to the ICH E2E guideline. The notice also indicates

that a plan for the post-approval investigation at the stage of new drug application should be made according to the ICH E2E guideline. In the ICH E2E guideline, it is stated, ‘for products with important identified risks, important potential risks or important missing information, the PVP should include additional actions designed to address these concerns.’ For products where no special concerns have arisen, ‘routine pharmacovigilance should be sufficient for post-approval safety monitoring.’ In addition, according to the E2E guideline, ‘when choosing a method to address a safety concern, sponsors should employ the most appropriate design.’ Until 2000, the DUIs were conducted irrespective of whether the drug had any ‘special concerns’ because it was a uniform requirement. This ‘uniformity’ was altered in 2000 and the trend was augmented when the E2E guideline was incorporated into Japanese regulation rules in 2005.

GPSP, being different from the GVP, are not license rules that the MAH must follow without exception. Rather, the GPSP is a ministerial ordinance stipulating duty rules for post-approval investigations and trials conducted only when necessary. According to the GPSP, a PMS supervisor that is independent from the sales department should control the post-approval investigations and trials. The department may or may not be located in the same section as that for the safety control management stipulated in the GVP. In the current GPSP, the investigations and trials are, as in the former GMSP, divided into three categories: ‘Drug Use Investigation (DUI),’ ‘DUI of Special Population’ and ‘Post-marketing clinical trial.’ In future, this classification may be rearranged to make it more compatible with the classification of ‘special concerns’ given in the E2E guidelines.

THE NEW TYPE OF INVESTIGATIONS USING PHARMACOEPIDEMIOLOGIC METHODS IN JAPAN

According to the E2E guidelines, the classic comparative observational studies, including the case–control study, cohort study and cross-sectional study, are essential in the individually designed study to evaluate adverse events. A brief introduction to each type of study is given in the ‘Annex’ of the guideline. In some of the recent investigations conducted in

Japan as a ‘DUI of Special Population,’ the standard design in pharmacoepidemiology is used, which is distinct from the old stereotyped ‘DUI.’ For example, a ‘DUI of Special Population’ is being conducted to study the association between gefitinib (a chemotherapeutic agent to treat non-small cell lung cancer) and interstitial lung disease (ILD). In the study, a nested case–control design is employed where all of the patients in participating hospitals are registered if the patient has 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. When the patient is registered, only a small amount of information, such as gender and age, is collected. A case is defined as an episode of ILD which develops during the 12-week observation period after registration. For each case, four controls are selected from the non-cases who are being followed at that time. From a case and four controls, the detailed information is collected to study the relative risk of the ILD for gefitinib and various other risk factors, including genetic factors such as single nucleotide polymorphisms, which may be associated with the development of ILD (Fukuoka *et al.*, 2005).

Though not carried out as research under the regulation of GPSP, a case–control study on the association between non-steroidal inflammatory drugs (NSAIDs) and upper gastrointestinal bleeding (UGIB) has recently been conducted in Japan. This case–control study was conducted to understand the association between NSAIDs and UGIB before the approval of any Cox-2 inhibitor in Japan. In the study, for each case identified in one of the participating hospitals, two community controls were selected from the population registry in the district where the case’s home was located by matching gender and age (Kubota *et al.*, 2005).

These two examples suggest that the study using the standard design for pharmacoepidemiology (nested case–control design and classic matched case–control design) is feasible in Japan. These studies may act as a prototype of the PMS studies, fulfilling the standard for the comparative observational studies given in the ICH E2E guidelines. The design for the pharmacoepidemiology studies may be employed more often in the future PMS in Japan, though the traditional stereotyped DUI may still prevail for several years to come.

NOVEL TREND OF PHARMACOVIGILANCE AND RISK MANAGEMENT BY THE REGULATORY BODY

Another change occurring in Japan are the activities conducted by the regulatory body itself, which are distinct from the regulation for the drug companies. Traditionally, the contribution of the regulatory body to drug safety has mainly been achieved through regulating the drug company, though there have been some exceptions including collecting spontaneous reports directly from health professionals. Many of the new activities still remain in the planning stage but the enterprises encompass a wide range of areas, including risk management planning. First, the research on the methodology and logistics for the data mining technique employed by several foreign regulatory bodies (e.g., the procedures using proportional reporting ratio (PRR) in the UK Medicines and Healthcare products Regulatory Agency (MHRA) and Bayesian Confidence Propagation Neural Network (BCPNN) in WHO Uppsala Monitoring Center) has been initiated inside PMDA (PMDA, 2005). The research in the PMDA aims to develop the procedures that can be used in the daily regulatory activity by the end of 2008. Second, a network of sentinel monitoring centers, consisting of a couple of hospitals, is being formed to provide the regulatory body with information associated with drug safety and other issues. According to the PMDA, the PMDA has already operated this system for recently approved concomitant anti-cancer drugs. Third, the information center for pregnancy and drug use will be made in the National Center for Child Health and Development (NCCHD) (MHLW, 2005a). In this network, the NCCHD functions as a centre for consultation with pregnant women who became anxious about the effect of a drug taken during pregnancy. The scheme will be run in collaboration with the hospital for sick children in Toronto, Canada. Similar to the Canadian 'Motherisk program,' the NCCHD collects information on the outcome of the pregnancy. The information obtained in the follow-up will be used in the regulation, including updates to the package insert. Fourth, the 4-year enterprise for compiling the 'ADR manuals' has been started in 2005 to provide the information related to the serious ADRs to health

professionals (MHLW, 2005b). The information may include a description of the clinical course of typical cases, diagnosis, laboratory data, risk factors and treatment for the ADRs. Fifth, the information to facilitate the patient's prognostic and preventive measures in the early stage of serious ADRs is being collected and will be distributed through the website and other media. Sixth, the medication guides for patients regarding the drugs which need special attention are being developed under the leadership of the regulatory body. This may again promote the appropriate use of drugs by the patients to minimize the chance of serious events and maximize the chance of their early detection.

ROLE OF ACADEMIA AND NON-GOVERNMENTAL BODIES IN THE FUTURE PHARMACOVIGILANCE IN JAPAN

Under the strict and somewhat intricate regulations concerned with post-approval safety, pharmacovigilance is generally regarded as the activity performed almost exclusively by the regulatory body in Japan. For instance, while Prescription-Event Monitoring in Japan was welcomed with a certain degree of enthusiasm during the pilot study (Kubota, 1999; Tanaka *et al.*, 2002), particularly among pharmacists, the activity has since been moderated. This is probably because direct funding from the MHLW was only available during the pilot study. However, more commitment of academic and non-governmental bodies to drug safety may be required in the near future. Indeed, in the six new enterprises by the regulatory bodies given in the previous section, many health professionals and specialists have already been involved. The activity of academia and/or non-governmental research bodies may also be required in the new type of investigations conducted by the drug companies under the regulations of the E2E guideline and GPSP. For example, in both of the two examples described in the section 'The new type of investigations using pharmacoepidemiologic methods in Japan', specialists, health professionals and/or scientific associations played an essential role in conducting the study.

RISK MANAGEMENT IN JAPAN

According to the draft for 'guideline on risk management system for medicinal products for human use' published by the European Medicines Agency (EMEA) in September 2005, a risk management system is defined as 'a set of pharmacovigilance activities and interventions designed to proactively identify, characterize, prevent or minimize risks relating to medicinal products' (EMEA, 2005). The activity of the risk management system includes risk communication and an assessment of the effectiveness of risk minimization interventions. As of late 2005, there has been no systematic approach in Japan to develop the official guideline specified for the risk management equivalent to the draft guideline issued by EMEA. However, some essential components of the risk management system are being gradually incorporated into the new regulations adopted in Japan. For example, the GVP indicates that the pharmacovigilance supervisor has the responsibility for planning and execution of measures to ensure safety in the MAH and the ICH E2E guideline has been adopted in the regulation for the pharmacovigilance activity.

Risk communication is an important tool for risk minimization. According to PAL (Article 77-3), the MAH has an obligation to provide information on the appropriate use of a drug for doctors and other health professionals. The information includes the results of the 're-examination' and 're-evaluation,' emergency information, such as 'dear doctor letter' and revision of precautions. Notice on 'Guideline for distribution of urgent safety information (Dear Doctor Letter)' was introduced in October 1989. To enhance the legal requirement, the Federation of Pharmaceutical Manufacturers' Association of Japan (FPMAJ) published the rules for enforced dissemination on the information during the post-approval period in 1994. The rules include the description of the box warning and contraindication (including contraindicated concomitant use of the drug) as well as the distribution of the 'Drug Safety Update' (DSU) published by the FPMAJ to health professionals for prompt and complete communication of the revision of precaution statement (the DSU is currently available from the PMDA's website (Drug Safety Update, 2005)). Notice on 'The preparation of explanation materials

on warning and precaution statements of new drugs' was announced in June 1997.

In addition to the regulations enforced by the regulatory body and voluntary rules made by the FPMAJ, the risk management plan can also involve academia and non-governmental bodies. One important example of this system is the regulatory guidelines for thalidomide. Thalidomide, marketed in the late 1950s in Europe, Canada and Japan as a treatment for morning sickness, was banned worldwide because of its teratogenicity. Thalidomide was withdrawn from the Japanese market in 1962. However, the usefulness of thalidomide was reappraised in the mid-1960s when the drug was found to be effective in the treatment of erythema nodosum leprosum (ENL). The widespread 'revival' of thalidomide occurred in the 1990s when it was found to be effective in the treatment of a refractory multiple myeloma and possibly several other diseases such as Behcet's disease, graft versus host disease and inflammatory bowel disease. In 1998, thalidomide was approved for the treatment of ENL in the US. In Australia, New Zealand, Turkey and Israel, thalidomide is approved for the treatment of multiple myeloma after the failure of standard therapies as well as ENL. In the US, the risk of thalidomide, particularly teratogenicity, is managed by the 'System for Thalidomide Education and Prescribing Safety' (STEPS), where all the patients and prescribing doctors are registered to the MAH. In other countries where thalidomide is approved, STEPS is also used with some modification.

Thalidomide is currently not an approved drug in Japan. In the late 1990s Japanese patients with multiple myeloma requested that thalidomide be used for their treatment. Since 2000, several thousand Japanese patients with multiple myeloma and other diseases have obtained thalidomide via the system of 'personal importation' for unapproved drugs. A clinical trial of thalidomide for multiple myeloma was started in 2005 and it is anticipated that thalidomide will be available as an approved drug in Japan from around 2006.

In December 2004, while thalidomide was not approved, the Japanese Society of Clinical Hematology (JSCH) published its own guidelines on the appropriate use of the drug for multiple myeloma. In the guidelines, it is indicated that doctors should register the patients prescribed thalidomide for multiple myeloma to the office of the JSCH. In addition, patients should be

properly educated to understand the risks of teratogenicity and other adverse reactions due to treatment with thalidomide. Patients should be made aware of effective methods of contraception and the safe storage of thalidomide in the home. Furthermore, doctors should report serious adverse events to the JSCH. In late 2005 or early 2006, a new web system for thalidomide registry will be operated to enforce the JSCH guideline. The website will be run by the 'University hospital Medical Information Network' (UMIN), which is recognized as the infrastructure for academic activities (UMIN, 2005). Upon approval of thalidomide, the MAH will be responsible for the risk management.

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 in place. Prior to the commencement of clinical trials in Japan, the involvement of academia and non-governmental bodies in risk management may be required for patients using unapproved drugs, as well as for patients who are not covered by the clinical trials for new drug applications.

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Part III

PHARMACOVIGILANCE AND SELECTED SYSTEM ORGAN CLASSES

Dermatological ADRs

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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 pre-marketing 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 sulphonamides and 5–10% for many antiepileptics. In a reported prospective survey, 90% of these drug eruptions were benign (Hunziker *et al.*, 1997). Because under-reporting 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 socioeconomic status of the patient and on access to health care, 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 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.

It is our opinion that the different clinical patterns of severe drug eruptions should be distinguished, while others prefer mixing all of them under the denomination of ‘hypersensitivity reactions’ (Knowles, Utrecht and Shear, 2000). Both conceptions are based on mechanistic considerations. The ‘mergers’ emphasize the role of ‘reactive metabolites’ of drugs as common initiators of all types of reactions. The ‘splitters’ underline the differences in clinical presentation, pathology of skin and visceral lesions, and biologic markers that suggest that the effector mechanisms are probably different (Roujeau and Stern, 1994).

PATTERNS OF CUTANEOUS ADRs

EXANTHEMATOUS DRUG ERUPTION

Exanthematous or maculo-papular eruptions, often reported as ‘drug rashes’ or ‘drug eruptions’, are the

most common ADRs 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 days 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 (Figure 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 (EBV, CMV, HHV6, Parvovirus B19, etc.), toxic eruptions, acute Graft-vs-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, associated with topical corticosteroid and systemic antipruritic agents. When the suspected drug is of paramount importance for the patient (e.g. antibacterial sulphonamides in AIDS patients) 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 ratio of this attitude should be carefully weighted 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 sulphonamides and most antiepileptic agents.

URTICARIA AND ANGIO-OEDEMA

Urticaria is a common, transient eruption of erythematous and oedematous papules and plaques, usually associated with pruritus. When dermal and subcutaneous tissues are involved, this reaction is known as angio-oedema. Most cases of angio-oedema are associated to urticaria. They can be complicated by a life-threatening anaphylactic reaction. Urticaria, angio-oedema and anaphylaxis may be a type I hypersensitivity reaction mediated by IgE antibodies (penicillin allergy). But other 'anaphylactoid' mechanisms, leading to direct and non-specific liberation of histamine or other mediators of inflammation, are also common for drug reactions (contrast media, NSAIDs including aspirin).

Clinically, itchy erythematous, oedematous papules and plaques develop in variable numbers and size (Figure 32.2). They are localized anywhere on the body, including the palm, soles and scalp. They frequently last a few hours and disappear within 24 hours, leaving the skin with a normal appearance. Angio-oedema is often associated with urticaria, consisting of pale or pink swellings which affect the face (eyelids, lips, ears, etc.) but also buccal 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 non-specific with a superficial and deep scarce infiltrate of mononuclear cells accompanied by eosinophils and neutrophils, oedematous 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 H₁ receptor blockers. Systemic steroids and an intramuscular injection of epinephrine are necessary in

an emergency if severe angio-oedema 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 (stings, food allergy, etc.). Antibiotics, especially penicillin, and general anaesthetics are classic causes of IgE-mediated hypersensitivity reaction. A radioallergosorbent test (RAST) or 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 angio-oedema are NSAIDs and angiotensin-converting enzyme (ACE) inhibitors. Angio-oedema occurs in 2 to 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 angio-oedema related to ACE inhibitors have a recurrence when using angiotensin 2 receptor antagonists (van Rijnsoever *et al.*, 1998). This suggests a pharmacologic 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, Mercurio and Elmets, 1995).

PHOTOTOXICITY

Phototoxic disorders are not rare and always predictable. It 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 (Figure 32.3). This is followed by hyperpigmentation. Photo-onycholysis and pseudoporphyrria (blisters on sun-exposed parts of the limbs) are less common clinical forms.

Phototoxicity is histologically characterized by epidermal cell degeneration with necrotic keratinocytes, oedema, 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 UV (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. Ultraviolet 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 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 photoallergic reactions, including antibiotics (sulphonamides, pyrimethamine, fluoroquinolones), fragrances, NSAIDs, phenothiazine, thiazide diuretics, and so on.

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 recommended, because of the risk of worse reactions even

with low UV doses. Topical corticosteroid, 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 corresponds to a cutaneous necrotizing vasculitis consisting of palpable purpuric papules which predominate on the lower extremities (Figure 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 allopurinol, NSAIDs, cimetidine, penicillin, hydantoin, sulphonamides and propylthiouracil.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

In 1980, Beylot *et al.* described an acute pustular dermatosis named 'Acute generalized exanthematous

pustulosis' (AGEP) (Beylot, Bioulac and Doutre, 1980). 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 under-estimated 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 (Roujeau *et al.*, 1991) 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 non-follicular pustules arise on a widespread oedematous erythema, burning pruritic or both (Figure 32.5). Oedema 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 oedema and perivascular polymorphous infiltrate are usually present. Leukocytoclastic vasculitis and focal necrotic keranocytes 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 to 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 pustules

in both diseases are clinically indistinguishable; the histopathology can be helpful.

Antibiotics (b β -lactam, some macrolides and quinolones) are the main drugs implicated in AGEP.

DRESS/HYPERSENSITIVITY

'Hypersensitivity syndrome' refers to a specific severe skin reaction. The acronym of 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 one in 1000 and one in 10 000 exposures with drugs such as antiepileptics and sulphonamides. 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 haematological alterations: eosinophilia and lymphocytosis with basophil lymphocytes (Shear and Spielberg, 1988; Roujeau and Stern, 1994; Callot *et al.*, 1996). Multivisceral involvement differentiates hypersensitivity syndrome from common exanthematous eruption. Some consider that Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) may occur as part of a 'hypersensitivity syndrome'. The skin lesions and visceral complications are actually different. Eosinophilia and atypical lymphocytosis are not observed in SJS and TEN.

These reactions are more frequent among persons of African ancestry. They begin 2 to 6 weeks after the first drug use, later than most other skin reactions. Fever and skin rash are the most common symptoms. Cutaneous manifestations begin as a morbilliform rash, which later becomes infiltrated with an oedematous follicular accentuation (Figure 32.6). Erythroderma, vesicles, tight blisters induced by dermal oedema, follicular as well as non-follicular pustules can also occur. Face, upper trunk and extremities are initially involved. Oedema 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 phos-

phatase, bilirubin levels and abnormal prothrombin time are present in about 50% of patients.

Histopathology exhibits a rather dense lymphocytic infiltrate in the superficial dermis and/or perivascular, associated with dermal oedema.

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. Special attention should be paid to viral infection and specially to HHV6, since several publications suggest a possible interaction between DRESS and reactivation of HHV6 or other lymphotropic viruses (Descamps *et al.*, 2001; Kano, Inaoka and Shiohara, 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), minocycline and sulphonamides are the most frequent causes of hypersensitivity syndrome; allopurinol, gold salts and dapsone may also induce this syndrome.

FIXED DRUG ERUPTION

A fixed drug eruption is 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 oedematous plaques, sometimes with a central blister (Figure 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 Fixed Drug Eruption may be difficult to distinguish from 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, sulphonamides 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 (Figure 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 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 are d-penicillamine and other drugs containing a thiol radical, like captopril and piroxicam. The remission after drug withdrawal is not always spontaneous, particularly in cases of pemphigus attributed to drugs that do not have a thiol part.

SJS AND TEN

SJS and TEN are rare, life-threatening, drug-induced skin reactions. The incidence of TEN is evaluated to 0.4 to 1.2 cases per million person-years and of SJS from 1 to 6 cases per million person-years (Roujeau and Stern, 1994). The immunopathologic pattern of early lesions suggests a cell-mediated cytotoxic reaction against epidermal cells. Widespread

apoptosis of epidermal cells is provoked by the activation of several pathways: the interaction of Fas antigen (cell surface death receptor) and Fas ligand but also perforin plus granzyme and TNFalpha.

With others we proposed to consider SJS and TEN as severity variants of the same drug-induced disease, and to distinguish SJS from erythema multiforme major (Bastuji-Garin *et al.*, 1993), the latter being mostly related to infections, especially with herpes (Auquier-Dunant *et al.*, 2002).

According to this proposal, 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 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 (Wolkenstein *et al.*, 1998).

Toxic epidermal necrolysis is characterized by the same lesions as SJS but with a confluence of blisters leading to a positive Nikolski 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 labelled overlap SJS-TEN) (Figure 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), 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 α production. High-dose intravenous immunoglobulins were disappointing in our experience.

Drug reactions are responsible for at least 70% of cases of both SJS and TEN (Knowles, Utrecht and Shear, 2000). Antibacterial sulphonamides, anticonvulsants, oxicam and pyrazolone NSAIDs, allopurinol and chlormezanone are the drugs associated with the higher risks. An international case-control study of SJS and TEN found relative risks of between 50 and 172 for new users (treatment duration of less than 2 months) of the above-mentioned drugs and also for corticosteroids (Roujeau *et al.*, 1995). In that study, 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 to 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 and rash (morbilloform, urticaria) and lymphadenopathy (Roujeau and Stern, 1994; Knowles, Utrecht and Shear, 2000).

It occurs 1 to 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, sometimes life-threatening, effect of warfarin, which typically begins 3 to 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 anti-coagulant, and purified protein C concentrate.

Heparin also induces thrombosis and necrosis in the skin and other organs. In this case, the discontinuation of the drug, treatment with warfarin or an antiplatelet drug is useful.

PSEUDOLYMPHOMA

Drug-induced pseudolymphoma corresponds to an 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 pseudolymphoma have been reported with hydantoin, butobarbital, carbamazepine, ACE inhibitors, amiloride, D penicillamine, and so on.

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 ADRs

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 vs. thorax and abdomen
- Photoexposed vs. 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 vs. mouth, scrotum vs. glans on genitalia, etc.). Only mucous membrane lesions indicate a severe reaction.

5. Duration of the eruption

6. Associated symptoms/signs

- Fever
- Pruritis
- Lymph node enlargement.

The documentation of cases should be completed by photographic pictures. Cheap disposable cameras and digital cameras 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 non-drug 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 ADRs

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INTRODUCTION

Disturbances of gastrointestinal function are common events that can be attributed to the ingestion of a wide range of drug classes. In the 1970s, it was reported that some 20%–40% of adverse drug reactions (ADRs) in hospital monitoring were gastrointestinal in origin (Hurwitz and Wade, 1969). More recent estimates of the incidence of ADRs in hospitalised patients (Bates, Leape and Petrycki, 1993; Bowman, Carlstedt and Black, 1994; Lazarou, Pomeranz and Corey, 1998; Bates *et al.*, 1995a,b) or of subjects admitted to hospital due to an ADR (Col, Fanale and Kronholm, 1990; Einarsen, 1993; Nelson and Talbert, 1996; Lazarou, Pomeranz and Corey, 1998; Roughead *et al.*, 1998; Pouyanne *et al.*, 2000) provide only limited information specifically about gastrointestinal events.

A study in over 4000 hospitalised patients in the United States found 247 ADRs among 207 admissions (Bates *et al.*, 1997). The examination of each by organ system affected showed that 18% of events were of gastrointestinal origin, predominantly nausea, vomiting and antibiotic-associated diarrhoea. An almost identical rate was reported in an observational study

of 1024 patients in an internal medicine ward in the United States (Bowman, Carlstedt and Black, 1994). The gastrointestinal system was the organ system affected in 17.8% of drug-related adverse events.

The findings from a prospective study in France showed that gastrointestinal events were the most frequent cause for admission to hospital for an ADR (Pouyanne *et al.*, 2000). Of 100 admissions, 27 were gastrointestinal, including 13 cases of gastrointestinal haemorrhage caused by anticoagulant drugs and 9 caused by the ingestion of non-steroidal 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 gastrointestinal bleeding, which usually was associated with either warfarin or NSAID therapy.

Many drugs causing gastrointestinal disorders have been recognised (Bateman and Aziz, 1998).

Well-established unwanted effects of drugs include changes in gastrointestinal motility, altered gastric emptying, disturbances of nutrient absorption, antimicrobial-associated colitis and pseudomembranous colitis. Furthermore, drug-induced lesions are documented for all sections of the gastrointestinal tract. These encompass a wide range of pathophysiological processes including inflammation, the formation of strictures, haemorrhage, ulceration and perforation. Others consist of symptoms such as nausea and vomiting (Quigley, Hasler and Parkman, 2001), diarrhoea (Fine and Schiller, 1999) or constipation (Locke, Pemberton and Phillips, 2000) in the absence of underlying pathology.

The medical literature on gastrointestinal ADRs is dominated by reports concerning the NSAIDs. Effects have been documented over many years, but it has been during the 1990s that the risk factors for upper gastrointestinal problems have been systematically examined. Over the same period, the small and large bowel toxicities of the NSAIDs have also become clearly identified.

In this chapter, we summarise some of the important literature and reviews from the 1990s concerning the adverse effects of NSAIDs on the gastrointestinal tract. We also review the medical literature of the 1990s to identify adverse gastrointestinal effects with other medications detected using a variety of pharmacovigilance techniques.

The oesophagus, despite its physiological defence mechanisms, is prone to injury induced by a wide variety of agents. Medication-induced oesophageal injury or 'pill oesophagitis' was first described in the 1970s (Pemberton, 1970). In most cases, direct oesophageal toxicity is the cause, and the condition is generally fully reversible on the withdrawal of treatment (Doman and Ginsberg, 1981; Kikendall, 1999a). Pill oesophagitis is often underdiagnosed; in many instances, it is incorrectly believed to be gastro-oesophageal reflux disease (Doman and Ginsberg, 1981; Bonavina *et al.*, 1987). Almost 1000 reports in the medical literature of pill oesophagitis attributable to about 100 different medications have been extensively reviewed (Kikendall, 1999a,b). Drugs most frequently implicated in pill oesophagitis (reports of ≥ 10 cases) include antibiotics (doxycycline, tetracycline hydrochloride and other unspecified tetracyclines, oxytetracycline, pivmecillinam), potassium

chloride, alendronate, ferrous sulphate and ferrous succinate, quinidine, naproxen, aspirin, emeproprium bromide, pinaverium bromide and alprenolol (Bott, Prakash and McCallum, 1987; Baehr and McDonald, 1998; Kikendall, 1999a,b; Graham, 2000).

In the upper gastrointestinal tract, NSAIDs are causally associated with peptic ulceration along with associated complications such as bleeding and perforation. Non-steroidal anti-inflammatory drugs also cause upper gastrointestinal haemorrhage 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.

Non-steroidal anti-inflammatory drugs 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.

Recently, an 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 (MMR) 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 gastrointestinal tract (Iredale, 1993). Acute colonic pseudo-obstruction is characterised 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; Stieger, Cantieni and Frutiger, 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, Falk and Bukowski, 1991), diltiazem (Mantzoros, Prabhu

and Sowers, 1994; Fauville *et al.*, 1995), morphine (Murthy, Ion and Winstanley, 1998), fludarabine (Campbell *et al.*, 2000), and enteral activated charcoal alone (Brubacher, Levine and Hoffman, 1996) and together with sorbitol and papaveretum (Longdon and Henderson, 1992) when given for the management of theophylline overdose.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

When grouped by category, NSAIDs are the most commonly prescribed of all drugs. More than 20 million prescriptions per year are written in the United Kingdom alone (Langman, 1988). In the United States, 2–3 million patients take daily NSAIDs and worldwide, it has been estimated that over 30 million people take NSAIDs each day (Gibson, 1988). The use of NSAIDs has been rising steadily since the 1970s, particularly amongst the elderly (Walt *et al.*, 1986). Approximately 50% of all NSAID prescriptions are for persons over 60 years old (Langman, 1988; Fries *et al.*, 1990).

Although NSAIDs reduce pain and inflammation and improve quality of life for patients with inflammatory disorders, it is widely recognised that such benefit is achieved at the risk of gastrointestinal injury. In the upper gastrointestinal tract, this may range from clinically insignificant blood loss and minor erosive changes to deep ulceration with the associated risk of haemorrhage or perforation. Adverse effects of NSAIDs are also recognised in the small and large intestine and range from asymptomatic enteropathy to severe complications such as ulceration, bleeding, perforation and stricture (Bjarnason *et al.*, 1993; Aabakken, 1999; Faucheron, 1999).

UPPER GASTROINTESTINAL LESIONS

The annual incidence of upper gastrointestinal bleeding associated with the use of NSAIDs has been reported to be from 50 to 150 cases per 100 000 (Gilbert, 1990; Laporte *et al.*, 1991) with chronic NSAID users experiencing a 1%–4% annual incidence of gastroduodenal perforation, ulcer or bleeding (Singh, 1998). In the United States, gastrointestinal

injury induced by NSAIDs is responsible for an estimated 107 000 hospitalised patients and 16 500 deaths annually (Singh, 1998; Wolfe, Lichtenstein and Singh, 1999). Estimates for the United Kingdom suggest that some 12 000 emergency upper gastrointestinal admissions (including over 2200 deaths) per annum are because of NSAID use (Blower *et al.*, 1997).

Studies of the prevalence of peptic ulceration in arthritic patients receiving NSAIDs have been reviewed (McCarthy, 1989). Crude prevalence rates of gastric and duodenal ulcer were 13% and 11%, respectively. Similar findings were reported from an endoscopic screening study of over 1800 rheumatoid or osteoarthritic patients (Geis *et al.*, 1991). Gastric ulcers were present in 14.8% of patients and duodenal ulcers in 10.2%.

Many investigators have addressed the question of the relative gastrointestinal toxicities of NSAIDs. Most assessments of relative toxicity have been derived from case-control studies. Despite the difficulties in the interpretation of these data, such as NSAIDs being used in different populations for diverse indications and at a range of doses, some clear differences have been found. In general, studies have shown that the risk of adverse upper gastrointestinal effects is lowest with ibuprofen and diclofenac. Piroxicam and azapropazone have consistently been associated with a high risk of upper gastrointestinal toxicity (Committee on Safety of Medicines, 1986; Somerville, Faulkener and Langman, 1986; Carson *et al.*, 1987a; Rossi, Hsu and Faich, 1987; Gabriel, Jaakkimainen and Bombardier, 1991; Griffin *et al.*, 1991; Laporte *et al.*, 1991; Henry, Dobson and Turner, 1993; Kaufman *et al.*, 1993; Savage *et al.*, 1993; Garcia-Rodriguez and Jick, 1994; Langman *et al.*, 1994).

These studies and others have been included in a meta-analysis to examine the relative risks of serious gastrointestinal complications reported with NSAIDs (Henry *et al.*, 1996). This showed that there are wide differences between individual NSAIDs in the risk of inducing gastrointestinal bleeding and ulcer perforation. Overall, ibuprofen was associated with the lowest relative risk, followed by diclofenac. Ranked highest for risk was tolmetin, piroxicam and ketoprofen, with the greatest risk being with azapropazone.

A meta-analysis of studies has also shown that long-term therapy with aspirin is associated with a

significant increase in the incidence of gastrointestinal haemorrhage (Derry and Loke, 2000). This occurred in 2.4% of patients taking aspirin compared with 1.42% taking placebo. Furthermore, it was shown that neither reducing the dose nor using modified release preparations reduced the incidence of gastrointestinal haemorrhage.

The risk of developing peptic ulcer disease and complications exists for the duration of NSAID treatment. However, the risk may be greatest in the first month of taking NSAIDs (Gabriel, Jaakkimainen and Bombardier, 1991; Griffin *et al.*, 1991; Henry, Dobson and Turner, 1993). Griffin *et al.* (1991) reported that persons with a shorter duration of exposure to NSAIDs had an increased risk for the development of peptic ulcer disease. The relative risk was 7.2 for those with a total duration of use of no more than 30 days, significantly greater than the relative risks of 3.7 and 3.9 for persons with 31–90 days and more than 90 days of use, respectively.

Meta-analysis of studies resulted in similar findings (Gabriel, Jaakkimainen and Bombardier, 1991). The highest measures of risk for adverse gastrointestinal events related to NSAID use were obtained from studies in which the duration of NSAID consumption was less than 1 month.

Higher doses of NSAIDs increase the risk of gastroduodenal ulceration and upper gastrointestinal complications (Carson *et al.*, 1987b; Gabriel, Jaakkimainen and Bombardier, 1991; Griffin *et al.*, 1991; Henry, Dobson and Turner, 1993; Garcia-Rodriguez and Jick, 1994; Langman *et al.*, 1994). The relative risk 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 programme in the United States (Griffin *et al.*, 1991). Patients had been hospitalised for confirmed peptic ulcer, and relative risks were compared with over 7000 controls. For users of NSAIDs, the risk increased with increasing dose, from a relative risk of 2.8 for the lowest to a relative risk of 8.0 for the highest dose category.

Similar findings were reported from a study in the United Kingdom (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-aspirin NSAID during the previous month, the risk of ulcer complications increased with dose. Non-steroidal anti-inflammatory drug users with a prior history of gastrointestinal disease are more likely to experience adverse gastrointestinal events when taking NSAIDs (Gabriel, Jaakkimainen and Bombardier, 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 gastrointestinal bleeding than are NSAID users with no past history of ulcer (Garcia-Rodriguez and Jick, 1994; Weil *et al.*, 2000).

Elderly women are often believed to be at a particular risk of NSAID-associated peptic ulcer complications. Whilst elderly patients are at a greater risk than younger patients (Garcia-Rodriguez and Jick, 1994), the effect of gender is less clear. Findings from studies have been inconsistent and whilst some investigators report that the risk for a serious gastrointestinal event appears approximately equal amongst men and women, others suggest that women may be at a somewhat greater risk (Griffin *et al.*, 1991; Henry, Dobson and Turner, 1993; Neutel, Maxwell and Appel, 2000).

The combined use of NSAIDs and corticosteroids is associated with approximately two to three times the risk of gastrointestinal toxicity than is the use of NSAIDs alone (Carson *et al.*, 1987a; Gabriel, Jaakkimainen and Bombardier, 1991; Piper *et al.*, 1991; Garcia-Rodriguez and Jick, 1994; Weil *et al.*, 2000).

Concomitant treatment with NSAIDs and corticosteroids increased the risk of hospitalisation due to gastroduodenal events in elderly patients (Piper *et al.*, 1991). Relative risk of hospitalisation 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 gastrointestinal bleeding (de Abajo, Garcia-Rodriguez and Montero, 1999) as has the concomitant use of NSAIDs and anticoagulants (Shorr *et al.*, 1993; Weil *et al.*, 2000).

Non-steroidal anti-inflammatory drugs are effective in the management of inflammatory disease because they inhibit cyclooxygenase (COX) and hence inhibit the production of prostaglandins (Vane, 1971). Two

COX isoforms exist, namely COX-1 and COX-2. Prostaglandins protect the upper gastrointestinal mucosa from damage and are a product of the activity of COX-1, a constitutive isoform. COX-2, however, is an enzyme that is induced to generate other prostaglandins that mediate pain and inflammation. The beneficial therapeutic effects of the non-selective NSAIDs are hence attributable to inhibition of the COX-2 enzyme, whereas the toxic effects on the upper gastrointestinal tract are a result of COX-1 inhibition (Vane and Botting, 1998).

The development of COX-2 selective NSAIDs (Jackson and Hawkey, 2000), such as celecoxib (Clemett and Goa, 2000) and rofecoxib (Hawkey *et al.*, 2001), promises to reduce the gastrointestinal problems of patients needing anti-inflammatory drug therapy. Studies suggest that in osteoarthritis and in rheumatoid arthritis, COX-2 inhibitors have similar efficacy to conventional NSAIDs in relieving pain and improving functional status but are associated with a lower incidence of upper gastrointestinal perforations, ulcers and bleeding (Clemett and Goa, 2000; Hawkey *et al.*, 2001).

INTESTINAL LESIONS

In the small intestine, NSAIDs may cause a low-grade enteropathy (increased intestinal permeability and low-grade inflammation with blood and protein loss), strictures, bleeding, lesions and perforation (Bjarnason *et al.*, 1993; Aabakken, 1999).

An estimate of the prevalence of NSAID-induced lesions in the small intestine is available from a prospective autopsy study involving over 700 subjects (Allison *et al.*, 1992). Non-specific small intestinal ulceration was found in 8.4% of 249 users of NSAIDs compared with 0.6% of 464 non-users. The prevalence of non-specific ulceration was higher in long-term users of NSAIDs (13.5%) compared with short-term users (6.3%). Three patients (4.1%) in the long-term NSAID group died as a direct consequence of peritonitis from perforated, non-specific small intestinal ulcers.

The ingestion of NSAIDs has also been associated with colonic ulcers, large intestinal perforation and bleeding, complications of diverticular disease (perforation, fistulae and bleeding) and relapse of inflammatory bowel disease (Bjarnason *et al.*,

1993; Faucheron, 1999). In addition, in the 1990s, there have been an increasing number of anecdotal reports of NSAID-associated colonic strictures or NSAID-induced colonic diaphragm disease in patients receiving diclofenac, indomethacin, sulindac, phenylbutazone, ibuprofen and etodolac (Eis *et al.*, 1997; Ribeiro *et al.*, 1998; Faucheron, 1999; Weinstock, Hammond and Brandwin, 1999; Smith and Pineau, 2000).

In the large intestine NSAIDs, in particular, the fenamates (mefenamic and flufenamic acid) may cause colitis. This may range from proctitis to pancolitis, although most histological reports are of mild non-specific colitis. Non-steroidal anti-inflammatory drugs have also been implicated in causing eosinophilic, pseudomembranous and collagenous colitis.

BISPHOSPHONATES

The bisphosphonate group of drugs is used for the management of disorders typified by enhanced bone resorption such as Paget's disease and osteoporosis. Alendronate, a drug that is indicated for the treatment of osteoporosis, has been associated with adverse oesophageal and gastric events. Case reports of oesophagitis, oesophageal ulcer and oesophageal stricture have been reported (Manconi and Bianchi Porro, 1995; Abdelmalek and Douglas, 1996; Colina *et al.*, 1997; de Groen *et al.*, 1996; Liberman and Hirsch, 1996; Naylor and Davies, 1996; Rimmer and Rawls, 1996; Kelly and Taggart, 1997; Levine and Nelson, 1997). Pamidronate also has been associated with oesophagitis (Lufkin *et al.*, 1994).

In addition to causing oesophageal injury, it has been shown in endoscopic studies in volunteers that alendronate, and likely risedronate, can cause acute gastric mucosal damage and gastric ulceration (Graham, 2000). The incidence of adverse gastrointestinal events in users of alendronate was assessed from computerised pharmacy claims of the United Health Group-affiliated health plans in the United States (Park *et al.*, 2000). Over 1400 persons who received alendronate prescriptions were identified. Amongst those who had no prior oesophageal or gastric diagnoses, the cumulative incidence of upper gastrointestinal events was 3.3% in females, 2% in males and 3% overall. This included 22 patients with

oesophagitis, 2 with oesophageal ulcer, 1 with gastric ulcer and 15 with gastritis/duodenitis.

SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

It has recently been suggested that the ingestion of selective serotonin re-uptake inhibitors is associated with upper gastrointestinal bleeding (de Abajo, Garcia-Rodriguez and Montero, 1999). From a general practice research database, 1651 cases of gastrointestinal 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 gastrointestinal bleeding was assessed. The use of selective serotonin re-uptake inhibitors was identified in 3.1% of patients with upper gastrointestinal bleeding compared with 1% of controls. The relative risk was unaffected by gender, age, dose or duration of treatment. The absolute risk of upper gastrointestinal bleeding was estimated as one case per 8000 prescriptions or one case per 1300 users. The authors also reported that the risk of upper gastrointestinal bleeding was greatly potentiated by the concomitant use of NSAIDs and, to a lesser extent, low-dose aspirin (de Abajo, Garcia-Rodriguez and Montero, 1999). Further studies using alternative methods to confirm these observations have been recommended (Po, 1999).

PANCREATIC ENZYME SUPPLEMENTS

Some 90% of patients with cystic fibrosis receive pancreatic enzyme supplements for management of the symptoms of exocrine pancreatic insufficiency (FitzSimmons, 1993). By reducing steatorrhoea and faecal fat excretion, the supplements improve the nutritional status of the patient. Pancreatic extracts have been used for many years, but in 1994, five cases of stricture of the ascending colon in children with cystic fibrosis who were receiving extracts were published (Smyth *et al.*, 1994). Additional cases (Campbell, Forrest and Musgrove, 1994; McHugh, Thomson and Tam, 1994; Oades *et al.*, 1994; Freiman and FitzSimmons, 1996; FitzSimmons *et al.*, 1997)

suggested that the strictures appeared to be temporally related to the recent introduction of high-dose pancreatic supplements.

These reports, and a further 35 cases of colonic stricture reported to the US Cystic Fibrosis Foundation, prompted the Foundation to organise a Consensus Conference to examine the use of pancreatic enzymes in patients with cystic fibrosis (Borowitz *et al.*, 1995). The Conference used the term 'fibrosing colonopathy' to describe 'a condition associated with ingestion of large quantities of pancreatic enzyme supplements' and which leads to colonic strictures. It was considered that patients at highest risk were those who were less than 12 years of age, have taken more than 6000 lipase units per kilogram per meal for more than 6 months, have a history of meconium ileus or distal intestinal obstruction, have had intestinal surgery or have a diagnosis of inflammatory bowel disease.

Although it was initially suspected that it was high-dose pancreatic supplements only that were causing fibrosing colonopathy, subsequently there were reports of the condition in children with cystic fibrosis who were receiving low-dose preparations (Jones *et al.*, 1995; Taylor and Steiner, 1995; Freiman and FitzSimmons, 1996; O'Keefe, 1996). However, a dose-related risk for the development of fibrosing colonopathy has been suggested (Smythe *et al.*, 1995; Bakowski and Prescott, 1997; FitzSimmons *et al.*, 1997).

A detailed review of early cases of fibrosing colonopathy and the chronology of events following the introduction in the United Kingdom and the United States of new forms of pancreatic supplements has been published (Bakowski and Prescott, 1997). The authors suggest that the patterns of use of the pancreatic supplements and the development of fibrosing colonopathy are highly suggestive of a dose-related causal role for preparations of which methacrylic acid co-polymer is a constituent of the enteric coating. This confirmed an earlier observation that methacrylic acid could be a key factor in the development of fibrosing colonopathy (van Velzen, 1995).

More recently, there have been anecdotal case reports of fibrosing colonopathy in two adult patients receiving pancreatic enzyme supplements (Hausler *et al.*, 1998; Bansi *et al.*, 2000). The first was of a 25-year-old woman who developed symptomatic

fibrosing colonopathy several months after beginning high-dose (17 000 lipase units per kilogram per day) pancreatic enzyme therapy (Hausler *et al.*, 1998). The second involved a woman in her late 20s who had undergone cholecystectomy for gallstone disease followed thereafter by endoscopic management of common bile duct stones (Bansi *et al.*, 2000). She later underwent a pylorus-preserving pancreaticoduodenectomy and in the subsequent 7 years received large amounts of pancreatic enzyme supplements. After developing a large bowel obstruction, a right hemicolectomy was undertaken and fibrosing colonopathy of the ascending colon and caecum was confirmed by histology.

ROTAVIRUS VACCINE

Rotaviruses are the main cause of severe dehydrating diarrhoea in young children worldwide, accounting for 125 million cases of diarrhoeal disease with more than 800 000 associated deaths (Greenberg, Matsui and Loutit, 1999). Estimates vary; but in the United States, rotavirus is a common cause of severe gastroenteritis in children where it accounts for 50 000–65 000 hospitalisations and for 20–70 deaths per annum (Greenberg, Matsui and Loutit, 1999; US Department of Health and Human Services, 1999a).

In 1998, a tetravalent rhesus-based rotavirus vaccine was licensed in the United States for the vaccination of infants. During the following 11 months, 15 cases of radiographically confirmed intussusception in vaccinated infants were reported to the United States Vaccine Adverse Events Reporting System (US Department of Health and Human Services, 1999a). Of the 15, most (87%) developed intussusception following the first dose of the three-dose vaccination schedule. Eight of the children required surgical reduction, and one required the resection of part of the distal ileum and proximal colon. Following review of the data, it was concluded that intussusception occurred with a significantly increased frequency after rotavirus vaccination (US Department of Health and Human Services, 1999b). Recommendations to vaccinate infants in the United States were subsequently withdrawn.

The above reports of intussusception prompted an investigation to further evaluate the potential

association with the vaccine (Murphy *et al.*, 2001). Infants aged at least 1 month, but less than 12 months, and who were hospitalised in 19 states of the United States between 1 November 1998 and 30 June 1999 were identified. Of 446 infants with intussusception, 429 were eligible to be included in a case-control analysis with 1763 matched controls. Four hundred and thirty-two of the 446 infants were also included in a case-series analysis. Among the infants with intussusception, 17.2% had received the rotavirus vaccine compared with 12.8% of the controls ($p=0.02$). There was an increased risk of intussusception for 3–14 days after the first dose of the vaccine. Case-series analysis showed the risk was also increased following the second dose of the vaccine, although this was smaller than the risk after the first dose. The authors concluded that the strong association between the rotavirus vaccine and intussusception supports the existence of a causal relationship.

MEASLES-MUMPS-RUBELLA VACCINE

A study published in 1995 suggested that there may be a link between measles vaccination and the subsequent development of Crohn's disease and ulcerative colitis (Thompson *et al.*, 1995). The study was reported by the Inflammatory Bowel Disease Study Group at the Royal Free Hospital School of Medicine in London.

The prevalence of Crohn's disease and ulcerative colitis was determined in three cohorts: (a) a vaccinated group of 3545 people who had received measles vaccine in 1964 as part of a measles vaccine trial, (b) a control group of 11 407 people born in 1958 who were unlikely to have been vaccinated due to their age and of whom 89% had reported measles by age 11 and (c) a second control group of 2541 partners of individuals in the vaccinated group whose vaccination history was not known.

Disease prevalence data were collected by means of a postal questionnaire. The vaccinated group and their partners were asked whether they had ever been told, by a doctor, that they had Crohn's disease, ulcerative colitis, coeliac disease or peptic ulcer disease. The unvaccinated group were asked about any condition that required regular medical supervision, the presence of any long-standing illness, disability or infirmity, and details of all out-patient appointments and hospital

admissions. Reports of Crohn's disease and ulcerative colitis were confirmed with the subject's physicians in the vaccinated and unvaccinated groups only.

Respondents were assumed to have inflammatory bowel disease if they reported it, and the diagnosis was not refuted by their physician. Reports of inflammatory bowel disease where no confirmation could be made were included.

Crohn's disease and ulcerative colitis were reported more often among the measles vaccine group than among the control groups. The difference in the prevalence of inflammatory bowel disease was significantly higher in the vaccinated group when compared with the unvaccinated group. It was reported that, compared with the birth cohort, there was a relative risk of 3.01 (95% confidence interval: 1.45–6.23) of developing Crohn's disease in the vaccinated group. The relative risk of developing ulcerative colitis was 2.53 (95% confidence interval: 1.15–5.58). There was no difference in the rates for coeliac disease.

By contrast, a case-control study in the United Kingdom, which included 140 patients with inflammatory bowel disease (83 with Crohn's disease), was unable to show an association with measles vaccination (Feeney *et al.*, 1997).

The Inflammatory Bowel Disease Study Group reported another study in 1998 that suggested an association between the combined MMR vaccine and gastrointestinal disease resulting in malabsorption, neurological damage and autism (Wakefield *et al.*, 1998).

Twelve children between the ages of 3 and 10 years were studied. All had been referred to a paediatric gastroenterology unit with a history of normal development followed by the loss of acquired skills, together with diarrhoea and abdominal pain. Gastroenterological, neurological and developmental assessments and a review of developmental records were performed.

All 12 children had intestinal abnormalities, including lymphoid nodular hyperplasia in 10. Histology showed patchy chronic inflammation in the colon in 11 children and reactive ileal lymphoid hyperplasia in 7 but no granulomas. Behavioural disorders included autism in nine children, disintegrative psychosis in one and possible postviral or postvaccinal encephalitis in two.

The onset of behavioural symptoms was associated, by the parents or the child's physician, with MMR vaccination in 8 of the 12 children, with measles infection in one child and otitis media in another. The average interval from MMR vaccination to the onset of behavioural symptoms was 6.3 days (range 1–14). Parents were less sure about the timing of onset of abdominal symptoms because children were not toilet trained at the time or because behavioural features made children unable to communicate symptoms.

Conflicting findings have been reported by long-term follow-up data for children receiving MMR vaccination in Finland (Peltola *et al.*, 1998; Patja *et al.*, 2000). A national surveillance system to detect serious adverse events was established in Finland when their MMR vaccination programme was launched in 1982. A potentially serious adverse event was defined as an event in any temporal association (no time limit was imposed) with MMR vaccination that fulfilled one or more of three characteristics: a potentially life-threatening disorder, the possibility that a chronic disease had been triggered by the vaccination or the patient had been hospitalised for reasons possibly attributable to MMR vaccine. Reports were collected from all hospitals and health centres from 1982 to 1996. During this period, about 3 million vaccine doses had been administered to 1.8 million individuals.

The health of children who had developed gastrointestinal symptoms, lasting 24 h or more following vaccination, was reviewed (Peltola *et al.*, 1998). The time between the reported event and the health review ranged from 1 year 4 months to 15 years (mean 9 years 3 months). Thirty-one children had gastrointestinal symptoms, of whom 20 were admitted to hospital. The most common symptom was diarrhoea (55%). The time from MMR vaccination to the onset of symptoms ranged from 20 h to 15 days. Symptoms generally resolved within a week. No evidence of an association between MMR and inflammatory bowel disease or developmental disorder was found.

All serious adverse event reports collected in the Finnish 14-year surveillance programme were analysed with the finding that serious events causally related to MMR vaccine were rare (Patja *et al.*, 2000). No cases of inflammatory bowel disease were detected.

The proposal continues (Wakefield and Montgomery, 2000) although it is apparent that other studies have failed to confirm associations between either Crohn's disease or autism and MMR vaccination (Elliman and Bedford, 2001). Independent prospective studies are urgently needed to resolve this important issue as parents in the United Kingdom vote with their feet and abstain from vaccinating their children.

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34

Haematological ADRs

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INTRODUCTION

The scope of haematology 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 haemostasis.

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 industrialised world, serious life-threatening haematological 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 recognised 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 non-malignant 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 reaction 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 which do occur, are discussed.

MECHANISMS OF ADR-CAUSING CYTOPENIAS

A reduction, below the recognised 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 anaemia (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 anaemia.

CYTOTOXIC DRUGS

Most cytotoxic drugs cause 'type A' myelosuppressive ADR 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 leukaemia 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 haemopoietic stem cells, damage to the stromal microenvironment of the marrow, inhibition of the production or release of haemopoietic 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 leucocyte antigen (HLA) phenotype (Dettling *et al.*, 2001). Analysis of a cohort of patients from the Long Island Jewish Medical Centre 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 B-38 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 leukaemia. 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, Van Loon and Weinshilboum, 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, Hall and McLelland, 1997). Polymerase chain reaction-based (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 (haemolysis) 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 ADR together with examples of implicated agents.

MECHANISMS OF ADR-AFFECTING HAEMOSTASIS

Clearly antithrombotic drugs such as oral and parenteral anticoagulants, thrombolytic and antiplatelet agents compromise haemostatic mechanisms at therapeutic doses as well as in overdose, in 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.

Haemostasis is obviously affected by ADRs causing thrombocytopenia, as discussed in the previous section.

Other drugs may predispose to haemorrhage by unintended effects on platelet function, by affecting the

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

Clinical findings: Pancytopenia, hypocellular marrow

Example drugs: *Antimicrobials:* Chloramphenicol, cotrimoxazole' sulphonamides, nitrofurantoin, zidovudine, quinacrine, amodiaquine, mepacrine, pyrimethamine, chloroquine, mebendazole. *Antirheumatics:* Gold, penicillamine, indomethacin, oxyphenbutazone, phenylbutazone, piroxicam, sulphasalazine, diclofenac, sulindac, allopurinol. *Anticonvulsants:* Phenytoin, carbamazepine, felbamate. *Psychotropic agents:* Phenothiazines, dothiepin, mianserin. *Cardiovascular drugs:* Captopril, lisinopril. *Other drugs:* Tolbutamide, acetazolamide, alpha-interferon

PRCA

Clinical findings: Anaemia, reticulocytopenia, absent marrow red cell precursors

Example drugs: Azathioprine, maloprim, sodium valproate, erythropoietin

Megaloblastic anaemia

Clinical findings: Anaemia, macrocytosis, megaloblastic erythropoiesis in marrow

Example drugs: Methotrexate, trimethoprim, phenytoin, azathioprine, hydroxycarbamide, fluorouracil, cytarabine, zidovudine

Sideroblastic anaemia

Clinical findings: Anaemia, ring sideroblasts in marrow

Example drugs: Isoniazid, pyridoxine, chloramphenicol, cycloserine, penicillamine, phenacetin, linezolid

Myelosuppression ± peripheral cell destruction

Agranulocytosis

Clinical findings: Severe neutropenia, sudden onset. Reduced marrow granulopoiesis or 'maturation arrest'

Example drugs: Propylthiouracil, carbimazole, methimazole, clozapine, sulphasalazine

Peripheral cell destruction

AIHA

Clinical findings: Anaemia, reticulocytosis, unconjugated hyperbilirubinaemia, positive direct antiglobulin (Coombs) test

Example drugs: Methyldopa, mefenamic acid, nomifensine

ITP

Clinical findings: Thrombocytopenia, normal plasma coagulation, normal marrow

Example drugs: Procainamide, quinidine, quinine, NSAIDs, heparin

Non-immune haemolysis

Clinical findings: Anaemia, reticulocytosis, unconjugated hyperbilirubinaemia, negative Coombs test

Example drugs: Dapsone, primaquine, nitrofurantoin, oxidant drugs in G6PD deficiency

TTP

Clinical findings: Thrombocytopenia, anaemia, reticulocytosis, jaundice. Normal plasma coagulation.

Microangiopathic picture (blood film)

Example drugs: Ticlopidine

production of plasma coagulation factors or 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 (APC) (e.g. oestrogen-containing medications) or by the stimulation of acquired antibodies to phospholipid (the 'lupus anticoagulant' phenomenon).

Table 34.2 lists mechanisms of haemostatic ADRs (for non-antithrombotic drugs) together with examples of implicated agents.

SOME EXAMPLES OF INDIVIDUAL ADR – PHARMACOVIGILANCE IN ACTION

MYELOSUPPRESSIVE ADR

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

Table 34.2. Mechanisms of ADR causing abnormal plasma coagulation.

Thrombocytopenia (Table 34.1)
Impaired platelet function
<i>Clinical features:</i> Bruising, mucosal bleeding, normal platelet count, normal plasma coagulation
<i>Example drugs:</i> Aspirin, NSAIDs, dypyrimadole, prostacyclin, theophylline, caffeine, dextran, high dose penicillin
Hypoprothrombinaemia
<i>Clinical features:</i> Bruising, prolonged prothrombin time
<i>Example drugs:</i> Cephalosporins
Disseminated intravascular coagulation
<i>Clinical features:</i> Bleeding, prolonged coagulation times, reduced fibrinogen, thrombocytopenia
<i>Example drugs:</i> Asparaginase
Increased activated protein C resistance
<i>Clinical features:</i> Increased risk of venous thromboembolic (VTE) disease
<i>Example drugs:</i> Oestrogen-containing medications: oral contraceptives, hormone replacement therapy
Lupus anticoagulant
<i>Clinical features:</i> Prolonged activated partial thromboplastin time, increased risk of VTE
<i>Example drugs:</i> Procainamide, quinidine, alpha-interferon

as prophylaxis to US troops in malarial areas in 1943–44, 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 characteristic skin rash often preceded the haematological complication.

Chloramphenicol

This broad spectrum antibiotic was introduced in 1948. Even before its clinical use, the theoretical possibility of haematological toxicity had been raised because of its chemical similarity to the antipyretic amidopyrine that has an association with neutropenia (Smadel and Jackson, 1944). Reversible changes affecting haemopoiesis 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 recent study in the United Kingdom, 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 United Kingdom, it is now obtainable ‘over the counter’ without medical prescription.

Gold and Penicillamine

Aplastic anaemia 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 non-steroidal 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 characterised by isolated anaemia and reticulocytopenia 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 neutralising antibodies to erythropoietin presenting with resistance to therapy in patients receiving the agent subcutaneously for renal anaemia. 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 American Food and Drug Administration (FDA) 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 stabilisers and lubricating oil in the plungers of the pre-filled 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 that will vary between laboratories but becomes progressively significant in terms of infection risk below $1.5 \times 10^9/l$. Agranulocytosis refers to severe neutropenia $< 0.5 \times 10^9/l$. 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, de Wolf and Vellenga, 1994). There is considerable overlap with drugs implicated in the aetiology 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 tranquillisers. 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 (CPMS) 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 $> 3.0 \times 10^9/l$ and the neutrophil count $> 1.5 \times 10^9/l$ 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 metabolised) 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).

Sulphasalazine

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 ADR

Nomifensine and Autoimmune Haemolytic Anaemia

Nomifensine was introduced in Europe in 1976 as a new tricyclic antidepressant with fewer anticholinergic and sedative effects than its older counterparts. The problematic toxicity of standard tricyclics in over-dosage made it an attractive alternative. Autoimmune haemolytic anaemia (AIHA) had not been observed during pre-licensing studies. Four cases were reported in the United Kingdom in 1978–79 (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 (HIT) 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 (LMWH) preparations (Warkentin, Chong and Greinacher, 1995). Unlike with other drug-induced immune thrombocytopenias (ITP), numerically severe thrombocytopenia is not usual, and the platelet nadir is typically around $50 \times 10^9/l$. It however 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 heparinised patients, then heparin should be discontinued and tests for platelet/PF4 antibodies undertaken. If continuing anti-coagulant treatment is required, then a direct thrombin inhibitor such as hirudin or argatroban is appropriate (Schiele *et al.*, 1995).

MANAGEMENT OF HAEMATOLOGICAL ADR

Once a haematological ADR is suspected, the two principal components of appropriate management are firstly the identification and withdrawal of any potentially implicated agent and secondly 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

Haematological 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 anaemia and thrombocytopenia, respectively. Recombinant growth factors such as granulocyte CSF (G-CSF) and erythropoietin can help to reduce the severity and duration of neutropenia and anaemia, 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 HAEMATOLOGICAL ADRs

INDIVIDUAL MONITORING

Regular full blood count (FBC) monitoring is clearly indicated when drugs associated with type A haematological 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 anaemia are again

Table 34.3. Some non-cytotoxic drugs for which routine blood count monitoring is justifiable.

Drug	Incidence of idiopathic myelosuppression (where assessed)
Gold salts	
Penicillamine	
Azathioprine	
Sulphasalazine	1 in 700 patients in first 3 months; thereafter risk is low
Clozapine	7–8/1000 in first year; 7/10 000 thereafter
Carbimazole, Methimazole, thiouracils	3/10 000/year, mainly in first 3 months of treatment
Azidothymidine	
Alpha-interferon	

important. Monitoring may prevent a minor cytopenia developing into a more severe aplasia by indicating the discontinuation of gold or penicillamine therapy where a prodromal gradual count reduction may precede a severe reaction. Monitoring itself will clearly not prevent a suddenly precipitate agranulocytosis with, e.g., 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, pre-treatment 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 (ADROIT) database that captures all reports for separate drugs and categorises haematological reactions into non-serious, 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 haematological ADR are potentially life threatening. Any patient receiving drug therapy who presents with symptoms of anaemia, unusual infection or bleeding should have simple screening tests including a FBC performed. Significant cytopenias or coagulation derangement should prompt the consideration of the possibility of ADR 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 ADRs

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INTRODUCTION

Because the liver is central to the biotransformation of virtually all drugs and foreign substances, drug-induced liver injury 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 correlation between liver toxicity in animals and humans remains poor (Lumley, 1990). This was highlighted by the tragic fialuridine trial, wherein potential mitochondrial injury leading to hepatic failure (resulting in 5 deaths and 2 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). Hepatotoxicity remains the principal cause of termination in clinical trials of new chemical entities, accounting for one-third of such terminations. Adverse hepatic reactions accounted for 24%

of post-marketing withdrawals in the United Kingdom since 1975 and have been the leading cause of such withdrawals between 1975 and 2005. Furthermore, the number of prescription drugs, including the new molecular entities, on the market has 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.

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 human for the prophylaxis, diagnosis or therapy of disease (Anon., 1969). These idiosyncratic or 'unexpected' reactions, which are the focus of this chapter, are to be distinguished from predictable reactions due to overdoses.

The problems of case definition and causality assessment of drug-induced liver injury have been addressed by an international group of experts, and their recommendations have provided a standardised framework for the evaluation of drug-induced hepatotoxicity (Benichou, 1990). When liver biopsy or autopsy has been performed, hepatotoxicity should be classified according to the histology. In the absence of histological data, the term 'liver injury' has been used to signify abnormalities of the biochemical tests. The liver injury is designated 'hepatocellular' when there is a twofold (or more) increase in alanine aminotransferase (ALT) alone or when the ratio of serum activity (activity is expressed as a multiple of upper limit of normal) of ALT to alkaline phosphatase (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. When increases in the liver tests have been of less than 3 months' duration, the liver injury is considered 'acute', and when the increase lasted more than 3 months, 'chronic liver injury' is considered to be present.

EPIDEMIOLOGY

METHODS OF ESTIMATING THE FREQUENCY OF ADVERSE HEPATIC REACTIONS

The epidemiology of adverse hepatic reaction remains poorly documented. Controlled clinical trials have the advantages of close and prospective surveillance as well as a control group. However, the median number of subjects exposed to a new drug at the time of marketing is usually around 1500, with rarely more than 100 patients receiving the product for more than a year (Rawlins, 1995). This is clearly inadequate as 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 recent withdrawal from the market of troglitazone highlights the realities of the drug development and the need for post-marketing surveillance. In the clinical trials of

troglitazone (representing a novel class of oral anti-hyperglycaemic agents), 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 transplantation (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 generalised to a wider population. Hence, in the United Kingdom and many other countries, post-marketing surveillance relies largely on spontaneous reporting (Rawlins, 1995), and data on adverse hepatic reactions have come most 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 recognised. However, only 10% of the serious and 2%–4% of non-serious reactions are usually reported (Rawlins, 1995). A relatively high rate of reporting may result from a high frequency of adverse reactions or may simply be because of 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 artefact (Devereaux *et al.*, 1995; Roughead, Gilbert and Primrose, 1999). In addition to the variability of reporting, the identification of cases in a non-systemic way introduces significant inaccuracy to the data. In a recent survey in the United Kingdom, about half of the reported adverse hepatic reactions were classified as 'unrelated' to the drugs under systemic evaluation (Aithal, Rawlins and Day, 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.

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. Established linkages such as the General Practice Research Database in the United Kingdom and Group Health Cooperative of Puget Sound in the United States have contributed valuable epidemiological information regarding drug-induced liver disease (Beard *et al.*, 1986; Derby *et al.*, 1993; Jick, Stender and Myers,

1999). However, most often the outcomes such as deaths, hospital admissions and discharge diagnoses, used in linkage studies, are those that pertain only to the more serious reactions or those that occur while the patient is in the hospital. The latter underestimates the frequency of adverse hepatic reactions as acute hospital inpatient stays are usually shorter than the latent period (5 days to 3 months) of most types of drug-induced liver disease.

Case-control studies are particularly useful when the outcome is rare. In the field of drug-induced liver disease, they have been applied to hepatic tumours, industrial hepatotoxicity and the role of aspirin in Reye's syndrome (Farrell, 1994).

FREQUENCY OF ADVERSE HEPATIC REACTIONS

Despite increasing awareness of hepatotoxicity and the availability of less toxic alternatives, the absolute frequency of hepatic drug reactions has not decreased in the last decade, in keeping with the increasing number of prescriptions and pharmacological agents available (Larrey, 2000). Hepatic injury accounts for 3.5%–9.5% of all ADR reports and up to 14.7% of fatal adverse reactions (Friis and Andreasen, 1992; Aithal, Rawlins and Day, 1999). A recent prospective population-based study from France suggested that the number of hepatic ADRs would be 16 times greater than that reported to the regulatory authorities (Sgro *et al.*, 2002). In this study, the global crude annual incidence rate was 14 per 100 000 population, and the standardised annual incidence rate was estimated to be 8.1 per 100 000 population (Sgro *et al.*, 2002). Acute serious liver injury requiring hospitalisation has been estimated to be 7–10 per 1 000 000 population per year (Ibanez *et al.*, 2002; Sgro *et al.*, 2002).

THE CONTRIBUTION OF DRUG-INDUCED HEPATOTOXICITY TO THE OVERALL BURDEN OF LIVER DISEASE

Drugs are responsible for between 2% and 6% of jaundice and about 10% of cases of 'acute hepatitis' (Lewis and Zimmerman, 1989; Whitehead, Hainsworth and Kingham, 2001). In industrialised nations such as the United States, ADRs account for up to 13% of cases of acute hepatic failure, while it is less common (5%) in

tropical countries such as India (Acharya *et al.*, 1996; Ostapowicz *et al.*, 2002). 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 aetiology of less than 1% of all liver tumours (Farrell, 1994).

RELATIVE FREQUENCIES OF DRUGS IMPLICATED

Advances in drug development have allowed the replacement of many potentially toxic drugs with 'safer' alternatives. For example, oxyphenisatin has been withdrawn as a laxative in most countries, alpha-methyldopa is now rarely used as an antihypertensive agent, and alternative, safer agents have replaced perhexiline. As might be expected, this has led to a change in the pattern of implicated drugs causing hepatotoxicity over the last four decades. In the 1960s, chlorpromazine was most commonly associated with hepatotoxicity (Cook and Sherlock, 1965), and in the 1970s, halothane continued to account for significant numbers of hepatotoxic adverse reactions in Europe and New Zealand (Friis and Andreasen, 1992; Pillans, 1996). Similarly, liver injury secondary to antitubercular drugs such as isoniazid continues to be reported worldwide (Acharya *et al.*, 1996; Lucena *et al.*, 2001; Ostapowicz *et al.*, 2002). As the relatively 'high-risk' agents have been replaced, relatively rare reactions to commonly prescribed 'low-risk' agents have become the most important cause of hepatotoxicity. Since 1995, non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and sulindac; antimicrobials such as co-amoxiclav, flucloxacillin and erythromycin; and H₂ antagonists have become important causes of hepatotoxicity (Pillans, 1996; Lucena *et al.*, 2001). In addition, hepatotoxicity due to substances that were previously thought to have little toxicity, such as 'Ecstasy' (recreational amphetamine) and herbal remedies are being increasingly recognised (Larrey, 1997; Andreu *et al.*, 1998; Aithal, 2005). A brief list of the drugs, which are important causes of hepatotoxicity and the pattern of the liver injury, is shown in Table 35.1.

Table 35.1. Drugs causing adverse hepatic reactions.

Acute hepatocellular and mixed pattern of liver injury (or acute hepatitis)
NSAIDs: diclofenac, ibuprofen, naproxen, nimesulide, piroxicam, sulindac
Anaesthetics: enflurane, halothane, isoflurane
Antimicrobials: ketoconazole, ofloxacin, sulphamides, 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, IL-12, tamoxifen
Others: etretinate, glipizide, herbal remedies, ranitidine
Acute cholestatic pattern of liver injury and cholestatic hepatitis
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
Chronic hepatitis and/or cirrhosis
Aspirin, diclofenac, halothane, herbal medicine (germander), isoniazid, methotrexate, methyldopa, nitrofurantoin, papaverine, 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, sulphonamides, sulphonylureas
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
Tumours
Androgens, oral contraceptives

For a more comprehensive list, see Farrell (1994), Pillans (1996), Desmet (1997), Erlinger (1997), Larrey (2000), Krahnenbuhl (2001), and Lucena *et al.* (2001).

DIAGNOSIS OF ADVERSE HEPATIC REACTION

The importance of drugs as a cause of liver injury lies not in the overall number of cases but in the severity of some reactions and their potential reversibility, provided the drug aetiology is promptly recognised. 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, Goldberg and Buskin, 1999). Failure to detect hepatotoxicity at an early stage has led to mortality in many reported cases of hepatotoxicity (Moulding, 1999). The long-term prognosis of drug-induced hepatotoxicity may be worse if the responsible agent is continued (Aithal and Day, 1999).

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. The 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. the specificity of the clinico-pathological pattern and its course,
2. the temporal relationship between intake/discontinuation of the suspected drug and onset/disappearance of hepatic injury and
3. the 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 Baye's 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).

International Consensus Criteria

In 1990, under the auspices of the Council for International Organizations of Medical Sciences (CIOMS), an international group of 'experts', proposed definitions of adverse hepatotoxic reactions and criteria for assessing causality of drug-induced liver disease to standardise the evaluation of drug hepatotoxicity by physicians, health authorities of different countries and pharmaceutical manufacturers (Benichou, 1990). For causality assessment, the French method of ADR assessment was adapted to suit the evaluation of drug-induced liver disease (Danan, 1988). 'International consensus criteria' combined the basic principles of 'chronological criteria' (establishing a temporal relationship between the drug treatment and reaction) and 'clinical criteria' (the exclusion of alternative causes for the particular pattern of liver injury) to determine the probability of the reaction being related to the drug. A detailed scoring system was developed (CIOMS scale) and validated using cases of drug-induced liver injury with known positive rechallenge (Danan and Benichou, 1993). The CIOMS scale performed well when these cases were assessed using the data prior to rechallenge. In a recent study (Aithal, Rawlins and Day, 1999), 86% of the suspected hepatic ADRs could be classified as 'drug related' or 'unrelated' using a simplified form of consensus classification (Table 35.2).

Even though the 'International consensus criteria' are considered to be the 'state of art', they 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.*, 1992a). 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

Table 35.2. Classification of suspected adverse reactions using International Consensus Criteria (simplified version).

Drug-related

1. The time from drug intake and withdrawal to the apparent onset of the reaction was 'suggestive' of drug hepatotoxicity (5–90 days from initial drug intake) or 'compatible' with drug hepatotoxicity (<5 or >90 days from initial drug intake and <15 days from drug withdrawal for 'hepatocellular' reactions or <30 days from drug withdrawal for 'cholestatic' reactions)
2. The course of the reaction after cessation of the drug was 'very suggestive' (decrease in the liver enzymes by >50% of the excess over the upper limit of normal within 8 days) or 'suggestive' (decrease in the liver enzymes by >50% within 30 days for 'hepatocellular' reactions and 180 days for 'cholestatic' reactions) of drug hepatotoxicity
3. Alternative cause of the reaction had been excluded by relevant investigations
4. There was a positive response to rechallenge (at least a doubling of liver enzymes) when such information was available

Reactions were classified as 'drug related' if all of the first three criteria were met or if two of the first three criteria were met in the presence of a positive rechallenge response

Drug-unrelated

1. The time from drug intake and withdrawal to the apparent onset of the reaction was 'incompatible' with drug hepatotoxicity (drug taken after onset of the reaction or reaction >15 from cessation of the drug except for slowly metabolised drugs)
2. Time course of the reaction after drug withdrawal 'not suggestive' of drug hepatotoxicity (decrease in liver enzymes <50% decrease in liver enzymes within 30 days for hepatocellular reactions and 180 days for cholestatic reactions). Both 'indeterminate' and 'inconclusive' cholestatic reactions were included in this group
3. The presence of an alternative cause for reaction

A reaction was classified as drug-unrelated if one or both of the first two criteria were met in the presence of an alternative cause for the reaction

Indeterminate

A temporal relationship between drug intake and the reaction in the presence of a likely alternative cause for the reaction or a temporal relationship between drug intake and the reaction not suggestive of drug-induced hepatotoxicity but no alternative cause for the reaction

classified as 'inconclusive' according to the consensus criteria. The CIOMS scale also defines 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

More recently, a simplified scoring system called the 'Clinical Diagnostic Scale' (CDS) (otherwise called the Maria & Victorino scale) has been developed (Maria and Victorino, 1997). Scores are attributed in seven different components of a given reaction (Table 35.3), and the reactions are 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 the CIOMS scale and the 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 (score >17) (Maria and Victorino, 1997). The reason for low scoring is because of the emphasis given to positive rechallenge as well as extrahepatic manifestations (maximum of 3 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 (unpublished data). Extrahepatic manifestations, considered to represent immuno-allergic reaction, are infrequent with hepatotoxicity due to many of the currently used drugs (Banks *et al.*, 1995; Haukeete *et al.*, 1999). None of the 180 patients in a large series of diclofenac hepatotoxicity would have scored maximum points for this component on the CDS (Banks *et al.*, 1995). Even though underscoring by the CDS attributes to a lower level of probability to an individual drug-related hepatotoxic reaction, a cut-off CDS score of >9 still remains useful in grouping the reactions that require further investigations and those wherein withdrawal of the drug is justified (Aithal, Rawlins and Day, 2000). Moreover, a numerical 'cut-off' is far easier to apply in routine clinical practice.

Table 35.3. The description of Clinical Diagnostic Scale.

Component elements	Scores attributed
I. Temporal relationship between drug intake and the reaction	
A.	
Time from drug intake until the onset of first clinical or laboratory Manifestations	
4 days to 8 weeks (or less than 4 days in cases of re-exposure)	3
Less than 4 days or more than 8 weeks	1
B.	
Time from withdrawal of the drug until the onset of manifestations	
0–7 days	3
8–15 days	0
More than 15 days (except in cases of prolonged persistence of the drug in the body after withdrawal (i.e. amiodarone))	-3
C.	
Time from withdrawal of the drug until normalisation of laboratory Values (decrease to values $\times 2$ the upper limit of normal values)	
Less than 6 months (cholestatic or mixed pattern) or 2 months (hepatocellular)	3
More than 6 months (cholestatic or mixed pattern) or 2 months (hepatocellular)	0
II. Exclusion of alternative causes (viral hepatitis, alcoholic liver disease, biliary obstruction, pre-existing liver disease, ischaemic hepatitis)	
Complete exclusion	3
Partial exclusion	0
Possible alternative cause detected	-1
Probable alternative cause detected	-1
III. Extrahepatic manifestations (rash, fever, arthralgia, eosinophilia, cytopenia)	
4 or more	3
2 or 3	2
1	1
None	0
IV. Intentional or accidental re-exposure to the drug	
Positive rechallenge	3
Negative or absent rechallenge	0
V. Previous report in the literature of cases of hepatotoxicity associated with the drug	
Yes	2
No (drugs marketed for up to 5 years)	0
No (drugs marketed for more than 5 years)	-3

Source: Adapted from Description of Clinical Diagnostic Scale (Maria & Victorino scale). Maria VA, Victorino RM (1997). Reprint from Maria and Victorino © 1997 with permission from Elsevier.

Systemic evaluation using causality assessment methods such as international consensus criteria or a 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

definitive 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, 1990). But, rechallenge of an incriminated drug can be dangerous and may even be fatal (Ransohoff and Jacobs, 1981; Lo *et al.*, 1998). Deliberate rechallenge may only be justified when continued treatment with the implicated agent is highly desirable.

ROLE OF LIVER BIOPSY

Drug-induced liver injury can cause any known pattern of liver pathology, although certain histological features are particularly suggestive of drug-induced aetiology (Anon., 1974). Liver biopsy is also an important way to exclude alternative causes of a given pattern of liver injury. However, liver biopsy is an invasive procedure with significant morbidity in 0.24% and mortality in 0.11% of subjects (Cohen *et al.*, 1992). Hence, benefits should be weighed against the risk, and liver biopsy should be considered only in circumstances where discontinuation of the suspected medication is undesirable or when a patient appears to have an as yet unrecognised form of drug-induced liver injury.

SPECIFIC TESTS

The exceptions to the lack of 'specific' markers of drug hepatotoxicity are the detection of liver–kidney microsomal type 2 (anti-P450 2C9) antibodies in tienilic acid–induced hepatitis, antimitochondrial type 6 antibody in iproniazid-induced hepatitis (Homberg *et al.*, 1985) and liver microsomal antibody (anti-P450 1A2) in dihydralazine-related liver injury (Bourdi *et al.*, 1990). Both tienilic acid and iproniazid were withdrawn because of the high incidence of hepatotoxicity, and dihydralazine is rarely used now in clinical practice.

IN VITRO TESTS

The difficulties encountered in the diagnosis of drug-induced liver injury have led to attempts to develop *in vitro* diagnostic tests. Assays have been devised to study the cytotoxic effect of metabolites generated by a hepatic microsomal drug-metabolising system of the peripheral blood mononuclear cells from patients suffering hepatotoxicity due to phenytoin and sulphonamides (Rieder *et al.*, 1989; Gennis *et al.*, 1991). The lymphocyte transformation test aims to demonstrate *in vitro* proliferation of a patient's lymphocytes in response to the drug in question. Considering the complexity of the immunological events necessary for the *in vitro* induction of specifically sensitised T cells, it is not surprising that the test is positive only in 30% of all patients with suspected

drug-induced liver injuries (Berg and Becker, 1995). The use of sera collected from healthy volunteers after drug intake (containing *ex vivo* drug antigens) and the addition of prostaglandin inhibitors to the cultures (to prevent the inhibition of lymphocyte response by prostaglandin-producing suppresser cells) can increase the sensitivity of the test up to 56% (Maria and Victorino, 1998). However, the fact that these *in vitro* tests are tedious and operator dependent has limited their widespread use.

MECHANISMS OF DRUG-INDUCED LIVER INJURY

The general mechanism by which most drugs induce liver injury is based on the unusual susceptibility of individual patients. For some drugs, the idiosyncratic reaction is immunologically mediated and for others metabolic idiosyncrasy may be responsible. Even though such classification of drug-induced liver injury is simplistic and the molecular basis of the idiosyncratic drug-induced liver injury is poorly understood, some key events have emerged as being particularly important.

METABOLIC IDIOSYNCRASY

The suggestion of dose dependence in some cases of drug-induced liver injury indicates that a host-dependent idiosyncrasy in the metabolism or excretion of these drugs may be responsible for hepatotoxicity. Although several xenobiotics are transformed by the cytochrome P450 system (CYPs) into stable metabolites, many others are oxidised into unstable, chemically reactive intermediates. These reactive intermediates attack hepatic constituents such as unsaturated lipids, proteins or DNA and can lead to liver cell death (Pessayre, 1995). The abundance of CYPs in the liver explains the major role of these metabolites in drug-induced hepatotoxicity. Furthermore, the centrilobular location of most CYPs accounts for the pericentral location of these lesions. When small amounts of reactive metabolites are formed, glutathione serves as a decoy target, sparing critical hepatic macromolecules. However, when large amounts of the reactive metabolite are formed, the formation of glutathione conjugates exceeds the

capacity of the liver to synthesise glutathione. The resulting depletion of glutathione together with direct covalent binding of the metabolite protein thiols has serious consequences. The oxidation of protein thiol groups results in the formation of disulphur bonds between different molecules of actin, resulting in destruction of the microfilamentous network beneath the plasma membrane (Mirabelli *et al.*, 1988). The depletion of protein thiol groups also decreases the activity of calcium translocases resulting in increases in intracellular Ca^{2+} that further damages the cytoskeleton (Bellomo and Orrenius, 1985). These and other effects of oxidative stress lead to the swelling and disruption on intracellular organelles ultimately resulting in hepatocyte necrosis.

Although it was initially thought that the toxicity of reactive metabolites only caused cell necrosis, this idea has been challenged in recent years (Pessayre *et al.*, 1999). It is now clear that the extensive formation of reactive metabolites can cause apoptosis, necrosis or both (Fau *et al.*, 1997; Shi *et al.*, 1998). Several compounds, such as acetaminophen and cocaine, transformed into reactive metabolites have been shown to cause DNA fragmentation of hepatocytes indicative of apoptosis (Shen *et al.*, 1992; Cascales *et al.*, 1994). The cellular mechanisms causing metabolite-induced apoptosis have been studied with germander, a medicinal plant used in weight control diets, the widespread use of which led to an epidemic of hepatitis in France (Larrey *et al.*, 1992b). Germander contains furano diterpenoids, which are activated by CYP 3A into electrophilic metabolites (Lekehal *et al.*, 1996). Extensive formation of glutathione depletion, which in combination with covalent binding of the metabolites, results in protein thiol oxidation (Lekehal *et al.*, 1996). The oxidation of protein thiols inactivates plasma membrane calcium translocases and increases the permeability of the mitochondrial inner membrane (the mitochondrial membrane permeability transition or MMPT), which through the release of cytochrome C leads to the activation of caspases (Fagian *et al.*, 1990). Caspases are cysteine proteases that cut proteins after an aspartate residue and are the major executioners of apoptosis (Thornberry and Lazebnik, 1998). Caspase activation in conjunction with increased intra-cellular calcium activates calcium-dependent endonucleases, which cut the DNA between nucleosomes, eventually

resulting in apoptosis (Fau *et al.*, 1997). Germander-induced apoptotic hepatocyte death is prevented by troleandomycin, which inhibits its metabolic activation by CYP 3A4 or by preventing the depletion of glutathione with cysteine (Fau *et al.*, 1997).

Factors Influencing Direct Toxicity Due to Reactive Metabolites

Hepatotoxicity from the reactive metabolites of drugs is a significant problem with drugs where the formation of reactive metabolites is low enough to ensure the absence of hepatotoxicity in most recipients (and therefore allowing the marketing of the drug) but is high enough to lead to 'idiosyncratic' toxicity in some 'susceptible' subjects. The reason for susceptibility could be either genetically determined or acquired.

Genetic Factors

The amount of reactive metabolite formed depends on a particular isoenzyme the hepatic level of which may vary between individuals. Genetic polymorphisms of drug-metabolising enzymes may contribute to an individual's risk to an ADR. Polymorphism in debrisoquine oxidation (CYP 2D6) leads to the accumulation of perhexiline resulting in liver injury in poor metabolisers (Morgan *et al.*, 1984) and increases the formation of reactive metabolites leading to chlorpromazine hepatotoxicity in extensive metabolisers (Watson *et al.*, 1988). Polymorphism in mephentoin hydroxylation (CYP 2C19) may predispose poor metabolisers to atrium (phenobarbital, febamate and difebarbamate)-induced hepatotoxicity (Horsmans *et al.*, 1984). Recent studies have shown susceptibility to isoniazid-induced hepatotoxicity was increased with the possession of both NAT2 genotype associated with slow acetylation and CYP 2E1 genotype leading to increased activity (Huang *et al.*, 2002, 2003).

Acquired Factors

Individual susceptibility to hepatotoxicity due to reactive metabolites may also be related to physiological, nutritional or therapeutic modifications in drug metabolism. For example, fasting leads to glycogen depletion and decreased glucuronidation, the depletion of glutathione and the induction of CYP 2E1

leading to an increased risk of paracetamol-induced liver injury (Price, Miller and Jollow, 1987; Whitcomb and Block, 1994). Acquired factors enhancing the rate of biotransformation of a drug to its reactive metabolites through the induction of CYP P450 isoenzymes play an important role in increasing the direct toxicity. Alcohol is a potent inducer of CYP 2E1 and to a lesser extent CYP 3A4. Subjects who consume alcohol regularly may therefore have increased the bioactivation of paracetamol (which is metabolised by CYP 2E1 and CYP 3A4), resulting in hepatotoxicity at conventional 'therapeutic' doses (Zimmerman and Maddrey, 1995). In individuals with heavy alcohol intake, this is compounded by the reduced glutathione synthesis and low glutathione stores due to the inhibition of glutathione synthetase and ethanol-related oxidative stress, respectively. Isoniazid also increases the toxicity of paracetamol by inducing CYP 2E1, whereas rifampicin, another microsomal enzyme inducer, increases the risk of hepatotoxicity due to isoniazid (Moulding, Redeker and Kanel, 1991; Pessayre *et al.*, 1977). Anticonvulsants (phenytoin, carbamazepine and phenobarbital) induce CYP 3A4 and can also enhance the toxic effects of paracetamol (Bray *et al.*, 1992). As an alternative mechanism of drug interaction leading to an increased risk of paracetamol-induced liver injury, zidovudine competes for glucuronidation of the toxic metabolite, thus reducing its excretion (Shriner and Goetz, 1992). Drug accumulation can result from metabolic inhibition caused by another drug. For instance, troleandomycin increases the risk of cholestasis with oral contraceptives by inhibiting the CYP 3A responsible for oestrogen oxidation (Miguet *et al.*, 1980).

The presence of underlying liver disease may predispose to dose-dependent drug toxicity, especially if the margin between therapeutic and toxic concentrations is small (Schenker, Martin and Hoyumpa, 1999). It is generally believed that pre-existing liver disease would neither induce nor worsen the idiosyncratic hepatotoxicity, although this issue has not been studied adequately. However, a recent study demonstrated a higher incidence of hepatotoxicity as well as more severe liver injury secondary to antituberculosis agents in hepatitis B virus (HBV) carriers when compared with non-carriers and with HBV carriers who did not receive antituberculosis therapy (Wong *et al.*, 2000).

IMMUNOLOGIC IDIOSYNCRASY

The clinico-pathologic features of some idiosyncratic drug reactions suggest that immunological mechanisms could play an important role in the pathogenesis of drug hepatotoxicity. These include (a) a fever, rash, lymphadenopathy, eosinophilia and involvement of other organs; (b) hepatic inflammatory infiltrates; (c) low frequency (<1/1000 users); (d) delay in appearance of the disease (2 weeks to several months); and (e) accelerated onset after rechallenge (Beaune and Lecoeur, 1997; Robin *et al.*, 1997). In hepatitis, secondary to sulphonamides, phenytoin and nitrofurantoin, the liver is implicated as part of a systemic hypersensitivity reaction, and evidence for immunological responsiveness to these drugs can be obtained by *in vitro* rechallenge with the drug or its metabolite (Spielberg *et al.*, 1981; Shear and Spielberg, 1988; Rieder *et al.*, 1989). Interestingly, the immune response may not be directed at the drug *per se* but at compounds arising because of its metabolism. Drug hepatotoxicity may therefore be the result of both metabolic and immunological idiosyncrasy. In this respect, the superimposition of CYP P450 and the immune system in the liver have potential disadvantages. The covalent binding of the reactive metabolites to 'self' proteins results in the formation of neo-antigens that 'mislead' the immune system into mounting an immune response against hepatocytes.

The initial and crucial event underlying the so-called 'immuno-allergic hepatitis' is the oxidative metabolism of a drug by a CYP P450 enzyme resulting in the formation of reactive metabolites. Electrophilic metabolites react with and covalently bind to nucleophilic groups of patients to form protein adducts. The best-studied example is that of halothane, which is oxidised into a reactive acyl chloride (CF_3COCl) by CYP P450 2E1. The metabolite reacts with the $\epsilon\text{-NH}_2$ group of the lysine residues of proteins to form trifluoroacetylated proteins (CF_3CO -lysine proteins) (Gut, Christen and Huwyler, 1993). The reactive metabolite may also bind covalently to the CYP 2E1 protein itself (Eliasson and Kenna, 1996). The alkylation of CYP P450 proteins may lead both to anti-P450 autoantibodies and to antibodies against the modified part of the protein. Therefore, a single drug such as halothane may concomitantly

give rise to both 'immune-allergic' and 'autoimmune' hepatitis.

FACTORS INFLUENCING IMMUNOLOGICALLY MEDIATED DRUG HEPATOTOXICITY

Genetic factors influencing the development of the immune-mediated drug hepatotoxicity can be grouped into factors affecting the amount of the reactive metabolite and therefore protein adduct formed and factors affecting the immune response to these adducts (Aithal, 2004). Dihydralazine hepatitis is a good example of how a 'metabolic' genetic factor can contribute to susceptibility to immune-mediated hepatotoxicity. Dihydralazine is predominantly acetylated by the polymorphic *N*-acetyl transferase 2. In slow acetylators, the majority of the drug is available for metabolic activation by CYP 1A2 into a free radical. Hence, the alkylation of hepatic proteins is more extensive, and the incidence of immune-mediated hepatitis is higher (Bourdi *et al.*, 1994).

The second group of genetic factors influencing susceptibility to immune-mediated hepatic drug reactions is the genes whose products are involved in immune regulation. Genetic polymorphism in major histocompatibility complex (MHC) molecules is the most obvious example. The presence or absence of a given human leukocyte antigen (HLA) molecule may determine the efficient presentation of an alkylated immunogenic peptide. Associations have been reported between HLA A11 and hepatotoxicity due to halothane, tricyclic antidepressants and diclofenac, HLA DR6 and liver injury secondary to chlorpromazine and nitrofurantoin, HLA B8 and clometacin hepatitis (Berson *et al.*, 1994). Two case-control studies involving Caucasian population have demonstrated that co-amoxiclav-induced jaundice is strongly associated with HLA DRB1*1501-DRB5*0101-DQB1*0602 haplotype (Hautekeete *et al.*, 1999, O'Donohue *et al.*, 2000). Subjects carrying the extended haplotype would be at nine times higher risk of developing ADR to co-amoxiclav (O'Donohue *et al.*, 2000). More recently, genetic polymorphism in gene-encoding immunomodulatory cytokines such as interleukin-10 (IL-10) and IL-4 has been shown to influence the risk of diclofenac-induced hepatotoxicity (Aithal, 2004).

SPECIFIC HISTOLOGICAL TYPES OF DRUG-INDUCED LIVER INJURY

Cholestasis

From experimental models, several mechanisms have been postulated for impaired bile secretion. They are the inhibition of Na⁺, K⁺-ATPase resulting in reduced uptake of bile acids, increased pericellular permeability and regurgitation into plasma of bile constituents, impaired intracellular transport due to cytoskeletal dysfunction, altered intracellular calcium homeostasis or altered canalicular carriers (Erlinger, 1997). A recent study demonstrated that oestrogen metabolites trans-inhibit the bile salt export pump in rat liver providing a molecular basis for drug-induced cholestasis (Stieger *et al.*, 2000).

Steatosis

Microvesicular steatosis occurs in conditions characterised by severe impairment of the mitochondrial β-oxidation process. Drugs can sequester co-enzyme A (aspirin valproic acid), inhibit mitochondrial β-oxidation enzymes (tetracycline) and, in addition, inhibit oxidative phosphorylation (amiodarone and perhexiline). When β-oxidation is severely impaired, fatty acids, which are poorly oxidised by mitochondria, are mainly esterified into triglycerides and accumulated as small vesicles (Fromenty, Berson and Pessayre, 1997).

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). 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, Goldberg and Buskin, 1999). 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, one-third of patients with drug-induced liver disease had persistently abnormal liver tests (liver enzymes and/or imaging) at median follow-up of 5 years, and the detection of fibrosis in the liver biopsy and continued drug intake after the initial liver injury predicted adverse outcome (Aithal and Day, 1999).

Management of acute hepatic failure secondary to idiosyncratic hepatic reaction is similar to that of viral hepatitis. 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, the mortality rate of 40% have been reported (Bjornsson and Olsson, 2005). Corticosteroid treatment has not been shown to be beneficial in the management of drug-induced hepatitis. There is no clear evidence that ursodeoxycholic acid therapy changes outcome in chronic cholestasis.

PREVENTION

Experience gained by wide clinical usage of a drug following marketing may assist in recognising individual risk factors and better definition of safe dosage. Strategies of avoiding the prescription in ‘at-risk situations’ and safer dosage regimes have reduced adverse hepatic reactions due to several drugs. Some such examples include the avoidance of reuse of halothane within 3 months, parenteral administration of large doses of tetracycline as well as its use in pregnancy and renal disease, aspirin in children and valproic acid in combination therapy in children under the age of 3 years (Farrell, 1994; Neuberger, 1998). The incidence of hepatic fibrosis with weekly low-dose methotrexate regimes is much lower than that reported with daily dose regimes (Boffa *et al.*, 1995; Aithal *et al.*, 2004a).

When a new drug is recognised to be associated with significant hepatic ADR, it has become common practice to recommend regular monitoring of liver enzymes

for the early detection of liver injury so that drug can be withdrawn before serious hepatotoxic reaction occurs. Although this is logical, the level of enzyme elevation at which the risk of serious, progressive hepatotoxicity is significant and yet the injury is completely reversible on the withdrawal of medication is still uncertain (Kaplowitz, 2005). In addition, compliance with such recommendation remains low (Gaham *et al.*, 2001).

Of even greater importance in the determination of individual risk is the inherited factors that affect the kinetics and dynamics of numerous drugs. Susceptibility to hepatic drug reaction depends principally on genetic factors that determine the metabolism, as well as the biochemical and immunological responses, to the metabolites. A major difference between genetic and environmental variation is that an inherited trait has to be tested for only once in a lifetime, whereas environmental effects change continuously. In the future, the discovery of pharmacogenetic traits will change with new technologies based on genomics. Rapid sequencing and single-nucleotide polymorphisms (SNPs) will play a major role in the linking of sequence variations with heritable phenotypes of drug response (Meyer, 2000). In fact, pharmacogenetics technology may enable a significantly better post-marketing surveillance system. In this proposed concept (Roses, 2000), hundreds of thousands of patients who receive the drug would have blood taken and stored in an approved location. As rare, serious adverse events are documented, DNA from patients who experienced the ADR could be compared with that from controls, who did not have adverse reaction while on the drug. This would enable ‘genetic fingerprints’ (SNP profiles) of the subjects susceptible to the adverse event to be determined. These adverse event profiles would be combined with efficacy profiles to produce a comprehensive medicine response profile. This would allow the selection of patients for both efficacy and lower complications of drug 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 (Easterbrook, 1999; Edwards and Biriell, 1995). 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 non-prescription 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 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).

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

Table 36.2. World Health Organization definitions – causality assessment of suspected adverse reactions.

Certain: 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.
Probable/likely: 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.
Possible: 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.
Unlikely: 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.
Conditional/unclassified: 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.
Unassessable/unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

With more than 30 000 prescription drugs in the United States 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 *Toxicology of the Eye* (1993) and Fraunfelder and Fraunfelder's *Drug-Induced Ocular Side Effects* (2001).

The National Registry of Drug-Induced Ocular Side Effects is also a source of help to the busy clinician (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,
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 rechallenged, 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
 or faxed: (503) 494-4286
 or e-mailed: 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 or are they an indication to stop therapy.

Goal of Ocular Evaluation

The goal is to find early changes, i.e. 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 (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 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.
- Progressive macular disease of any type.
- Significant kidney or liver disease is 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, Fraunfelder and Edwards, 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, i.e. 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 (Fraunfelder, 2005; Fraunfelder and Pomeranz, 2005; Egan and Fraunfelder, 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 sildenafilevels in the blood. The side effects based on dosage start at 15–30 min and usually peak 1h after ingestion of the drug.

- 50 mg gone in 1h
- 100 mg gone in 2h
- 200 mg gone in 4–6h

Guidelines for Following Patients (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 PDF
- 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®, BECONASE®, VANCENASE®, VANCERIL®) (BUDESONIDE – RHINOCORT®)

Primary Use

For treating asthmatic, allergic and chronic lung diseases.

Clinical Concerns

A report in the *Journal of the American Medical Association* (Garbe, Suissa and Lelorier, 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 is 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 (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 recommends 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 is not in itself an indication to stop the drug,
- retinal changes can occur even at 20 mg dosage levels and
- optic neuritis 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 (After Macaluso, Shults and Fraunfelder, 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, i.e. 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 (NLP). Finally, the degree of amiodarone neuropathy may not be equal in each eye for a few months but 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, Fraunfelder and Keates, 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®), ALENDRONIC ACID (FOSAMAX®), IBANDRONATE, ZOLENDRONATE (ZOMETA®), RISEDRONATE SODIUM (ACTONEL®), CLODRONATE (BONEFOS®), ETIDRONATE DISODIUM (DIDROCAL®) 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 non-specific 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
- Non-specific 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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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 United States, 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, Khoury and Mannino, 1997).

FREQUENCY AND VARIETY OF MEDICATION USE AMONG PREGNANT WOMEN

In the United States alone, 119 new drug or biologic applications were approved by the Food and Drug Administration (FDA) in 2004. In the same year, an additional 147 approvals were issued by the FDA for new or expanded uses of currently marketed drugs or biologics (U.S. FDA, 2005). 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 United States 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 United States, 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 United States 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, Belanger and Bracken, 2003), epilepsy 0.4%–1.0% (Yerby, 2000; Holmes, Wyszynski and Lieberman, 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 under treat) could lead to events, such as uncontrolled seizure activity or psychiatric episodes, which 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.

PRE-MARKETING SOURCES OF DATA REGARDING REPRODUCTIVE AND DEVELOPMENTAL SAFETY OF PRENATAL DRUG EXPOSURES

The traditional methods for evaluating drug safety in the pre-marketing 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 pre-clinical 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 post-marketing 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.

POST-MARKETING 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 U.S. 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 health-care 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, Corbin and Sundell, 1997) and acyclovir (Andrews *et al.*, 1992; Preboth, 2000), whereas several others are presently ongoing. A current listing is available on the U.S. FDA’s Office of Women’s Health website (<http://www.fda.gov/womens/registries/registries.html>). 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 pregnant woman herself. Although pregnancy outcome reports can be collected retrospectively, most current drug registries also identify and follow exposed pregnancies prospectively, i.e. 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 to 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, Pastuszak and Ito, 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, Pastuszak and Ito, 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, Wyszynski and Lieberman, 2004). Another approach is that used by the antiretroviral drugs in 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 post-marketing commitments or initiated by other groups interested in generating pregnancy safety data, the U.S. FDA has produced a guidance document (U.S. 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 recently approved 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 (U.S. FDA Office of Women's Health, 1999). 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 (ICBDMS), which has been in existence since 1974 (Erickson, 1991; Khoury *et al.*, 1994).

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 pre-defined 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 United States and is the general design of the U.S. National Birth Defects Prevention Study (Carmichael *et al.*, 2006). These methods are also used on an ongoing basis in programs such as the Slone 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 (ECLAMC) 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, i.e. 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, Shapiro and Mitchell, 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, Mitchell and Shapiro, 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, James and Erickson, 1994), 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 – e.g. 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, Kallen and Wiholm, 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 United States (Chung and Myrianthopoulos, 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 (Olsen *et al.*, 2001) and are in the process of being organized in the United States 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 as well as 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, Rydhstroem and Aberg (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. Teratology Information Services 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 (ENTIS) (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 sufficiently 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. 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 (Jones *et al.*, 1989; Chambers *et al.*, 2001; Lyons Jones, Johnson and Chambers, 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 discharge data across the Canadian population have been used to evaluate adverse outcomes of pregnancies complicated by asthma (Wen, Demissie and Liu, 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, Shatin and Clouse, 2000). Similarly, information from the Group Health Cooperative of Puget Sound in the United States has been used to examine the association between topical tretinoin (Retin-A) and major birth defects (Jick, Terris and Jick, 1993). The General Practice Research Database in the United Kingdom 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 off 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 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. 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 limitation is not insurmountable if it is possible to incorporate some level of validation.

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, and 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 S.T.E.P.S. 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 United States 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 S.M.A.R.T. program (System for Management of Accutane Related Teratogenicity). As of March 2006, in the United States, this effort has been increased to a level in many respects comparable with the thalidomide prevention program. The new 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.

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 pre-marketing reproductive toxicity studies. If the cross-species predictive value of these experiments can be increased, then it may be possible in the pre-clinical 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, Kimmel and Mendola, 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. 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). 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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Renal Adverse Drug Reactions

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INTRODUCTION

The kidney is particularly vulnerable to adverse drug reactions (ADRs) (Porter, Palmer and Henrich, 2003). Because it excretes many of their metabolites, it is exposed to high concentrations of these drugs. Moreover, several renal transport processes potentially lead to accumulation of drugs in renal cells. 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 renal failure (ARF).

Drug-induced decrease in renal function is a major side effect in clinical practice. ARF is defined as an acute onset of severe deterioration of renal function necessitating renal replacement therapy. In the context of clinical studies, nephrotoxicity is more readily defined as a predefined level of decrease of renal function. In chronic renal failure (CRF) 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 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, due 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).

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 summarised in Table 38.1).

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 ARF contributing

Table 38.1. 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, oedema
Regulation of blood pressure	Hypertension, orthostatic hypotension
Regulation of acid-base status	Alkalosis, acidosis
Stimulation of erythropoiesis by erythropoietin	Anaemia

to 4–19% of the cases (Hou *et al.*, 1983; Shusterman *et al.*, 1987; Nash, Hafeez and Hou, 2002; Payen and Berton, 2005), also in developing countries (Jha *et al.*, 1992). Antibiotics (aminoglycosides, amphotericin B and piperacillin), non-steroidal anti-inflammatory drug (NSAIDs), cyclosporine and angiotensin-converting enzyme (ACE) inhibitors are high on the list (Nash, Hafeez and Hou, 2002). Especially in the setting of the intensive care unit (ICU), drug-induced renal failure is very frequent. The reason is that many precipitating factors such as hypovolaemia, true hypovolaemia 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 ARF 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 (Baraldi *et al.*, 1998). In children drugs are a rare cause of ARF (Moghal, Brocklebank and Meadow, 1998).

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 lead to CRF. Prospective studies firmly linked the disease to the chronic use of analgesic mixtures. The relationship has been established for mixtures containing phenacetin (Dubach, 1983) as well as for mixtures not containing phenacetin (Elseviers and De Broe, 1995). In the same patients, urinary tract tumours 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).

MECHANISMS OF RENAL ADVERSE DRUG REACTIONS

Drugs may adversely affect renal function by inducing structural injury to components of the nephron and/or by interfering with the filtration and transport processes or regulatory pathways (Table 38.2).

Drugs interfering with glomerular blood flow may induce functional renal impairment. Cyclosporine and epinephrine cause preglomerular arteriolar vasoconstriction resulting in a decrease in intra-glomerular 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 of postglomerular vasoconstriction mediated by angiotensine II. Disruption of these counter-regulatory mechanisms by the administration of NSAIDs or of drugs interfering with angiotensine II (ACE inhibitors and angiotensine II receptor blockers) can produce

Table 38.2. The classification of various drugs on pathophysiologic categories of acute renal failure.

Functional impairment	NSAIDs, ACE inhibitors, cyclosporine, cephalothin, amphotericin receptor blockers, diuretics, interleukins, cocaine, mitomycin C, tacrolimus, oestrogen, 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, tolmetin, zomepirac, contrast media, sulphonamides, thiazides, phenytoin, furosemide, allopurinol, cimetidine, omeprazole, phenindione
Tubular obstruction	Sulphonamides, methotrexate, methoxyflurane, glafenin, triamterene, ticrynafen, acyclovir, ethylene glycol, protease inhibitors, suprofen
Hypersensitivity angitis	Penicillin G, ampicillin, sulphonamides
Thrombotic microangiopathy	Mitomycin C, cyclosporine, oral contraceptives

Adapted from Porter, Palmer and Henrich (2003) (with permission).

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 those taking diuretics (Adhiyaman *et al.*, 2001).

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 randomised clinical trial, the incidence of severe hyperkalaemia was minimal, patients with renal failure or pre-existing hyperkalaemia being excluded from the trial. In subsequent years, however, case reports of life-threatening hyperkalaemia in patients treated with spironolactone appeared in the literature (Schepkens *et al.*, 2001). It became evident that hyperkalaemia is episodic in these patients and linked to ARF. The main causes for ARF in this setting were dehydration and worsening heart failure. In a population-based time-series analysis recently conducted in Canada, an increase was found in hyperkalaemia-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 related neither to dose nor to the duration of treatment, but susceptible 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 ARF cases. Clinically, the disease is characterised by bilateral lumbar pain, fever and skin rash. Many patients exhibit hyper-eosinophilia, hypereosinophyluria and increased IgE 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 β -lactams, and NSAIDs.

The particular susceptibility of the tubular cell to nephrotoxic injury has several reasons. Tubular solute transport and other renal metabolic processes utilise considerable oxygen and are susceptible to the action of metabolic inhibitors. It is worthwhile to note 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, Tulkens and Molitoris, 2003). Aminoglycosides are polar drugs that are freely filtered via 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 38.1). 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.*, 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 maximises 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. ARF may result from tubular

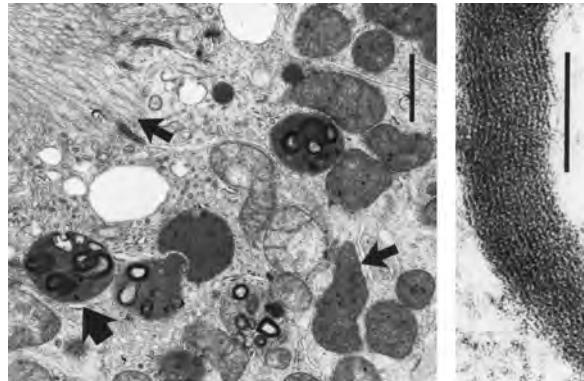


Figure 38.1. Ultrastructural appearance of proximal tubular cells in aminoglycoside-treated patients (4 days at therapeutic dose). Lysosomes (large arrow) contain dense lamellar and concentric structures. Brush border, mitochondria (small arrow) and peroxisomes are unaltered. Upon higher magnification, the structures in lysosomes show a periodic pattern. The bar in the upper part represents 1 µm, in the lower part 0.1 µm (De Broe *et al.*, 1984 – with permission).

obstruction due to intratubular precipitation of the drug or its metabolite. This mechanism has been incriminated in the clinical syndrome of bilateral flank pain and ARF associated with the use of suprofen (Henann and Morales, 1986; Hart, Ward and Lifschitz, 1987). This renal adverse drug reaction led to the withdrawal of this NSAID from the market in 1986 (Chapter 1 of this book). Because suprofen is a uricosuric agent, one might speculate that it could lead to intratubular or ureteral precipitation of uric acid (Abraham *et al.*, 1988). More recently, there have been reports of this type of renal adverse event following high-dose intravenous acyclovir and during treatment with protease inhibitors.

The immunosuppressive drug cyclosporine is of particular interest since it can display all types of nephrotoxicity (reviewed in Bosmans and De Broe, 2006). Cyclosporine profoundly alters renal and glomerular haemodynamics. 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 hyperkalaemic 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 vacuolation 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 38.2). 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 haemolytic-uraemic 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, haemolytic anaemia and deteriorating renal function.



Figure 38.2. 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.

DIAGNOSIS OF RENAL ADVERSE DRUG REACTIONS

None of the described functional or morphologic alterations to the kidney are pathognomonic to ADR. So, general principles of renal diagnostic procedures apply to the evaluation of 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-hour urine collection, which is cumbersome and prone to error. Therefore, it is now generally accepted to calculate creatinine clearance using nomograms like the Cockcroft–Gault formula (Cockcroft and Gault, 1976; Gault *et al.*, 1992) or the MDRD formula (Levey *et al.*, 1999, 2000) (Table 38.3). Care must be taken always to compare the result of the creatinine clearance calculation to 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 (EDTA) 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 points to a pathological condition of the glomerulus, changing the permselectivity of the filter. Under normal conditions, a minute amount of low molecular weight proteins are filtered, which then undergo 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.

Table 38.3. The calculation of creatinine clearance/glomerular filtration rate.

The Cockcroft–Gault formula (Gault <i>et al.</i> , 1992)	
$\frac{140 - \text{age (years)} \times \text{weight (kg)}}{72 \times \text{Screat (mg/dl)}} (\text{ml/min})$	Male (18–92 years)
The MDRD formula (Levey <i>et al.</i> , 1999, 2000)	Female (18–92 years) $\times 0.85$
$186 \times \text{Screat}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (if African American)} (\text{ml/min}/1.73 \text{ m}^2)$	

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 localised in specific segments of the nephron. For example, alanine aminopeptidase, alkaline phosphatase and γ -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. Secondly, 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 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. Recently, for example, *in vitro* studies involving renal cells in culture suggested that the underlying mechanism of the proteinuria associated with the use of rosuvastatin was inhibition by the statin of the endocytotic uptake of proteins by the

proximal tubular cell (Verhulst, D'Haese and De Broe, 2004). Several permanent and immortalised cell lines of human and non-human 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. Especially, 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, Robson and Wagener, 1998). Drug interactions interfering with drug disposition may lead to nephrotoxicity. Inhibition of drug-metabolising 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 recognised, rhabdomyolysis and ARF may result. The risk for ARF 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 hypovolaemia or reduced effective circulating volume) are well-recognised risk factors for hospital-acquired ARF (Shusterman *et al.*, 1987). The latter risk factor for nephrotoxicity is modifiable by intervention prior to the 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 due 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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Anaesthetic Adverse Drug Reactions

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INTRODUCTION

Anaesthesia 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 anaesthesia include the intravenous anaesthetic 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 United Kingdom, the incidence and severity of anaphylactic reactions are unclear. A report of suspected anaphylactic reactions associated with anaesthesia from the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and British Society for Allergy and Clinical Immunology (2003) from 1 January 1995 to 22 June 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 anaesthesia, and 10% are fatal compared with 4% for all drugs. It is possible that the intravenous route for many anaesthetic agents predisposes patients to these reactions, and more than 90%

of reports occurred immediately or soon after induction of anaesthesia. The MHRA yearly average for reported suspected anaphylactic reactions related to anaesthesia 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 estimates that in the United Kingdom there are 500 anaphylactic reactions annually by using epidemiological data from France and Australia. Previous estimates for the United Kingdom ranged from 350 to 5000 patients per year (Clarke and Watkins, 1993).

Anaesthetists 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 complied from data in 1998 identified the sedative agents most often used for over 72 hours 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 United Kingdom 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 anaesthetic 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 non-steroidal anti-inflammatory drugs (Reuben, Ablett and Kaye, 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 anaesthesia and surgery identified an overall anaesthetic 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 anaesthetic 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 post-marketing surveillance of morbidity and mortality to improve patient safety during anaesthesia and critical care.

In the United Kingdom in the late 1970s, Lunn and Mushin identified the pharmacological causes of anaesthetic 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 anaesthetic 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 United Kingdom 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 anaesthetics (Fisher and Baldo, 1994). Since 1984 in France, there has been an epidemiological study of suspected anaphylactic reactions occurring during anaesthesia. 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 hours and occasional false negative tests) and specific IgE and skin tests 6 weeks later (AAGBI, 2003; Mertes and Laxenaire, 2002).

The most common drugs implicated in these type of reactions were the neuromuscular blocking agents with an incidence of 1 in 6500 anaesthetics compared with an overall incidence of 1 in 13 000 (Laxenaire, 1999). The specific substances identified in this multi-centre outpatient study as possible causes of allergic

phenomenon 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 anaesthetic drugs are considered to be rare. The AAGBI report (2003) was unable to identify allergic reactions to inhalational agents but a few have been reported in the United Kingdom (Table 39.10) through yellow forms onto the database of the MHRA.

Fisher and colleagues have identified the presenting clinical features of anaphylaxis during anaesthesia in 555 patients (Whittington and Fisher, 1998). In order of frequency they are; no pulse, difficulty inflating the lungs, flushing, oxygen desaturation, cough, rash, dysrrhythmias, urticaria and oedema. The cardiovascular system is most often destabilised, 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 anaesthesia 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%), oedema (33% including generalised 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 (2003) include immediate management (depending on the severity), immediate and late investigations and centralised reporting.

A diagnosis of an anaphylactoid reaction to anaesthetic 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, Laxenaire and Alla, 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, Fisher and Harle, 1991). It should be recognised 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 anaesthetic drugs are more common in females than males even when the gender ratio of anaesthetised patients is taken into account. Age was only identified as a factor for latex allergies, but allergies to anaesthetic 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 documented reaction to a specific anaesthetic 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 anaesthetic administration. There is no evidence for generalised screening before surgery but, given the importance of a positive history of adverse drug reaction, primary prevention and accurate documentation is essential.

Although the majority of adverse drug reactions to anaesthetic drugs occur at the time of anaesthesia, there are many reported delayed reactions after general anaesthesia. These include exfoliative dermatitis, Stevens–Johnson syndrome and other events (Fisher and Baldeo, 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 summarised 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 39.1). 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 analysed here. The data contains 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 39.1). Table 39.2 summarises the category classifications for the reactions. Table 39.3 summarises 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,

Table 39.1. 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%)

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 phenomenon. However, many more reactions reported with etomidate related to central nervous system excitation with convulsions in the majority of reactions (Table 39.4). Involuntary muscle movements can be severe, and epileptiform electroencephalographic activity has been demonstrated on induction of anaesthesia 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 39.4). 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 39.2 in the category of adrenal insufficiency. The main evidence came from 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 hours. 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 has been made recently (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. Hypertriglyceridaemia and pancreatitis are uncommon complications (Possidente *et al.*, 1998), and hepatobiliary fatalities are recorded in Table 39.3. For propofol, the event that limits its use in children in the ICU is highlighted in the 'metabolic' column of Table 39.2 (see below for adverse drug reactions in children) and has been called the propofol infusion syndrome. It is not confined to children and has been identified in an adult (Perrier,

Table 39.2. The number of total reactions (R) to the intravenous induction agent indicated and the fatalities (F) in that category.

	Thiopentone		Methohexitone		Etomidate		Propofol		Ketamine	
Categories	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
Haemopoetic	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	213	21	217	5	2777	80	136	3

Baerga-Varela and Murray, 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 [ethylene-diaminetetraacetic 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, Davis and Washington, 2001).

Fatal reports of allergic reactions are recorded in Table 39.3. The severity of these events is striking but the vagaries of the reporting system should be considered. For example, in Table 39.2 in the large

Table 39.3. Data from the drug analysis print on single drug reports for intravenous agents submitted up to January 2004.

Drugs	Thiopentone		Methohexitone		Etomidate		Propofol		Ketamine	
Reactions	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal
Cardiovascular										
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	1		
Extrasystoles									1	1
Ventricular fibrillation							6	2		
Acute cardiac failure	9	2	4	1			23	4		
Coronary artery occlusion							1	1		
Myocardial ischaemia							3	1		
Myocardial infarction					1	1	5	1		
Cardiorespiratory failure	1	1					2	2		
Pulmonary oedema	4	2	1	1						
Pulmonary hypertension							1	1		
Cerebrovascular										
Cerebral haemorrhage	1	1					1	1		
Brain stem ischaemia	1	1								
Cerebral embolism							1	1		
Others										
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 39.3. *Continued.*

Drugs	Thiopentone		Methohexitone		Etomidate		Propofol		Ketamine	
Reactions	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal	Total	Fatal
Disseminated intravascular coagulation							1	1		
Coma	4	1								
Suicide/non accidental overdose	1	1					3	3	1	1
Cerebral oedema							2	1		
Motor neurone disease			1	1						
Intrauterine death							1	1		
Respiratory disorders										
Anoxia			1	1						
Acute respiratory distress syndrome							3	1		
Pneumothorax	2	1								
Respiratory failure	2	1								
Respiratory depression	5	3								
Bronchospasm	76	3	13	1	14	1	155	6		
Exacerbation of asthma					1	1				
Laryngeal oedema							7	1		
TOTAL (non-allergies)	136	32	38	19	21	5	430	68	3	3
Allergies										
Anaphylactic reaction	54	14	9	1			42	8		
Anaphylactic shock	1	1					7	1		
Anaphylactoid reaction	24	4	7	1			39	3		
TOTAL (allergies)	79	19	16	2	0	0	88	12	0	0
Total	215	51	54	21	21	5	518	80	3	3

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.

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 anaesthetic 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

Table 39.4. Neurological and peripheral vascular reactions reported in the Etomidate Data Analysis Print ($n = 217$).

Reaction	Number
Neurological	
Convulsions	22
Grand mal convulsion	21
Myoclonic seizure	7
Loss of consciousness	2
Chorea	2
Extrapyramidal disorder	2
Dyskinesia	1
Focal convulsion	1
Hypoaesthesia	1
Paraesthesia	1
Hypotonia	1
Muscle rigidity	1
Peripheral vascular	
Venous thrombophlebitis	12
Vein thrombosis	2
Venous thrombosis	2
Vasculitis	1
Arterial thrombosis	1
Thrombosis	1
Vasodilation	1

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 centres contributing to data from anaesthetic outpatient allergy clinics in 1990–91 reported in 1993 that an immune mechanism had been demonstrated in 813 of 1585 patients and of these 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, 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 39.5–39.7) record fatalities and allergies in the atracurium, pancuronium, vecuronium and tubocurarine groups. Fatalities would not present to out-patient allergy clinics, and so these data are useful in identifying 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 39.8–39.10. Table 39.9 summarises a predominance of reports relating to the hepatobiliary system, and halothane, isoflurane, desflurane, isoflurane,

Table 39.5. 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%)

Table 39.6. The number of total reactions (R) to the neuromuscular or antagonist drug indicated and the fatalities (F) in that category.

Categories		Atracurium	Cis atracurium	Gallamine	Pancuronium	Rocuronium	Suxamethonium	Tubocurarine	Vecuronium	Neostigmine	
	R	F	R	F	R	F	R	F	R	F	R
Cardiovascular	184	8	10	1	12	1	15	1	44	1	266
Cerebrovascular	1	1	0	0	0	0	0	0	1	0	16
Congenital	1	0	0	0	0	0	0	0	1	0	0
Metabolic	6	0	0	0	0	0	1	0	13	0	0
Hearing	1	0	0	0	0	0	1	0	0	0	0
Eye	3	0	0	0	0	0	0	0	2	0	0
Allergies	100	6	5	0	8	0	10	2	41	0	160
Gastrointestinal	2	0	0	1	0	0	1	0	7	0	0
General	35	0	1	0	4	0	17	1	8	0	47
Haemopoietic	4	0	0	0	0	0	1	0	3	1	0
Hepatobiliary	2	0	0	0	0	0	0	0	0	0	0
Injuries/poisoning	1	0	0	0	0	0	0	0	0	0	0
Investigation/ procedure	0	0	0	0	0	0	0	2	0	0	0
Musculoskeletal	9	0	1	0	0	0	3	1	36	4	0
Neurological	32	0	2	0	0	0	11	0	3	0	21
Peripheral vascular	10	0	0	1	0	0	1	0	6	0	0
Psychiatric	3	0	0	0	0	0	0	0	3	1	0
Renal	4	0	0	0	0	1	0	0	1	0	0
Respiratory	134	2	6	0	5	1	12	2	20	0	123
Skin	138	0	1	0	1	0	7	0	16	0	48
Surgical/medical interventions	1	0	0	0	0	0	0	0	1	0	0
TOTAL	680	17	26	1	32	2	73	6	140	2	741
									52	1	178
										53	6
										48^e	3

^a plus 1 from a mixture with multiple constituents;^b plus 2 from a mixture with multiple constituents;^c plus 3 from a mixture with multiple constituents;^d plus 9 from a mixture with multiple constituents;^e plus 17 from a mixture with multiple constituents.

Table 39.7. Data from the drug analysis print on single drug reports for neuromuscular-blocking agents or their antagonists submitted up to January 2004.

Table 39.7. *Continued.*

Reactions	Atracurium	Cisatracurium	Gallamine	Pancuronium	Rocuronium	Suxamethonium	Tubocurare	Vecuronium	Neostigmine
	T	F	T	F	T	F	T	F	T
Musculoskeletal									
Malignant hyperthermia					2	1	14	3	
Myoglobinuria						2	1		
Psychiatric									
Suicide					1	1		1	1
Respiratory disorders									
Respiratory gas exchange disorder			1	1					
Pneumonia						1	1		
Bronchospasm	96	2	3	1	6	1	84	2	
Apnoea						13	3		
Laryngeal oedema							2	1	
Total (non-allergies)	152	11	1	6	2	11	4	3	337
Allergies							37	0	18
Allergic							10	1	
Anaphylactoid reaction	30	2			3	1		41	4
Anaphylactic reaction	71	4			6	1		100	9
Anaphylactic shock							8	2	
Total (allergies)					9	2	0	159	16
Total	253	17	1	1	6	2	20	6	53
							29	6	4
								3	

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 39.8. A summary of the data analysis prints for nitrous oxide gas and the inhalational anaesthetic 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.

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 39.10 where hepatic failure and hepatic necrosis predominate.

Halothane is well recognised to cause hepatic damage because it is metabolised 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 metabolised, 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 reported in the data analysis prints are small (Table 39.9) 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 39.9).

LOCAL ANAESTHETICS

Table 39.11 shows the results of the UK data analysis prints for the local anaesthetics 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 anaesthetic drugs have been reported:

- nerve toxicity with hyperbaric lidocaine delivered intrathecally through a microcatheter during long term use;
- reduced metabolic breakdown, for example, by drugs altering plasma cholinesterase activity or CYP450 enzymes can allow toxic concentrations of local anaesthetic drugs to build up; and
- reduction of liver blood flow, for example, by hypotension will decrease the hepatic clearance of amide local anaesthetics.

Lidocaine data (Tables 39.11–39.13) are divided into three categories because lidocaine has a different toxicity profile when combined with a vasoconstrictor, such as epinephrine (adrenaline) or phenylephrine. In anaesthesia, 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 39.12 and 39.13 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

Table 39.9. The number of total reactions (R) to the gas or inhalational anaesthetic drug indicated and the fatalities (F) in that category.

	Halothane		Desflurane		Isoflurane		Sevoflurane		Enflurane		Methoxyflurane		Trichloroethylene		Nitrous oxide	
Categories	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	2	0	0	2	0	0	0	0	0	1 ^a	1
Endocrine	0	0	1	0	0	0	0	0	0	0	1	0	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	0	0	16	0	0	0	0	0	9	0
Haemopoetic	7	0	0	0	2	0	0	0	2	0	0	0	0	0	4	0
Hepatobiliary	505	182	1	0	48	6	0	0	32	3	1	0	4	1	9	2
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	0	0	11	0	0	0	0	0	1	0
Neurological	22	0	0	0	17	0	0	0	59	0	0	0	2	0	9 ^b	0
Peripheral vascular	0	0	1	0	1	0	0	0	0	0	0	0	1	0	1	0
Pregnancy	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Psychiatric	7	0	0	0	3	0	0	0	4	0	0	0	0	0	4 ^c	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 ^a	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 ^a	0
TOTAL	822	211	37	8	165	9	30	3	165	5	5	0	11	3	83 ^d	13

^a plus 1 from a mixture with multiple constituents;

^b plus 4 from a mixture with multiple constituents;

^c plus 3 from a mixture with multiple constituents;

^d plus 10 from a mixture with multiple constituents.

pre-prepared should be used with a concentration of 1 in 200 000. What this data does not identify is the co-administration effects of volatile anaesthetic agents such as halothane with lidocaine solutions containing epinephrine. In this situation, the volatile anaesthetic agent can sensitize the myocardium and this leads to dysrhythmias.

The reactions for bupivacaine also demonstrate cardiovascular events; they reflect myocardial bupivacaine toxicity that may be refractory to treatment

(Table 39.9). Accidental intravenous injection of bupivacaine can lead to fatal cardiac arrhythmias particularly in association with a Bier's nerve block (intravenous regional anaesthesia). The first alert of this scenario was published in 1983. Subsequently, bupivacaine has not been recommended for intravenous regional anaesthesia. The preferred drug is prilocaine that is less toxic (Table 39.11 shows no deaths) but which in infants may induce methaemoglobinemia.

Table 39.10. Data from the drug analysis print on single drug reports for the gas and inhalational agents submitted up to January 2004.

Table 39.10. *Continued.*

Drugs	Halothane		Desflurane		Isoflurane		Sevoflurane		Enflurane		Methoxyflurane		Trichloroethylene		Nitrous oxide	
Reactions	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T	F
Adult Respiratory Distress Syndrome									1	1						
Total (non-allergies)	544	210	37	8	8	7	3	3	13	5	0	0	3	3	14	12
Allergies																
Anaphylactoid	1	1														
Anaphylactic					2	2									1	1
Total (allergies)	1	1	0	0	2	2	0	0	0	0	0	0	0	0	1	1
Total	545	211	37	8	10	9	3	3	13	5	0	0	3	3	15	13

* similar symptoms but classified in different classes.

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.

Table 39.11. A summary of the data analysis prints for the local anaesthetic 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.

ANALGESICS, SEDATIVES AND THEIR ANTAGONISTS

Tables 39.14, 39.15 and 39.16 show a selection of adverse effects from opioid and non-steroidal anti-inflammatory analgesics, sedative and antagonists that are used mainly during anaesthesia. The risks associated with their long-term use in the ICU are described in the Section 'Introduction'. In this situation their side effects can be more severe.

SPECIFIC PROBLEMS

ANAESTHETIC 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 anaesthetic drugs. Ten of these were from the use of inhalational anaesthetic agents alone and thirteen 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 39.2) 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 hyperlipidaemia, 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, Glazier and Bauman, 2001). Acute renal failure can then result from rhabdomyolysis, and myocardial dysfunction with bizarre, wide QRS complexes develop without hyperkalaemia. The death

Table 39.12. The number of total reactions (R) to the local anaesthetics indicated, when administered as single constituent products, and the fatalities (F) in that category.

Categories	Lidocaine	Lidocaine and epinephrine	Lidocaine and phenylephrine	Bupivacaine	Levo-Bupivacaine	Ropivacaine	Procaine	Prilocaine								
Cardiovascular	R 125	F 8*	R 70	F 2	R 1	F 0	R 72	F 15	R 5	F 0	R 4	F 1	R 4	F 0	R 21	F 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	0	6
Eye	14	0	11	0	0	0	13	0	0	0	0	0	1	0	0	3
Metabolic	4	1	2	0	0	0	2	0	0	0	0	0	0	0	0	4
Allergies	45	4	17	0	0	0	16	0	0	0	0	0	0	0	0	12
Gastrointestinal	50	0	38	0	0	0	11	0	0	0	2	0	0	0	0	21
General	126	0	97	0	0	0	32	0	0	0	4	0	2	0	0	39
Haemopoetic	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	0	2
Musculoskeletal	10	0	10	0	0	0	14	0	0	0	3	0	0	0	0	5
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	0	47
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	0	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	0	4	0	3	0	0	0
TOTAL	815	20*	443	2	5	0	375	23	19	0	32	2	15	0	204	0

* plus 3 from multiple constituent products (2 cardiovascular; 1 anaphylactic)

Table 39.13. Data from the drug analysis print on single drug reports for local anaesthetic agents submitted up to January 2004.

	Lidocaine*		Lidocaine + epinephrine		Lidocaine + phenylephrine		Bupivacaine		Levo-bupivacaine		Ropivacaine	
	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F
Cardiovascular												
Sudden death unexplained	1	1					1	1				
Pulmonary embolism	1	1					1	1				
Cardiac arrest	6	3					15	9			1	1
Bradycardia	12	1										
Electromechanical dissociation							2	1				
Cardiorespiratory failure							3	2				
Acute circulatory failure	4*	1*	4	1								
Left ventricular failure	1*	1*	1	1								
Myocardial infarction	1	1										
Ventricular fibrillation	2	1					3	1				
Cerebrovascular disorders												
Cerebral haemorrhage	1	1										
Ruptured cerebral aneurysm							1	1				
Metabolic												
Diabetic ketoacidosis	1	1										
Haematology												
Thrombocytopaenia	1	1										
Injury												
Overdose	3	2										
Infection												
Septicaemia							1	1				
Neurology												
Convulsions							28	1				
Grand Mal convulsion							25	1				
Spinal claudication	1	1										
Renal disorders												
Renal failure												
Pregnancy												
Stillbirth							2	2				
Respiratory disorders												
Respiratory arrest							5	1				
Anoxia							2	1				
Asphyxia											1	1
Respiratory failure	4	1										

(continued)

Table 39.13. *Continued.*

	Lidocaine*		Lidocaine + epinephrine		Lidocaine + phenylephrine		Bupivacaine		Levo-bupivacaine		Ropivacaine	
Reactions	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F
Skin												
Angioedema	9	1										
Total (non-allergies)	42+5*	16+2*	0	0	0	0	0	0	0	0	2	2
Allergies												
Anaphylactic shock	5	1										
Anaphylactoid	13	2										
Anaphylactic	17	1+1*										
Total (allergies)	35	4+1*	0	0	0	0	0	0	0	0	0	0
Total	77+5*	20+3*	5	2	0	0	69	23	0	0	2	2

* lidocaine as a constituent of a preparation containing multiple chemical agents e.g. lidocaine + epinephrine.

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 39.14. A summary of the data analysis prints for selected analgesic agents and the benzodiazepine, midazolam, and its antagonist.

Drugs	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%)

of the patient is usually from myocardial collapse with severe metabolic acidosis and multisystem organ failure (involving 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 sedation in paediatric intensive care while monitoring for adverse events (Festa, Bowra and Schell, 2002). The maximum infusion dose that was considered dangerously high was $\geq 10\text{ mg/kg/h}$ for more than 72 hours. The propo-

fol infusion syndrome is a rare complication first reported in paediatric 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 anaesthesia act. Anaesthetic 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 (Schnick and Rupreht, 1989). Drugs that induce this reaction include opioids, benzodiazepines, phenothiazines, ketamine, etomidate, butyrophophones, propofol, nitrous oxide, halogenated inhalational agents and H₂-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 39.15. The number of total reactions (R) to the analgesic, sedative or antagonist drug indicated and the fatalities (F) in that category.

	Alfentanil		Fentanyl		Ketorolac		Naloxone		Flumazenil		Remifentanil		Midazolam	
Categories	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	0	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 ^a	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
Haemopoetic	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 ^b	0	1 ^b	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	1	0	0	0	0	0	0	0	0
Neurological	23	0	83	1 ^c	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 ^a	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 ^d	26	251	5	52	1	35	4	90	4	659	26

^a plus 1 from a mixture with multiple constituents;

^b reported as 'difficult anaesthetic';

^c plus 3 from a mixture with multiple constituents;

^d plus 7 from a mixture with multiple constituents.

Table 39.16. Data from the drug analysis print on single drug reports for analgesic agents or their antagonists submitted up to January 2004.

Table 39.16. *Continued.*

	Alfentanil		Fentanyl		Ketorolac		Naloxone		Remifentanil		Midazolam	
Reactions:	Total	F	Total	F	Total	F	Total	F	Total	F	Total	F
Asphyxia	1	1									1	1
Laryngeal oedema	1	1										
Total (non-allergies)	2	2	51	20	9	5	2	1	6	4	88	24
Allergies												
Anaphylactoid reaction			13	2							3	1
Anaphylactic reaction	9	1	20	4								
Anaphylactic shock	1	1									3	1
Total (allergies)	10	2	33	6	0	0	0	0	0	0	6	2
Total	12	4	84	26	9	5	2	1	6	4	94	26

* similar symptoms but classified in different classes.

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.

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Pharmacovigilance in Pediatrics

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BACKGROUND AND INTRODUCTION TO PEDIATRIC ISSUES

There are two very humane behaviours adults have, which can or have resulted in poor outcomes for children. The first behaviour is to give children medicines that have been developed for adults. Denying children a 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, is not 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 behaviour 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.^{1,2} 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.

The impetus for the formation of the United States' 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,

¹ Shirkey, H., Therapeutic orphans. *Pediatrics* 1968; 76: 119–20.

² Wilson, J.T., Update in the therapeutic orphan. *Pediatrics* 1999; 104: 585–90.

a sweet-tasting flavouring, were used by the manufacturer's chemist in an effort to market an elixir of sulfanilamide.³ 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 effective for the labelled indication.⁴ The 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., grey 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 which still exist today.

Despite urging, in 1977⁵ and 1995⁶ from the American Academy of Pediatrics, 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.²

At the very end of the 20th century, the US Congress passed legislation which changed the world of pediatric drug development. In addition, the FDA had put into place a series of efforts to encourage pediatric drug development and assessments. A number of

FDA's regulatory efforts were also incorporated into legislation. The main components of these changes were as follows:

1. An incentive of 6 additional months of marketing exclusivity for products studied in response to the FDA issuance of a document called a Written Request for pediatric studies. This incentive element was first enacted in the Food and Drug Administration Modernization Act (FDAMA) of 1997⁷ and renewed in 2002 in the Best Pharmaceuticals for Children Act (BPCA).⁸
2. The requirement that the sponsor of a product to be studied in adults, and would have the same use in children, also conduct and submit pediatric studies or a plan and timeline for pediatric studies. This final regulation was published by FDA in 1998⁹ and enacted into law by Congress in the Pediatric Research Equity Act (PREA)¹⁰ of 2003.
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 first proposed this approach in 1992¹¹ and finalized this regulation in 1994.¹² Congress then incorporated the concept into its 2002 BPCA.
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

⁷ Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–15.

⁸ Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107–9.

⁹ Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. 63 Federal Register 66631 (1998).

¹⁰ Pediatric Research Equity Act (PREA) of 2003, Pub. L. No. 108–55.

¹¹ Specific requirements on content and format of labelling for Human Prescription Drugs. Revision of 'Pediatric Use' Subsection on the Labelling, Proposed rule, 57 Federal Register 47423 (1992).

¹² Specific requirements on content and format of labelling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection on the Labelling, Final Rule. 59 Federal Register 64242 (1994).

³ Federal Food, Drug and Cosmetic Act, Pub. L. No. 75–717, 52 Stat. 1040 (1938).

⁴ Drug Amendments of 1962, Pub. L. No. 87–781, 76 Stat. 780 (1962).

⁵ American Academy of Pediatrics, Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 1977;60: 91–101.

⁶ American Academy of Pediatrics, Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 1995; 95: 229–37.

should be publicly available. Since the implementation of BPCA, study results from trials conducted in response to FDA's Written Request are posted in summary form on FDA's website.¹³ This summary is made public irrespective of the approval status of the application. This does not occur for pediatric studies conducted in response to PREA.

5. A specific focus on monitoring pediatric adverse events was put in place. Many new products have been and will be studied in pediatrics. The BPCA required a special safety review for adverse events for the year after a product received its extra 6 months of pediatric exclusivity. The adverse events are to be provided to the newly mandated Office of Pediatric Therapeutics, then a review is to be presented to the Pediatrics Advisory Committee and their recommendations obtained on any necessary actions. The review of products assessed under this program, the presentations to the pediatric advisory committee and the transcripts of the meeting can be accessed via FDA's website.¹⁴

WHY PEDIATRIC STUDIES AND A SPECIAL FOCUS ON SAFETY REPORTING ARE NECESSARY?

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 which 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 which have not been studied for an indication obtained in one pediatric subgroup, and for other indications which have not been studied in any or most pediatric subgroups, but are marketed for adults.
5. Children have unique exposures through pre-natal (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 which are usually not tested for bioavailability, drug-drug or 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

¹³ Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies, <http://www.fda.gov/cder/pediatric/summaryreview.htm>.

¹⁴ Safety Reporting: Drugs Granted Pediatric Exclusivity, <http://www.fda.gov/oc/opt/pediatricsafety.html>.

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, behaviour, development and cognitive abilities, there is a clear need to develop focused, long-term studies and surveillance which 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.

EXPERIENCES FROM SPECIFIC FOCUSED PEDIATRIC POSTMARKETING REVIEW

To fulfill its Congressionally mandated requirement that all adverse events reported during the year after a product has received pediatric exclusivity be referred to the Office of Pediatric Therapeutics at the FDA, and a review of the safety reports be publicly presented to the Pediatric Advisory Committee, the FDA has developed a thorough approach for the review and report of pediatric adverse events.

The methods for the specific pediatric post-exclusivity review include an analysis of all adverse events reported to FDA's Adverse Event Reporting System (AERS) during the one year after exclusivity was granted to the product. It is important to understand the timing with respect to approval of products for a new pediatric indication, and the new labelling and marketing for the pediatric use. BPCA requires a pediatric-exclusivity determination within the 3 months after submission of the studies. The review of the data to make a decision about efficacy, safety and dosing in the pediatric population takes 6 months (exception, time frame is 10 months if the pediatric data are submitted as part of an NDA). Thus, the action (e.g., approval or non-approval) occurs at least 3 to 4 months after exclusivity is determined. As a consequence, a product may have been on the market for its approved pediatric indication only a few months when its 1-year post-exclusivity anniversary occurs. There maybe limited reporting of pediatric adverse events to the AERS system in the 1-year

post-exclusivity because of this situation. FDA may also look at all pediatric AEs reported since marketing of the product when there are limited pediatric data in the AERS system for the 1-year post-exclusivity period. An assessment is also made of how much the drug is used in the pediatric population. In addition, published literature, the summaries of the clinical, pharmacology and toxicology reviews, the trials conducted for exclusivity and the product's labelling 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 which have been submitted to the agency are then reviewed and other known studies which have been conducted but *not* submitted to the Agency may also be requested for submission and review.

Between June of 2003 and November 2005, there have been eight Pediatric Advisory Committee meetings to review the safety analysis of 50 products which have been granted pediatric exclusivity. Twelve therapeutic categories of products have been involved (see Figure 40.1). The reviews for 39 products raised no new concerns that were not already adequately labelled. In four reviews, the committee expressed a desire that additional monitoring occur and an updated analysis be presented to the committee in another 1 to 2 years. This has usually occurred when there were very few reports and the committee thought additional time might provide a better assessment or limited reports had some concerning aspect. For seven products, the committee expressed concerns warranting further study, better labelling and/or further

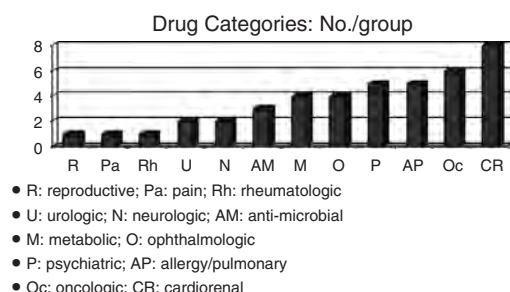


Figure 40.1. Categories of products. Reproduced by permission of Rosemary Johann-Liang, MD., Deputy Director, Division of Drug Risk Evaluation, Office of Surveillance and Epidemiology, CDER, FDA.

Table 40.1. Drug products for which the Pediatric Advisory Committee expressed safety concerns warranting better labelling or further study or review during 2003–05

- Opioid Transdermal System Issues
 - Fentanyl Transdermal Patches
- SSRI Neonatal Syndrome
 - Sertraline, Paroxetine
- Antidepressants and Suicidality
 - Sertraline, Paroxetine, Venlafaxine, Nefazodone, Citalopram
- Stimulants used to treat ADHD
 - Methylphenidate, Amphetamines

review, and/or reporting. These products can be categorized into four areas as follows:

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 which 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.

The products associated with the above are listed in Table 40.1.

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 which 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 which 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; and
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 caretakers assume it is part of the normal maladies that beset childhood development.

1. *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 caretakers 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 (L/HR/KG) such that they may require twice the dose per body weight compared to adults. There have been a number of products where younger, pre-school 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.

2. 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.

3. 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, caretakers 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.

4. 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 caretakers. The younger the child, the fewer ways he/she

can visibly react to an untoward effect of drugs. An infant’s repertoire of reactions are 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 caretakers for this population. The younger verbal child has a limited vocabulary to express his or her discomfort or pain. Because behaviour is normally changing, parents may be confused or think a child’s behaviour 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 spontaneous reports which are compiled by various regulatory agencies, the largest system being the database maintained by the FDA. The FDA Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA’s postmarketing safety surveillance program for all approved drugs and therapeutic biologic products. It is comprised of mandatory reports from manufacturers as required by regulation and voluntary reports from health-care professionals and consumers through the MedWatch program. FDA codes all reported adverse events using a standardized international terminology, MedDRA (the Medical Dictionary for Regulatory Activities). FDA staff use reports from AERS in conducting postmarketing drug surveillance and compliance activities and in responding to outside requests for information.

The reports in AERS are evaluated by FDA staff to monitor drug safety and detect new safety signals.

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 labelling information, sending out a 'Dear Health Care Professional' letter, or re-evaluating an approval decision.

The limitations of 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 under-reporting in children. First, health-care professionals may be less likely to report suspected adverse reactions for drugs that are unlicensed or used off-label.^{15,16,17,18} 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 health-care practitioners and consumers. Third, adverse drug reactions arising from in-utero or breast milk exposures and manifesting during the neonatal period may be underreported because maternal history of pregnancy drug exposures are poorly documented or their potential contribution to neonatal problems are under-appreciated. Fourth, delayed adverse drug reactions, 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 caretakers may fail to report them. The result is relatively few pediatric reports entering 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 non-existent 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 of which become the single most important source of information of adverse drug reactions in pediatric patients and to a lesser extent information on the drug's benefits.

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 labelling. 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 not a requirement yet, sponsors can play a significant role in postmarketing surveillance by submitting periodic safety update reports (PSUR) 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 United States, postmarketing drug adverse events surveillance data are available from sources other than spontaneous reporting systems such as emergency department-based systems and epidemiologic data from automated claims databases. The National Electronic Injury Surveillance System (NEISS), which collects data on all injuries from a

¹⁵ Blumer, J.L. Off-label uses of drugs in children. *Pediatrics* 1999; 104(suppl. 3): 568–602.

¹⁶ American Academy of Pediatrics, Committee on Drugs. Use of drugs not described in the package insert (off-label uses). *Pediatrics* 2002; 110: 181–3.

¹⁷ Bush A. Safety of medicines in children. *Expert Opin Drug Saf.* 2003; 2(2): 109–12.

¹⁸ Turner, S., Nunn, A.J., Fielding, K. and Choonara, I. Adverse drug reactions to unlicensed and off-label drugs on pediatric wards: a prospective study. *Acta Paediatr* 1999; 88: 965–8.

probability sample of emergency departments (ED) in approximately 100 hospitals, recently evaluated an active drug adverse event surveillance program using ED chart reviews in six sites.¹⁹ The results indicated that although the predictive value positive for Adverse Drug Reactions (ADRs) was high, 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 adverse drug reactions. 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 (TESS) 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.

Population-based, computerized administrative health databases linked to drug utilization data and outcomes have been gaining popularity in evaluation of drug safety. Among these, the largest and best known internationally is the General Practice Research Database (GPRD) maintained by the Medicines and Healthcare products Regulatory Agency (MHRA).²⁰ GPRD is a longitudinal 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 health care via the National Health Service throughout the United Kingdom. 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, quantification of population risk of drugs including those of rare outcomes. Because the data are collected prospectively and are longitudinally linked, GPRD can particularly be useful in evaluating pediatric drug adverse effects with long latency such as adverse effects on growth, cognitive development and neoplasia.

Other population-based, computerized databases commonly used for pharmacovigilance are organized at regional or health-care setting level. Examples include the Saskatchewan Health Database²¹ that contain linked data on prescription drug, hospital services, physician services and vital statistics for all residents in one province in Canada. Examples of the health care setting-based databases are TennCare (state-based Medicaid program), the Kaiser Foundation database and the Harvard Pilgrim database (health maintenance organizations) who were awarded contracts for drug safety research by the FDA in 2005. 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.

The potential to identify and report suspected drug adverse events can greatly be enhanced by the implementation of the requirement for electronic medical records for all patients. Electronic medical records 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 electronic medical record for all patients becomes a reality, postmarketing safety assessments will have to employ one or more of the available resources described above.

¹⁹ CDC. Assessing the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance Project – Six Sites, United States, January 1–June 15, 2004. *MMWR* 2005; 54(15): 380–3.

²⁰ Wood, L. and Martinez, C. The General Practice Research Database: role in pharmacovigilance. *Drug Saf.* 2004; 27(12): 871–81.

²¹ Downey, W., Beck, P. and McNutt, M. Health databases in Saskatchewan. In *Pharmacoepidemiology*. 3rd edn. Strom BL, ed. New York, Wiley, 2000, pp. 325–46.

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 extrapolation 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 pre-market safety assessments are limited by 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 which are unique to pediatrics. Examples include the use of ciprofloxacin in neonates and its effect on teeth,²² valproic acid and liver toxicity,²³ isotretinoin and depression/suicide,²⁴ 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 include the following findings:

1. serious and unexpected drug adverse events that are unique to pediatrics, i.e., not described in the approved product labelling;

²² Lumbiganon, P., Pengssa, K. and Sookpranee, T. Ciprofloxacin in neonates and its possible adverse effect on the teeth. *Pediatr Infect Dis J* 1991; 10: 619–20.

²³ Dreifuss, F.E., Santalli, N., Langer, D.B., Sweeney, K.P., Moline, K.A. and Menander, K.B. Valproic acid hepatic fatalities: a retrospective review. *Neurology* 1987; 37: 379–85.

²⁴ Wysowski, DK, Pitts, M. and Beitz, J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001; 45: 515–19.

2. serious drug adverse events that may be related to a labelled event but differ from the labelled event because of:
 - greater severity (hepatic necrosis vs. increase in liver enzymes or hepatitis in the labelling);
 - greater specificity (cerebro-vascular accidents vs. cerebral thrombo-embolism 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 FAVOURABLE 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 emerge continually during the post-approval phase as more patients are exposed to the drug. These new data can reflect the results of both labelled 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 favourable to unfavourable. 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 labelling. This continuous process of updating the product labelling 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 favourable 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, multi-faceted 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, health-care 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 periodic safety updates (PSURs) would include an analysis to update the benefit/risk ratio for a drug's use for its approved indication and its off-label use 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.

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The Cardiovascular Spectrum of Adverse Drug Reactions

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Undesired sequelae of pharmacologic agents encompass a wide range of adverse cardiovascular effects, including proarrhythmic, atherogenic, myopathic and valvular consequences (Table 41.1). In this chapter, we will focus on three agents, each demonstrating a different undesired clinical cardiovascular drug effect. The mode of identification and subsequent scientific investigators and regulatory steps are summarized for dofetilide's proarrhythmic characteristics, cardiac valvular effects of appetite suppressants and oestrogen's venous thrombogenicity.

DOFETILIDE

Dofetilide is a specific class III antiarrhythmic agent indicated for the maintenance of and conversion to normal sinus rhythm in highly symptomatic patients

with persistent atrial fibrillation and atrial flutter (Pfizer Inc., 1999). It prolongs action potential duration and refractoriness of both the atrial and the ventricular myocardium (Boriani *et al.*, 2004). As with most other drugs which prolong the action potential, dofetilide carries a risk of proarrhythmia. Following oral administration, there is a dose- and concentration-dependent increase in the corrected QT interval (QTc) that can lead to torsade des pointes (Boriani *et al.*, 2004), a life-threatening arrhythmia. In the clinical development programme, the incidence of torsade des pointes was dramatically reduced when lower dosages were administered and when dosage was decreased for patients with impaired renal function (Torp-Pederson *et al.*, 1999). Dofetilide is the first antiarrhythmic agent for which studies of overall mortality risk were conducted before market approval was requested. These studies showed

Table 41.1. Examples of drug cardiotoxicity

Cardiac effect	Drug
Cardiomyopathic	Doxorubicin (Singal and Iliskovic, 1998)
Proarrhythmic	Terfenadine (Monahan <i>et al.</i> , 1990)
	Cisapride (Rampe <i>et al.</i> , 1997)
Atherothrombotic	Protease inhibitors (Zhou <i>et al.</i> , 2005)
	Cyclooxygenase inhibitors (Bresalier <i>et al.</i> , 2005; Konstantinopoulos and Lehmann, 2005)
Valvulopathic	Anabolic steroids (Hartgens and Kuipers, 2004; Payne, Kotwinski and Montgomery, 2004)
	Appetite suppressants (MMWR, 1997)

neutral effect on death in patients taking dofetilide who had heart failure or previous myocardial infarction (Torp-Pederson *et al.*, 1999; Kober *et al.* 2000), in contrast to some other antiarrhythmic agents for which overall mortality either has increased or has not been studied (Coplen *et al.* 1990; Teo, Yusuf and Furberg, 1993; Fuster *et al.*, 2001). Dofetilide was approved by the Food and Drug Administration (FDA) in 1999. Because of the risk of torsade des pointes identified in the clinical development programme, the FDA mandated a risk management programme which required in-hospital initiation of dofetilide therapy, and restricted its availability to hospitals and prescribers who have received appropriate education on dofetilide treatment initiation and dosing.

Shortly after dofetilide was approved for use in the United States, the FDA also approved sotalol HCl, a new sotalol product with the same indication as dofetilide (Berlex Laboratories, 2000). As with dofetilide, sotalol is also associated with a dose- and concentration-dependent incidence of QT-prolongation and torsade des pointes (Wang *et al.*, 1986). Comparable incidence of torsade de pointes has been reported for sotalol and dofetilide (Brendorp, 2002). The product labelling for sotalol HCl contained detailed dosing and monitoring recommendations similar to the language in the product labelling for dofetilide. However, the FDA did not request a risk management programme for sotalol as this drug had already been marketed in the United States for the treatment of ventricular arrhythmias.

Because of the uniqueness of the dofetilide risk management programme, a series of studies was conducted by the Duke Center for Education and Research on Therapeutics to evaluate the acceptance and effectiveness of the mandatory provider education

programme for the use of dofetilide (LaPointe *et al.*, 2002, 2003a,b). One study evaluated whether the mandated risk management programme for dofetilide was effective in improving adherence to labelled dosing and monitoring recommendations at Duke University Medical Center (LaPointe *et al.*, 2003b). It was found that the recommended starting dose was prescribed more frequently in the dofetilide group than in the sotalol group and a higher number of patients in the dofetilide group when compared with the sotalol group received the baseline tests for potassium, magnesium, serum creatinine, and an electrocardiogram. Dofetilide was used less often than sotalol during the study period (47 patients vs 117 patients). The investigators raised the issue that the low usage of dofetilide might reflect an unintended, negative consequence of the risk management programme.

Another study assessed the opinions and knowledge retention of practitioners after participation in the dofetilide risk management programme at Duke (LaPointe *et al.*, 2002). In general, practitioners felt the risk management programme for dofetilide was necessary although they either disagreed or were undecided as to whether dofetilide was potentially more dangerous than other antiarrhythmic agents or whether a similar programme should be required for other antiarrhythmic agents. This study showed that the knowledge-retention questions were answered correctly more often by the physicians and pharmacists than by the nurses. It was noted that the other two smaller community hospitals within the Duke Health Care system opted not to include dofetilide in their formularies, and thus did not complete the education programme. This may indicate the perceived burden of the programme, a lack of resources within smaller

community hospitals to complete the risk management programme, or both.

The experience of implementing the dofetilide risk management programme was reported from several other institutions with different approaches (Tran *et al.*, 2001; Freeland, Worthy and Zolnierz, 2003). The pharmacy and therapeutics committees at most institutions required that policies and procedures be developed for dofetilide use prior to putting the drug on the formulary. The dofetilide risk management programme has been successfully implemented in many institutions. However, some have been hesitant to incorporate dofetilide into their formularies, as the development of procedures for the dofetilide risk management programme is time-consuming and requires multidisciplinary expertise, including pharmacists, physicians and nurses.

Very limited data on postmarketing experience with dofetilide have been published. The reported postmarketing clinical experience suggests that the conversion of persistent atrial fibrillation with dofetilide was comparable to the premarketing studies, and demonstrated a similar safety profile (Prystowsky *et al.*, 2003; Guanzon and Crouch, 2004).

The experience with dofetilide illustrates one approach in which a postmarketing risk management programme can minimize the risk identified in a clinical development programme. The dofetilide experience has also presented challenges in implementing risk management programmes intended to maximize benefits and minimize medication risks.

APPETITE SUPPRESSANTS

In contrast to the experience with dofetilide, in which an adverse drug effect was identified during product development, the consequences of appetite suppressants were detected serendipitously. Phentermine was approved by the FDA for appetite suppression in 1959, fenfluramine in 1973, and dexfenfluramine in 1996. The former two were approved for short-term use, and all three drugs were approved for use as single agents. In the 1990s, prescription of fenfluramine in combination with phentermine and for periods longer than a few weeks was widespread. From 1995 to 1997, 14 million prescriptions were written for fenfluramine

or dexfenfluramine, exposing an estimated 1.2–4.7 million persons to these agents (MMWR, 1997).

In July 1997, physicians in Minnesota reported 24 women with valvular heart disease who had taken fenfluramine–phentermine for 2–28 months (Connolly *et al.*, 1997). The women were identified during evaluation of conditions such as congestive heart failure, heart murmurs, or arrhythmias. Echocardiographic features of the dysfunctional valves resembled those seen in carcinoid heart disease; in five, valvular incompetence was severe enough to require cardiac surgery. Because of the morphologic similarity to carcinoid valvular disease, which has been attributed to high circulating levels of serotonin, the authors hypothesized that the valvular damage seen with fenfluramine might be due to its promotion of serotonin release and inhibition of serotonin reuptake. Phentermine is a nonadrenergic agent which impedes pulmonary clearance of serotonin, and which might potentiate the effect or concentration of circulating serotonin.

The Minnesota report, in conjunction with an FDA public health advisory, rapidly spawned additional case reports (Cannistra, Davis and Bauman, 1997; Graham and Green *et al.*, 1997; Kurz and Van Ermen, 1997). A trio of larger clinical studies, each of different design, was published in September 1998 in the *New England Journal of Medicine*.

In the first study, echocardiograms were performed on 257 of 295 participants in prior appetite suppressant studies at Hennepin County Medical Center and in gender, age and body mass index-matched controls (Khan *et al.*, 1998). Study participants had taken fenfluramine 60–120 mg + phentermine 30 mg daily, dexfenfluramine 30 mg daily alone, or in combination with phentermine 30 mg daily. Mean duration of treatment was 20.5 ± 12 months. Echocardiographic aortic and mitral insufficiency was scored (none, trace, mild, moderate or severe) by two blinded readers; if they disagreed, the study was reviewed by a third reader. FDA criteria for valvular abnormality were applied, that is, aortic valvular disease of mild or greater severity and mitral valvular disease of moderate or greater severity ($\kappa = 0.79$ for correlation between readers). Valvular insufficiency was identified in 3/233 control subjects (1.3%) and 53/233 appetite suppressant consumers (22.7%). In multivariate analysis which included age, gender, body mass

index, blood pressure, and diabetes as covariates, and control subjects as the reference group, the odds ratios (95% confidence intervals) for valvular abnormality were 12.7 (2.9–56.4), 24.5 (5.9–102.2), and 26.3 (7.9–87.1) for dexfenfluramine, dexfenfluramine + phentermine, and fenfluramine + phentermine use, respectively.

The second study compared patients who had been prescribed dexfenfluramine ($n = 6532$), fenfluramine ($n = 2371$), or phentermine ($n = 862$) with age, gender, and weight-matched controls in the UK General Practice Research Database (Jick *et al.*, 1998). During follow-up of about 4 years, the database identified 22 new diagnoses of valvular abnormality. Eleven patients were excluded when other causes of valvular disease, such as rheumatic heart disease or mitral valve prolapse, were identified by medical record review. The remaining 11 subjects had been referred to cardiologists for recent symptom onset or new heart murmur. In eight patients, valvular insufficiency was confirmed by echocardiography and in three by clinical examination. All 11 patients had been prescribed dexfenfluramine or fenfluramine, a cumulative incidence of 14.2 per 10 000 (95% confidence interval 7.8–26.2). No valvular abnormalities were identified in untreated subjects or those prescribed phentermine.

The third study performed echocardiograms on participants in a randomized, double-blind trial comparing dexfenfluramine (15 mg bd), sustained-release dexfenfluramine (30 mg daily) and placebo, which was ongoing at the time dexfenfluramine was withdrawn from the US market (Weissman *et al.*, 1998). Echocardiograms were performed on 1072 of 1212 randomized participants and interpreted by blinded readers; mean exposure was 72 days. Using FDA criteria for valvular abnormality (aortic insufficiency of mild or greater severity and mitral insufficiency of moderate or greater severity), valvular disease was not significantly more prevalent in the combined dexfenfluramine groups compared with placebo. When any degree of valvular insufficiency was compared between the treatment groups, aortic ($p = 0.03$) and mitral insufficiency ($p = 0.01$) were more frequent in the combined dexfenfluramine groups compared with placebo.

In November 1998, the American College of Cardiology and American Heart Association (ACC/AHA)

recommended evaluation of appetite suppressant users, including history and physical examination, with echocardiography in those with signs or symptoms of valvular disease (Bonow *et al.*, 1998). Subsequent meta-analyses have tempered initial estimates of the frequency of valvular insufficiency associated with appetite-suppressant use, supporting the ACC/AHA statement that routine echocardiography was not recommended for all of the millions of individuals exposed.

Pooled data from six controlled cohort studies yielded a relative risk ratio of 2.32 for aortic insufficiency (95% confidence interval 1.79–3.01) and 1.55 for mitral insufficiency (95% confidence interval 1.06–2.25) (Loke, Derry and Pritchard-Copley, 2002). A second analysis which included ten studies found a prevalence odds ratio of 2.2 (95% confidence interval 1.7–2.7) for aortic insufficiency meeting FDA criteria among individuals treated for at least 90 days with fenfluramine derivatives (Sachdev *et al.*, 2002). The odds ratio for mitral insufficiency of moderate or greater severity was 1.6 (95% confidence interval 1.05–2.3).

The experience with appetite suppressants illustrates the role of fortuitous observation in identifying adverse drug effects and the potential for inaccuracy of early risk estimates due to methodologic weaknesses.

OESTROGEN AND VENOUS THROMBOEMBOLISM

Identification and confirmation of the adverse effects of postmenopausal hormone therapy illustrate yet a third approach to risk assessment. Oestrogen has been used to treat menopausal symptoms since 1933 when emmenin was introduced. Premarin, a more easily manufactured oestrogen, was approved in 1942 (CDER, 1997; FDA, 2003). By the 1960s, 12% of women in the United States were using postmenopausal oestrogen 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, Stefanick and Stafford, 2004). Analysis of

data from a large cohort study in the United States showed that 45% of postmenopausal women used oestrogen for at least a month and more than 20% used it for 5 or more years, 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 and colleagues in the early 1990s, current postmenopausal hormone use was 58.7% among women with prior hysterectomy compared to 19.6% among women with intact uteri (Keating, Manassie and Stevenson, 1999). 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 to 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 oestrogens, 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 oestrogen regardless of their hysterectomy status. After the National Heart, Lung and Blood Institute-funded Postmenopausal Oestrogen/Progestin Interventions (PEPI) trial reported an increased risk of endometrial hyperplasia when women with intact uteri were treated with unopposed oestrogen in 1995, most women with intact uteri were switched to combination oestrogen-progestin therapy (The Writing Group for the PEPI Trial, 1996). 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 oestrogen 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; Spitzer, 1997).

The relationship between VTE and exogenous oestrogen was explored in several small case-control and cohort studies in the 1970s (BCDSP, 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.

The 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 ten VTE cases were identified among women on active hormone therapy 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 oestrogens (0.625 mg daily) alone was twice that of women taking any of three oestrogen plus progestin regimens (Table 41.2), but the overall number of cases was small.

The Heart & Oestrogen/Progestin Replacement Study (HERS) randomized 2763 women with documented coronary heart disease to placebo or conjugated equine oestrogens 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 1.4–5.0); the relative hazard for deep venous thrombosis was 2.8

Table 41.2. Annualized rates (%/year) of venous thromboembolism in randomized trials of postmenopausal hormone therapy

	Placebo	Unopposed oestrogen	Oestrogen 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 ≥ 4	0.20		0.40
WHI Oestrogen Plus Progestin trial	0.17		0.35
WHI Oestrogen Alone trial	0.21	0.28	

(95% confidence interval 1.3–6.0) and for pulmonary embolism was 2.8 (95% confidence interval 0.9–8.7) with oestrogen plus progestin.

The Women's Health Initiative (WHI) includes two randomized, placebo-controlled hormone trials, one with unopposed conjugated oestrogens (0.625 mg daily) in 10 739 women with prior hysterectomy, and the other with conjugated oestrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily in 16 608 women with intact uterus. In the trial of unopposed oestrogen, the hazard ratio for VTE was 1.33 (95% confidence interval 0.99–1.79) (WHI Writing Group, 2004). In the trial of combination oestrogen plus progestin, the hazard ratio for VTE was 2.06 (95% confidence interval 1.57–2.70) (Cushman *et al.*, 2004). In these predominantly healthy women, the annualized rates of VTE were lower than in HERS (Table 41.2), but the studies demonstrated a similar pattern of risk by year of treatment. In the WHI Oestrogen Plus Progestin trial, the yearly hazard ratios 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.

In a Bayesian meta-analysis which included PEPI and HERS, but not the WHI, the overall relative risk of VTE with postmenopausal hormone therapy was 2.14 (95% credible interval 1.64–2.81) (Miller, Chan and Nelson, 2002). This meta-analysis also supported the observation in HERS that the greatest risk for thromboembolic events with oestrogen was during the first year (relative risk 3.49, 95% credible interval 2.33–5.59).

The labels for oestrogen formulations have been repeatedly updated to reflect new findings, including the risk of VTE. A major change was made in 1998, when a warning was added 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... 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 (FDA, 1998).

Following release of the WHI results in 2002, a black box statement pertaining to cardiovascular risks

was added to the label for oestrogen. This statement read, 'The women's health initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.' The warning goes on to state that the FDA assumes these findings will hold for all HRT formulations containing oestrogen and suggests that HRT drugs should be used in the lowest doses necessary for the shortest duration possible (FDA, 2003).

The WHI experience altered the way the medical community, lay public and regulatory agencies viewed the entire issue of drug safety. Awareness of the need for long term randomized studies of commonly accepted therapies has been enhanced, along with the importance of 'real world' follow-up studies of drugs – many of which were approved long before current pharmacovigilance guidelines.

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Drugs and the Elderly

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THE AGEING POPULATION AND CHANGING DEMOGRAPHY

The past century has seen major changes in the age structure of Western countries. For example, Americans and UK citizens live far longer than previously. Thus, a person born in the United States 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, Carnes and Desesquelles, 2001).

These changes have been brought about by an improved standard of living with better housing, clean water and immunisation programmes, together with better medical treatments, especially drugs. The past 50 years have also seen a major change in the age structure of the population. In 1951, the population of England and Wales contained 4.83 million persons aged 65 or over, but by 30 years later, the figure had risen to 7.57 million and now exceeds 8 million elderly people. More important is the number of old elderly persons (over 75 years), the number of whom has roughly doubled in the same time period. These trends over time are set to continue, and it is forecast that there will be continued expansion of the elderly population over the next 30 years (Figure 42.1).

DISEASE PREVALENCE AND DRUG USE IN THE ELDERLY

The prevalence of many diseases is age related and several may co-exist in the same patient. These include hypertension (Hawthorne, Greaves and Beevers, 1974), osteoarthritis (Lawrence, 1977) and prostatic hypertrophy (Berry *et al.*, 1984). Age-specific mortality rates for cardiovascular and cerebrovascular diseases, together with data for cancers, are shown in Table 42.1 (British Heart Foundation, 2000) and morbidity data in Table 42.2 (British Heart Foundation, 2001).

Cardiovascular and cerebrovascular problems related to atheroma are the most common causes of death in the elderly and are also a major source of suffering. Nevertheless, a huge majority of old people have osteoarthritis of the joints and the lower limbs (Blackburn *et al.*, 1994) causing pain and disability without threatening life.

Several studies have examined the nature and prevalence of medicines prescribed for old people living in the community. One of the best known is that by Cartwright and Smith (1988) which was based on a random sample of people aged 65 and over drawn from the electoral registers of 10 parliamentary constituencies in England. Information was obtained

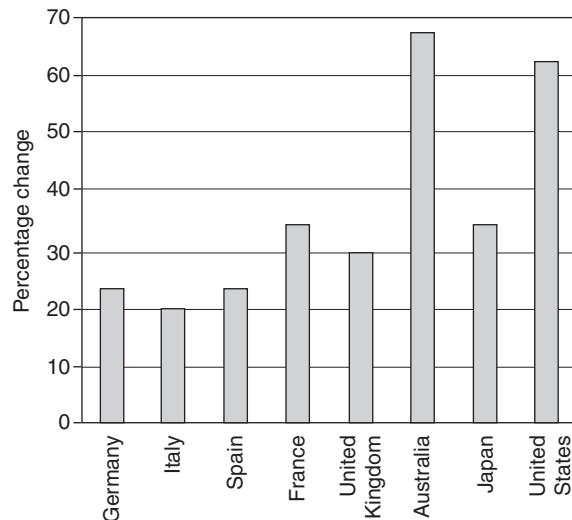


Figure 42.1. Percentage growth in number of 60 and over, 2000–20.

Source: Department of Trade & Industry. Foresight, Ageing Population Panel (2000) The Age Shift. DTI. Reproduced with permission from Dept. of Trade & Industry.

from 805 patients (78%) of the 1032 included in the original sample. Of these 805 patients, 60% had taken one or more prescribed medicines within the preceding 24 hours. Drugs for the diseases of heart and circulation were widely prescribed, and diuretics formed a therapeutic category in most widespread use. Diuretics were followed by analgesics, hypnotics, sedatives and anxiolytics, drugs for rheumatism and gout and then β -adrenoceptor antagonists. Similar findings were recorded in two studies from Southampton (Ridout Waters and George, 1986; Sullivan and George, 1996). A review by Jones and Poole (1998) confirmed the rising use of cardiovascular drugs amongst elderly people and widespread use of agents with an effect on the central nervous system. There was, however, some geographic variation in the use of medicines for musculo-skeletal and joint disease. By contrast, the use of drugs with an action on the central nervous system varies according to individual circumstances: psychotropic agents are used particularly in patients in residential nursing homes and in

Table 42.1. Deaths by cause, sex and age 1998, United Kingdom.

		Age under 35	Age 35–44	Age 45–54	Age 55–64	Age 65–74	Age 75 and over
All disease of the circulatory system (390–459)	MEN	575	1600	5 575	13 616	32 751	68 101
	WOMEN	392	634	1 923	5 632	20 244	105 667
	TOTAL	967	2234	7 498	19 248	52 995	173 768
Coronary Heart Disease	MEN	148	1004	3 971	8 795	21 622	38 002
	WOMEN	40	180	837	3 080	11 167	47 307
	TOTAL	188	1184	4 808	12 875	32 789	85 309
Stroke	MEN	134	246	730	1 775	5 269	16 338
	WOMEN	120	255	611	1 323	4 708	34 299
	TOTAL	254	501	1 341	3 098	9 777	50 637
Cancer	MEN	883	1280	5 034	12 675	26 048	35 447
	WOMEN	781	1949	5 613	10 206	19 695	37 004
	TOTAL	1664	3229	10 647	22 881	45 743	72 451

Source: Adapted with permission from Coronary Heart Disease Statistics, BHF (2000).

Table 42.2. Prevalence of treated CHD by sex and age 1994/98, England and Wales.

No. of cases	Age 0–34 (%)	Age 35–44 (%)	Age 45–54 (%)	Age 55–64 (%)	Age 65–74 (%)	Age 75–84 (%)	Age 85 and over (%)	
Men	107 777	0.015	0.50	2.90	9.34	17.51	21.68	20.53
Women	87 289	0.010	0.18	1.26	4.83	10.81	16.16	17.17

Source: Adapted with permission from Coronary Heart Disease Statistics: Morbidity Supplement, BHF (2001).

long-term care (McGrath and Jackson, 1996). A recent investigation, however, has shown that medication undertreatment is a problem of equivalent magnitude to that of medication overuse in long-term care settings of elderly residents (Sloane *et al.*, 2004). Overall, the use of prescription medications by older persons is increasing rapidly both to treat a large range of diseases as well as non-disease-specific symptoms.

Besides prescribed medicines, elderly people as a group are high consumers of non-prescription medication. Indeed, it has been estimated that over 50% of elderly people take one or more over the counter (OTC) preparations every day (Chrischilles, Segar and Wallace, 1992b). Those OTCs most commonly taken are oral analgesics, vitamins and tonics, but recently, the popularity of herbal medicines has increased (Barnett, Denham and Francis, 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 which are characteristic of drug therapy in the elderly: long duration and polypharmacy. 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 Waters and George, 1986). This may account for the increased rates of gastrointestinal bleeding in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) (Langman *et al.*, 1994). This latter problem highlights the need for improvements in repeat prescribing and for regular review of medication in the elderly.

POLYPHARMACY

There are several legitimate reasons for polypharmacy in the elderly. First, as indicated previously, the prevalence of many diseases is age related and several may co-exist in the same patient. Secondly, 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 ischaemic heart disease (Gurwitz, 2004). A third reason for giving more than one drug simultaneously is to counteract or minimise the risk of side effects (type A

adverse reaction) occurring. The difficulty with this approach is that adverse drug effects may be misinterpreted as a new medical condition and another drug is prescribed to treat the observed effects leading to a 'prescribing cascade' (Rochon and Gurwitz, 1997). Finally, patients are also being targeted by pharmaceutical companies in the so-called direct-to-consumer advertising, which is likely to have the effect of increasing polypharmacy in older people.

In the study by Cartwright and Smith (1988), the average number of medicines prescribed for the patient was 2.8, but many patients living in the community received more than this. In an American telephone survey of non-institutionalised ambulatory adults, the highest overall prevalence of medication use was in those over 65 years, of whom 12% took at least 10 medications (including prescription, OTC and herbal treatments) during the preceding week; and 23% of females and 19% of males had used five or more prescription drugs over the same time (Kaufman *et al.*, 2002). Such polypharmacy can cause confusion leading to errors in medicine taking, particularly amongst those over the age of 85 (Parkin *et al.*, 1976; Vestal, 1978).

INTERACTIONS IN RELATION TO MULTIPLE DRUG PRESCRIBING

Adverse drug reactions (ADRs) are common in the elderly. This is frequently a consequence of multiple drug prescribing which leads to the occurrence of drug-drug interactions. The risk of potentially inappropriate drug combinations is also increased by the greater number of physicians prescribing medications for an elderly patient (Tamblyn *et al.*, 1996). Drug interactions represent a change in either the magnitude or the duration of action of one drug caused by the presence of the second. This may enhance or reduce the efficacy of one or both of the drugs or a new effect may appear which is not seen with either of the drugs alone. Interactions may be pharmacokinetic or pharmacodynamic. The most important adverse interactions occur with drugs that have easily recognisable toxicity and a low therapeutic index (i.e. the dose or plasma concentration of drug which is effective lies close to that which causes toxicity) (Lin and Lu, 1998). Current knowledge of drug-drug interactions

has increased dramatically over the recent years, but studies rarely involve the frail elderly who will be more susceptible to the adverse effects of interacting medications. 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 interactions may result in impaired drug absorption from the gastrointestinal tract. The rate at which a drug is absorbed may be decreased by drugs such as anticholinergics, which inhibit gastric motility; conversely, drugs such as metoclopramide (which increase gastric motility) may enhance the absorption rate. Certain drugs form chelates and complexes with other drugs, altering their solubility and absorption. For example, agents that bind to digoxin in the gut (such as antacids and cholestyramine) reduce the extent of its absorption by 20%–35% (Brown and Juhl, 1976). However, despite these potential interactions few drug–drug interactions affect drug absorption to a clinically significant extent (May, Dipiro and Sisley, 1987; McInnes and Brodie, 1988). Drugs that undergo extensive first-pass metabolism may be affected by other drugs, which alter liver blood flow or compete for metabolism. For example, the non-selective monoamine oxidase inhibitors (MAOIs), such as phenelzine, reduce the first-pass metabolism of tyramine (found in cheese, tomatoes and chocolate), pseudoephedrine (in cough mixtures) and many other direct and indirect sympathomimetic agents (Tollefson, 1983). As a result, large amounts of these amines reach the sympathetic nervous system, where they stimulate the interneuronal release of norepinephrine. MAOI prevents norepinephrine breakdown, producing a syndrome of sympathetic over-activity characterised by headache, hypertension, excitement and delirium (Tollefson, 1983).

Drugs may also affect the distribution of others within the body. When two or more highly protein-bound drugs are administered concurrently, competitive binding by one may increase the free fraction or unbound portion of the other. The importance of this interaction has probably been overstated. For example, the NSAIDs may displace warfarin from its binding site and increase its anticoagulant effect, but

this effect is negligible *in vivo* (O'Callaghan, Thompson and Russell, 1984); it is much more likely that the NSAIDs inhibit warfarin metabolism (O'Reilly *et al.*, 1980). Similarly, tolbutamide-induced hypoglycaemia with the addition of azapropazone has been reported (Waller and Waller, 1984). Although the interaction may have been due to displacement of the oral hypoglycaemic agent from albumin leading to enhanced hypoglycaemia, inhibition of tolbutamide metabolism by the NSAID was probably more important (Andreasen *et al.*, 1981).

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). The enzymes responsible for transforming drugs in humans belong to six CYP subfamilies, that is CYP1A, 2A, 2C, 2D, 2E and 3A. Each subfamily contains a number of different isoforms. It has been estimated that about 90% of human drug oxidation can be attributed to six of these, that is CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A, and enzyme inhibition interactions have been reported with all (Kinirons and Crome, 1997; Seymour and Routledge, 1998). Each CYP isoenzyme may metabolise many drugs, so the potential for drug–drug interactions is high in patients taking several medications (Lin and Lu, 1998). For example, in a group of elderly male patients, cimetidine inhibited the metabolism of procainamide, giving rise to toxic plasma concentrations of the antiarrhythmic (Bauer, Black and Gensler, 1990).

Other drugs which are similarly affected by cimetidine are benzodiazepines, β -adrenoceptor blockers, tricyclic antidepressants, theophylline, phenytoin and oral anticoagulants. Although few of these drug–drug interactions are of clinical significance (Sax, 1987), caution is indicated when cimetidine is given concomitantly with drugs that have a narrow range of therapeutic concentration such as warfarin, theophylline and phenytoin: in one study, 2 days of cimetidine therapy decreased theophylline clearance by 39% (Jackson *et al.*, 1981). Other common inhibitors of one or more CYP isoenzymes

include amiodarone, fluconazole, erythromycin, clarithromycin, sulphonamides, ciprofloxacin, omeprazole and paroxetine. Occasionally, clinically severe interactions can occur as has been shown with combined administration of terfenadine and ketoconazole (Honig *et al.*, 1993; Monaghan *et al.*, 1993) and erythromycin (Honig *et al.*, 1992) and itraconazole (Pohjola-Sintonen *et al.*, 1993), resulting in prolongation of the QT interval and torsade des pointes. At present, there is no evidence that CYP inhibition by these agents is affected by age (Kinirons and Crome, 1997). 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 require further study in older persons (Kinirons and O'Mahony, 2004).

Liver enzyme induction by one drug may lead to inactivation of the second drug. Well-recognised examples include the decreased efficacy of warfarin seen with barbiturate therapy and the reduced efficacy of dihydropyridine calcium-channel blocking drugs with carbamazepine therapy (Capewell *et al.*, 1988). 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 (Lin and Lu, 1998). For example, the distribution of hexobarbital before and after treatment with rifampicin was studied in young and elderly volunteers. Rifampicin produced differential increases in hexobarbital metabolism with 90- and 19-fold increases in the young and elderly volunteers, respectively (Smith *et al.*, 1991).

Finally, drug–drug interactions may occur in the kidney resulting in altered drug elimination. This subject has been recently reviewed by Bonate, Kelly and Weir (1998), who concluded that clinically significant drug interactions due to a renal mechanism are relatively rare. Five potential mechanisms exist for drug interactions in the kidney (Table 42.3), and the best recognised is competitive inhibition of tubular secretion leading to an increase in drug concentration. An example of this interaction is the

Table 42.3. Mechanisms for drug–drug interactions at the renal level.

-
1. Displacement of bound drug results in an increase in drug excretion by glomerular filtration
 2. Competition at the tubular secretion site resulting in a decrease in drug excretion
 3. Competition at the tubular reabsorption site resulting in an increase in drug excretion
 4. Change in urinary pH and/or flow rate that may increase or decrease the drug excretion depending on the pKa of the drug
 5. Inhibition of renal drug metabolism
-

co-administration of probenecid with penicillin. Non-competitive interference with drug secretion may also occur, for example prolonged treatment with thiazide diuretics causes a compensatory increase in proximal tubule reabsorption of sodium, resulting in increased lithium reabsorption (Peterson *et al.*, 1974). This interaction has resulted in serious lithium toxicity due to lithium accumulation (Mehta and Robinson, 1980). NSAIDs also decrease the renal elimination of lithium by up to 60%, but the mechanism is uncertain (Amdisen, 1982; Jefferson *et al.*, 1986). Similarly, the administration of quinidine results in an increase in the plasma concentration of digoxin in over 90% of patients (Bigger, 1982). Although this is partly due to displacement of digoxin from its binding sites in tissues, its renal clearance is reduced by 40%–50% with regular administration of quinidine. Similar interactions have been reported with amiodarone (Moysey *et al.*, 1981; Oetgen *et al.*, 1984) and verapamil (Pederson *et al.*, 1983), leading to 70%–100% increases in serum digoxin concentrations. Although the precise mechanisms have not been elucidated, recent reports suggest that inhibition of ATP-dependent P-glycoprotein-mediated drug transport in renal tubular cells (Inui, Masuda and Saito, 2000) by verapamil and quinidine may lead to decreased renal tubular elimination of digoxin (Fromm *et al.*, 1999; Verschraagen *et al.*, 1999).

Drug transport systems may be important in tissues other than the kidney and are found in the membrane of epithelial cells in the intestinal wall and blood-brain barrier. P-glycoprotein plays an active role in the uptake and efflux of many substrates including various drugs. Polypharmacy may have specific relevance for elderly patients treated with substances that affect drug transporters due to adverse interactions (Kinirons

and O'Mahony, 2004). For example, ciclosporin is a substrate of both CYP3A and *P*-glycoprotein; other drugs affecting either mechanism may alter its pharmacokinetics (Kovarik and Koelle, 1999). Despite this, the available pharmacokinetic data suggests that no dose modification of ciclosporin is required in the elderly.

PHARMACODYNAMIC INTERACTIONS

An antagonistic pharmacological interaction between two drugs may counteract the intended therapeutic effects. For example, co-administration of NSAIDs and antihypertensives may lead to a reduced hypotensive effect due to sodium retention by the analgesics. One Australian study found that 12% of almost 3000 non-institutionalised elderly patients studied were taking NSAIDs and anti-hypertensive medication simultaneously. Furthermore, NSAID usage was an independent risk factor for hypertension in this age group (Johnson *et al.*, 1993).

Finally, 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 β -adrenoceptor blockers are administered with verapamil or diltiazem (Krikler and Spurrell, 1974; Edoute *et al.*, 2000).

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). Non-specific complaints such as confusion, lethargy, weakness, dizziness, incontinence, depression and falling may indicate an underlying drug–drug interaction. The drug interactions of clinical importance in the elderly have been reviewed by Seymour and Routledge (1998) and are listed in Tables 42.4 and 42.5. In some cases, the cause of the interaction is complex, involving both pharmacokinetic and pharmacodynamic mechanisms. For example, epileptic patients with psychiatric comorbidity may be particularly vulnerable because of combined use of psychotropic and antiepileptic drugs. In particular, antidepressants and antipsychotic drugs are believed to lower the seizure threshold (Allredge, 1999; Coleman, 2004). In general, the potential for drug–drug interactions in psychiatric patients is high because of the need for combined therapy to treat co-morbid psychiatric disorders, to treat the adverse effect of a medication or to treat concomitant medical conditions. In particular, the selective serotonin uptake inhibitors fluoxetine and paroxetine are potent inhibitors of CYP2D6 and have the potential to increase the plasma concentrations of many of the major tranquillisers, including haloperidol and thioridazine; fluvoxamine inhibits the metabolism of many of the benzodiazepines (Sproule *et al.*, 1997).

Table 42.4. Drug interactions that may lead to an enhanced effect.

Drug A	May interact with drug B	Effect of interaction	Mechanism of interaction
ACE inhibitors	NSAIDs	Hyperkalaemia, reduced renal function	Additive nephrotoxic effects
Antidepressants (tricyclic)	Enzyme Inhibitors	Increased effect of A	Reduced clearance of A
Antihypertensive agents	Vasodilators (e.g. nitrates for angina) antipsychotics and some antidepressants	Postural hypotension	Combined hypotensive effects
Aspirin (acetylsalicylic acid) (low dose)	NSAIDs	Peptic ulceration	Additional risk of peptic ulceration
Carbamazepine	Enzyme inhibitors, verapamil	Increased effect of A	Reduced clearance of A
Corticosteroids (oral)	NSAIDs (including aspirin)	Peptic ulceration	Corticosteroid prevents healing
Ciclosporin	Enzyme inhibitors	Increased effect of A	Reduced clearance of A
Digoxin	Amiodarone, diltiazem, verapamil	Increased effect of A	Reduced clearance of A

Table 42.4. *Continued.*

Drug A	May interact with drug B	Effect of interaction	Mechanism of interaction
Digoxin	Diuretics (loop and thiazides)	Increased effect of A (e.g. arrhythmias)	Diuretic induced hypokalaemia
Diuretics (potassium sparing)	ACE inhibitors, potassium supplements	Hyperkalaemia, impaired renal function	Combined potassium elevating effects
Lithium	NSAIDs, thiazide diuretics	Increased effect of A	Reduced clearance of A
Phenothiazines and butyrophenones	Anticholinergic drugs (e.g. some antihistamines and tricyclic antidepressants)	Excessive anticholinergic effects (e.g. constipation, urinary hesitancy, dry mouth, confusion)	Combined anticholinergic effects
Phenytoin	Enzyme inhibitors	Increased effect of A	Reduced clearance of A
Quinolones	NSAIDs	Seizures	Pharmacodynamic interaction at CNS effector site
Theophylline	Enzyme inhibitors Quinolones	Increased effect of A	Reduced clearance of A

Reproduced from Seymour RM, Routledge PA (1998) by permission of Aids International Ltd, Auckland, New Zealand.

Table 42.5. Drug interactions that may lead to a reduced effect.

Drug A	May Interact with Drug B	Effect of Interaction	Mechanism of Interaction
Antidepressants	Enzyme inducers	Reduced effect of A	Increased clearance of A
Antihypertensives (e.g. ACE inhibitors, thiazides and β -adrenoceptor antagonists (β -blockers))	NSAIDs	Reduced effect of A	Pharmacodynamic antagonism of antihypertensive effect of A
Calcium antagonists	Enzyme inducers	Reduced effect of A	Increased clearance of A
Corticosteroids	Enzyme inducers	Reduced effect of A	Increased clearance of A
Ciclosporin	Enzyme inducers	Reduced effect of A	Increased clearance of A
Digoxin	Cholestyramine, colestipol	Reduced effect of A	Reduced absorption of A
Quinolones	Cholestyramine, colestipol	Reduced effect of A	Reduced absorption of A
Theophylline	Enzyme inducers	Reduced effect of A	Increased clearance of A
Thyroxine	Enzyme inducers	Reduced effect of A	Increased clearance of A

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ALTERED PHARMACOKINETICS IN THE ELDERLY

Elderly patients may also develop drug-related problems even when their medication is confined to a single agent or non-interacting 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.

ABSORPTION

Following oral administration, most drugs dissolve in the stomach. Little absorption takes place here because of the small surface area and low pH, which means that drugs which are weak bases are in an ionised state. Absorption primarily takes place in the

small intestine because of the large surface area and high pH, which favours the unionised state of most drugs. With increasing age, many changes occur in the gastrointestinal tract which should make the rate and extent of absorption less predictable, including a reduction in acid secretion in the stomach, decreased gastric emptying, diminished splanchnic blood flow and decreased gastrointestinal mobility (Geokas and Haverback, 1969; Evans *et al.*, 1981; Greenblatt *et al.*, 1982; Goldberg and Roberts, 1983; 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 recent review by Cusack (2004) concludes that studies performed in the last decade assessing extent of absorption by comparing area under the curve (AUC) after oral and IV administration and rate of absorption using Tmax 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. It is clear that a small change in hepatic function may result in a large increase in bioavailability in those drugs which undergo a high presystemic first-pass metabolism (Montamat *et al.*, 1989; Woodhouse, 1994). For example, decreased presystemic extraction in the elderly may lead to increases in the bioavailability of propranolol (Castleden and George, 1979) and nifedipine (Robertson *et al.*, 1988), but usually not to a clinically significant extent. The changes may be more marked, however, in the frail and hospitalised elderly (Woodhouse, 1994). Bioavailability may also be regulated by presystemic extraction by small bowel cytochrome P-450 3A4 and by the extrusive action of *P*-glycoprotein on the surface of cells in the small bowel. Limited data do not support the effect of ageing on either process (Cusack, 2004).

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 (Edelman and Leibman, 1959; Forbes and Reina, 1970; 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 such as paracetamol (Divoll *et al.*, 1982) or ethanol (Vestal *et al.*, 1977) 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 ‘hang-over’ 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; Campion, de Labrey and Glynn, 1988). 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 as these are determined by hepatic or renal clearance of free drug. On the other hand, α -l-acid glycoprotein increases with age, and basic drugs such as lignocaine display increased protein binding in elderly patients (Cusack *et al.*, 1980).

Metabolism

Although some drugs are eliminated directly by the kidneys, many undergo metabolism in the liver first. 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 metabolised 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).

The metabolic pathways involved in the biotransformation of drugs may be divided into two phases (Williams, 1967). Phase 1 reactions comprise oxidative, reductive or hydrolytic processes which render the compound less lipophilic but can be fully or partly active. Products of phase 1 may then undergo phase 2 reactions which involve glucuronidation, sulphation or acetylation. The resulting conjugates are much more polar than the parent compound, usually have little or no pharmacological activity and are generally excreted in the urine. 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 concentrations and an increased risk of adverse reactions (Woodhouse, 1994). In particular, a reduction in plasma aspirin esterase activity, paracetamol conjugation and metabolism of metoclopramide and theophylline have been reported in frail elderly patients (Wynne *et al.*, 1990, 1993; Groen *et al.*, 1993; Israel *et al.*, 1993).

Metabolism of many 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, desmethyl-diazepam, which has a half-life of up to 220 hours in elderly people. However, other benzodiazepines, such as lorazepam, undergo conjugation reactions in the liver, and their metabolism is unaltered by age. These compounds which do not give rise to active

compounds may therefore be safer for elderly people to use than the other benzodiazepines (Williams and Lowenthal, 1992).

Age may not be the only factor that affects drug metabolism. Cigarette smoking, alcohol intake, dietary considerations, drugs, illnesses and caffeine intake may be equally important (Vestal *et al.*, 1975; Montamat *et al.*, 1989). In addition, hepatic blood flow rather than microsomal enzyme activity is the major determinant of total clearance of many drugs which 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) have been reported in elderly people. Such drugs include propranolol (Castleden and George, 1979), clomethiazole (Nation *et al.*, 1976) and morphine (Baillie *et al.*, 1989), and the reduced clearance is compatible with a decline in liver blood flow.

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 β -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/minute 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 which are dependent on the kidney for elimination will accumulate to toxic levels if given in

the usual doses to elderly people. Examples include digoxin (Smith, 1973), atenolol (McAinch, 1977) and amiloride (George, 1980). 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 *et al.*, 1990). Furthermore, many drugs themselves adversely affect renal function in the elderly, for example aminoglycosides, diuretics, NSAIDs and angiotensin-converting enzyme (ACE) 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).

As drug elimination is correlated to creatinine clearance, estimating the creatinine clearance may be helpful in deciding whether a dose reduction is necessary. A useful method that may be used at the bedside is the Cockcroft formula (Cockcroft and Gault, 1976):

$$\begin{aligned} \text{Creatinine clearance (male)} \\ = & \frac{1.23 \times (140 - \text{age}) \times \text{body weight (kg)}}{\text{plasma creatinine } (\mu\text{moll}^{-1})} \\ \text{Creatinine clearance (female)} \\ = & \frac{1.04 \times (140 - \text{age}) \times \text{body weight (kg)}}{\text{plasma creatinine } (\mu\text{moll}^{-1})} \end{aligned}$$

The diagnostic value of age and creatinine clearance (calculated by the Cockcroft formula) for the prediction of potentially toxic drug plasma levels has been reviewed by Muhlberg and Platt (1999). They found that 256 geriatric patients with many different illnesses have been studied in 17 pharmacokinetic studies with 17 different drugs, including angiotensin-converting enzyme inhibitors, NSAIDs, antibiotics, beta-blockers, bronchodilators and benzodiazepines. Mathematical simulation and pharmacokinetic methods were used to determine whether a dose reduction was necessary in elderly patients with a reduced creatinine clearance determined by the Cockcroft formula. For most drugs studied, elevated plasma levels at steady state could be correctly predicted when the creatinine clearance was $< 40 \text{ ml/min}$, particularly when age was taken into account, suggesting that a dose reduction was necessary. This confirms the usefulness of the Cockcroft formula for clinical use

in elderly patients taking drugs which are eliminated in the kidney and which are toxic at higher plasma concentrations. When using drugs with a low therapeutic ratio, estimation of the creatinine clearance helps determine the initial dose but, when possible, should be supplemented by therapeutic drug monitoring (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).

Warfarin acts by inhibiting the synthesis of clotting factors II, VII, IX and X by inhibiting regeneration of vitamin K oxide. Early studies suggested that responsiveness to warfarin increases with age (O'Malley *et al.*, 1977), possibly because of greater inhibition of vitamin K-dependent clotting factors per plasma concentration of warfarin in this age group (Shepherd *et al.*, 1977). However, two retrospective studies have failed to show any association of increased age and bleeding complications (Gurwitz *et al.*, 1988) or deviation from target international normalised ratio (Britt *et al.*, 1992). Nonetheless, elderly patients were found to require, on average, a lower dose of warfarin than younger patients to maintain the same degree of anticoagulation (Redwood *et al.*, 1991). Although there is uncertainty as to the precise mechanism of the increased sensitivity to warfarin amongst elderly people, one possibility is an increased sensitivity to enzyme inhibition rather than differences in substrate availability (Jackson, 1994). Warfarin is a racemate of R and S stereoisomers and is subject to interindividual variability in stereospecific metabolism, which may be exaggerated in the elderly.

Elderly people also show increased sensitivity to the effects of the benzodiazepines; this may be due to altered tissue sensitivity or different rates of entry of the drug into the central nervous system, as well as the alteration in pharmacokinetics already mentioned. For example, the extent and duration of action of nitrazepam on psychomotor function was more marked in elderly subjects despite the plasma concentrations being similar in young and old, suggesting increased sensitivity of the ageing brain to this benzodiazepine (Castleden *et al.*, 1977). Similarly, the plasma concentration of diazepam required to induce a predetermined level of sedation for dental and endoscopic procedures fell progressively between the ages of 20 and 80 years (Cook, Flanagan and James, 1984). Although there is some evidence of pharmacodynamic tolerance developing to the sedative effects of benzodiazepines with long-term use (Swift *et al.*, 1984), dizziness, fainting, blackouts and falls are more common in elderly people taking these drugs regularly (Hale, Stewart and Marks, 1985). Furthermore, benzodiazepines appear to adversely affect the safety of the older driver, particularly when compounds with long half-lives or very high doses are used (Ray, Thapa and Shorr, 1993).

In many cases, the increased response to a drug in an elderly patient can be explained by pharmacokinetic changes. For example, the administration of nifedipine to elderly people is associated with a reduction in first-pass metabolism and clearance compared with young volunteers. This results in higher and more prolonged plasma concentrations and explains the increased hypotensive effect in this age group (Robertson *et al.*, 1988). However, altered homeostatic mechanisms due to impaired baroreceptor function in the elderly may also contribute (Gribbin *et al.*, 1971). In younger patients, a fall in blood pressure leads to a compensatory tachycardia partly offsetting the fall in cardiac output, but with increasing age this effect is reduced. This means that the heart-rate response to standing is diminished and may cause orthostatic hypotension, which is defined as a reduction in systolic blood pressure of at least 20 mmHg occurring in response to a change from a supine to an upright position (Mets, 1995). The prevalence of orthostatic hypotension has been reported to be between 10% and 30% for elderly people and is particularly

associated with the use of antihypertensive medication (Mets, 1995).

On the other hand, β -adrenoceptors may show a reduction in both numbers (Schocken and Roth, 1977) and responsiveness to agonists and antagonists with age (Dillon *et al.*, 1980; Ullah, Newman and Saunders, 1981; Kendall *et al.*, 1982; Feldman *et al.*, 1984; Pan *et al.*, 1986; Scarpace, 1986). Despite this, elderly patients with hypertension appear to respond well to β -adrenoceptor blockers, but they may be more troubled by postural hypotension due to the impaired homeostatic mechanisms already mentioned. Similarly, although there is a decline in function in the renin-angiotensin system with age (Skott and Geise, 1984), the ACE inhibitors cause a greater reduction in blood pressure in elderly people (Ajayi, Hocking and Reid, 1986), particularly after the first dose (Cleland *et al.*, 1985). This may relate to higher baseline blood pressure in the elderly.

ADRs IN THE ELDERLY

These age-related changes in pharmacokinetics and pharmacodynamics in addition to increased prescribing rates and multiple drug therapy leave the elderly patient vulnerable to drug-related adverse events.

DEFINITION OF AN ADR

An ADR can be described as any undesirable effect produced by a drug, and the World Health Organisation (WHO) has suggested that it is any response to a drug which is noxious and unintended and which occurs at doses used in humans for prophylaxis, diagnosis or therapy (WHO, 1970). This definition does not include intentional or accidental poisoning or drug abuse, and it has been suggested that it should also exclude therapeutic failures (Karch and Lasagna, 1975).

ADRs have been divided into two classes: type A and type B (Rawlins and Thompson, 1977). Type A reactions are pharmacologically predictable for the known activity of the drug – for example the dry mouth associated with the use of the tricyclic antidepressants due to anticholinergic effects – and are common, dose-related and usually not serious. Conversely, type B reactions are unpredictable and

usually more serious (e.g. anaphylactic shock with penicillin). They may be caused by hypersensitivity to the drug or by an 'idiosyncratic' reaction.

Unfortunately, it is often difficult to establish a clear cause-and-effect relationship between the drug and the reaction. To try to overcome this difficulty, ADRs have been classified as definite, probable, possible, conditional or doubtful (Karch and Lasagna, 1975). However, this classification relies on clinical judgement. Difficulties may arise when the patient is taking several medications or when the symptoms attributed to the drug, such as headache or nausea, are non-specific and subjective. Attempts have been made to improve precision in the diagnosis of ADRs by developing algorithms to standardise assessments of presumed ADRs (Karch and Lasagna, 1977; Leventhal *et al.*, 1979; Naranjo *et al.*, 1981). These algorithms ask a series of questions in sequence, and the answers are scored to measure the probability that a given clinical event was an ADR. Questions include the timing of the event relative to exposure to the drug, whether the event represents a known reaction to the drug, the possible role of the patient's condition at the time and the effects of drug withdrawal and, where appropriate, rechallenge.

INCIDENCE OF ADRS IN THE ELDERLY

Many studies have suggested that ADRs are a common problem in elderly patients and are the cause of 3%–12% of hospital admissions in this age group (Williamson and Chopin, 1980; Smucker and Kontak, 1990; Lindley *et al.*, 1992; Moore *et al.*, 1998; Mannesse *et al.*, 2000; Onder *et al.*, 2002). Various risk factors have been identified. These include prescription of unnecessary or interacting drugs or drugs with relative or absolute contraindications (Lindley *et al.*, 1992). One of the most important predictors of ADRs is the total number of drugs given simultaneously (Leach and Roy, 1986; Bax *et al.*, 1987).

Medication selection is known to be an important factor influencing the likelihood of ADRs, and prescribing practices change as safer, superior alternatives to existing medications become available. In the 1990s, Beers and colleagues developed explicit criteria for potentially 'inappropriate medications' in elderly patients, and more recently, these criteria were

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 der Hooft *et al.*, 2005). It has also been demonstrated that ADRs are particularly likely in patients who have had a fall before admission or in those presenting with gastrointestinal bleeding or haematuria (Mannesse *et al.*, 2000). More recently, Hajjar and colleagues (2003) have attempted to identify possible risk factors for ADRs in older outpatients using a literature search to identify potential factors followed by a two-round survey based on the Delphi consensus method of an expert panel of five physicians and five pharmacists. The panel identified nine patient characteristics including polypharmacy, multiple chronic medical problems, previous ADRs and dementia. The most prevalent medication-related risk factors were opioid analgesics, warfarin, NSAIDs, anticholinergics and benzodiazepines.

Fewer studies have been done to determine the incidence of ADRs during hospital admission, but the incidence is about 5% with a range from 1.5% to over 20% (Seidl *et al.*, 1966; Hurwitz, 1969; Skott and Geise, 1984; Leach and Roy, 1986; Lindley *et al.*, 1992). The incidence is higher in the elderly. For example, in a prospective study of 1160 in-patients who were prescribed medication during admission, 10.2% experienced an ADR, and in patients over 60 years the incidence was higher, at 15.4% (Hurwitz, 1969). Seidl *et al.* (1966) found that while 13.6% of a resident hospital population in the United States acquired an ADR during hospitalisation, the incidence was as high as 24% in patients in their 80s. In addition, ADRs have been shown to be risk factors for delayed discharge from hospital (Skott and Geise, 1984) as well as early hospital readmission (Chu and Pei, 1999). Finally, in the out-patient population, about 5%–10% of patients have ADRs (Chrischilles, Segar and Wallace, 1992b; Gurwitz *et al.*, 2003).

Some medicines are much more likely than others to cause problems when prescribed to elderly people. Three groups of drugs consistently cause problems in this age group: cardiovascular drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and drugs acting on the central nervous system. In one study, for example, antihypertensives, diuretics and β -adrenoceptor blockers accounted for 55% of reported ADRs

(Chrischilles *et al.*, 1992a). Regardless of which drug class causes the adverse event, and whether this results in or prolongs hospital admission, ADRs clearly represent a significant cause of morbidity in the elderly.

IMPLICATIONS FOR DRUG DEVELOPMENT AND USE

The need for research in elderly persons has been addressed by Williams and Denham (1998). It should be clear from the studies referred to in this chapter that the effects of drugs can alter significantly with age as a consequence of changes in body composition and physiology and the effectiveness of various detoxifying mechanisms. Additional factors include the presence of disease, polypharmacy and possible differences in patient behaviour. Consequently, doses of drugs required to achieve desired results in elderly people may be substantially different from those used in younger persons. Furthermore, the risk of ADRs and interactions is enhanced by the presence of concomitant diseases and remedies for them. The use of quality indicators for drug use in older persons to decrease the incidence of preventable drug-related morbidity has been reviewed recently (Hanlon *et al.*, 2003). Suggested indicators included drugs to avoid, drug-disease interactions, drug-drug interactions, drug duplication and required monitoring.

The optimisation of drug prescribing in the elderly has recently been highlighted in the United Kingdom by the introduction of the National Service Framework in Older People (Department of Health, 2001). This highlights 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. Electronic prescribing will increase the potential to link prescribing and clinical outcomes enabling feedback and an opportunity to direct prescriber's thinking by issuing 'alerts' in real time – the so-called decision support (Jackson *et al.*, 2004). Electronic prescribing has been seen as a promising tool in solving many of the problems of prescribing in the elderly by providing realtime information for drug selection, prescription checks, and clinical drug information from databases (Venot, 1999).

The benefits and harms of many drug treatments in older patients are often not provided by standard clinical evidence. The need for clinical trials to involve elderly people is obvious, therefore, if treatments are to be used safely and effectively in this age group. Yet, the major part of the so-called therapeutic explosion which occurred during the twentieth century relied on research carried out in younger patients, and there were casualties. These included the development of a hepato-renal syndrome associated with the use of benoxaprofen (Hamdy, Murnane and Perera, 1982) and problems with other NSAIDs (Castleden and Pickles, 1988). The need for dose modification for agents such as triazolam (Greenblatt *et al.*, 1991) was identified, as was the need for attention to labelling and modification of package inserts. However, by the time that a new medicine has been marketed, experience with its use remains confined to a relatively small number of people, of whom only a proportion will be elderly and fewer will be frail elderly. There is, therefore, a need for careful pharmacovigilance to identify unexpected adverse effects such as those produced by terodilane. This agent, which was introduced for use in urinary incontinence due to detrusor muscle instability, was subject to prescription event monitoring by the Drug Safety Research Unit in Southampton (Freemantle *et al.*, 1997). The latter system relies on reporting of significant events such as 'a broken leg' which may be due to hypotension, ataxia or metabolic bone disease. In the case of terodilane, an excess of fractures was identified, many of which were the result of falls. Further investigations revealed that the cause was syncope due to torsade des pointes which can be identified by means of Holter Monitoring (Committee on Safety of Medicines, 1991).

Although prescription event monitoring is likely to identify important adverse reactions occurring at a low frequency, we rely on other systems to identify those which occur more rarely. Most of these are the so-called type B adverse effects. Examples include agranulocytosis caused by co-trimoxazole and by oxyphenbutazone, eventually shown by voluntary reporting systems, for example the yellow card system operated by the Committee on Safety of Medicines, to occur predominantly in old people (Inman, 1977). This led to the advice to avoid using co-trimoxazole in the elderly and the revocation of the licence for oxyphenbutazone. Fortunately, the need for clinical

studies and trials in the elderly is now recognised by all major drug regulatory bodies. Thus, in Europe, official recognition by the European Commission occurred in the 1970s, and a regulatory requirement (Directive 78 of the 318 of the EC) and similar regulations were introduced by the Food and Drugs Administration in the United States (Food and Drug Administration Center, 1989; International Conference on Harmonisation, 1993).

In an era of evidence-based medicine, good quality evidence of the benefits and harms of medicines is scarce for elderly patients and neglects certain diseases altogether. Valuable contributions can be made by studying drug utilisation over time, investigating variations in pharmacokinetics and pharmacodynamics with age and applying pharmacovigilance principles, in addition to extending the age range of clinical trials. Challenges exist in translating research into meaningful endpoints that older patients will understand to allow them to make valid decisions about whether to take medications or not. Clinicians will have to be ready to meet this challenge in our ageing population.

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Part IV

KEY CURRENT TOPICS

US Activities in Risk Management of Pharmaceutical Products

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INTRODUCTION

The mission of the Food and Drug Administration (FDA) is to protect the public health by assuring the safety, efficacy and security of human drugs. FDA considers risk management to be a continuous process of (1) learning about and interpreting a product's benefits and risks, (2) designing and implementing interventions to minimize a product's risks, (3) evaluating interventions in light of new knowledge that is acquired over time and (4) revising interventions when appropriate.¹

The avoidance of serious harm is the most commonly asserted justification for public health regulation (Gostin, 2000). Pharmaceutical risk management is the overall and continuing process of minimizing a drug's risks throughout its life cycle to optimize its benefit/risk balance. Risk information emerges continuously throughout this life cycle,

during both the investigation and marketing phases through both labelled and off-label uses.

This chapter will provide an overview of recent US regulatory activities in risk management and its evolving role in post-marketing surveillance of pharmaceutical products.

In May 1999, the Task Force on Risk Management issued its report to the Commissioner of FDA.² Traditionally, FDA has filled several important roles in minimizing the risks associated with medical product use by establishing and enforcing product quality standards intended to prevent defective products from reaching the market. Furthermore, this report challenged the traditional model by its careful analysis of the challenges faced in managing risks within the context of the broader healthcare delivery system (Figure 43.1).

FDA evaluates the safety profiles of drugs available in the United States using a variety of tools and

¹ *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, March 2005, <http://www.fda.gov/cder/Guidance/6358fnl.htm>.

² *Managing the Risks of Medical Products: Creating A Risk Management Framework*, May 1999, <http://www.fda.gov/oc/tfrm/riskmanagement.pdf>.

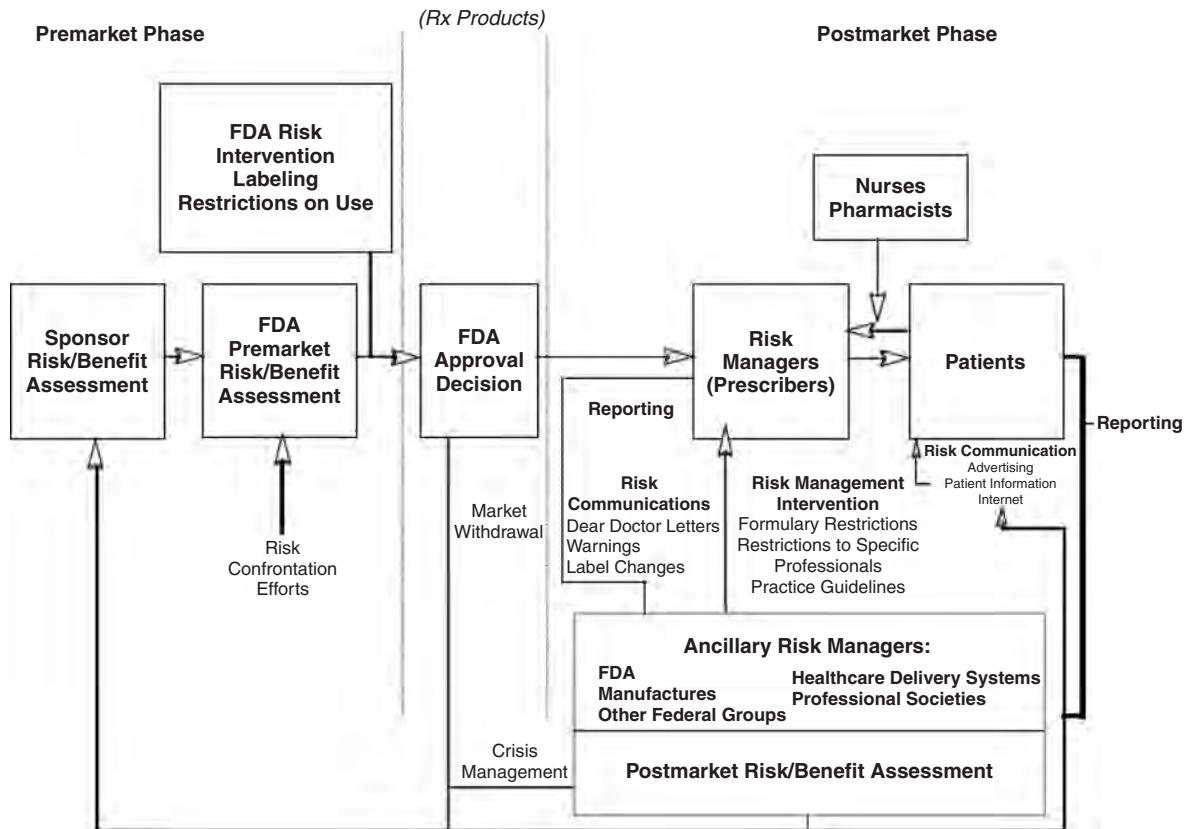


Figure 43.1. Complex system for Managing the Risks of Medical Products.

disciplines throughout the life cycle of the drugs. Under US regulations,³ manufacturers of approved drug and biologic products are required to promptly report all adverse drug experience information obtained or otherwise received by the manufacturer from any source, foreign or domestic, including information derived from commercial marketing experience, post-marketing epidemiological/surveillance studies, reports in the scientific literature and unpublished scientific papers. FDA also accepts reports directly from healthcare providers and consumers. Currently, the agency's adverse event database has over 3.5 million reports with increasing numbers reported annually (Figure 43.2).

This system of post-marketing surveillance reporting [the adverse event reports system or adverse

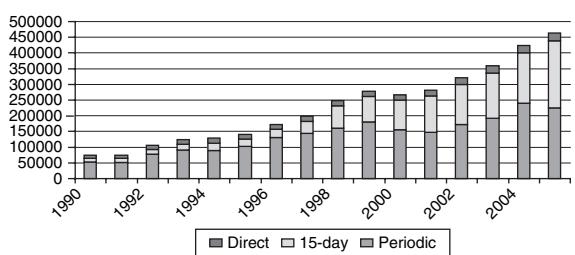


Figure 43.2. Reports to the FDA Adverse Event database.

event reporting system (AERS)] and risk assessment programmes serves to identify adverse events that did not appear during the drug development process. The successful implementation of electronic submissions is a high priority for the center. Further improvements in this system include electronic submission of adverse drug reports that will result in more timely receipt and evaluation of adverse event reports

³ 21CFR31.80 Postmarketing reporting of adverse drug experiences.

at considerable cost savings both to FDA and to those submitting the reports. Data mining provides an important tool in facilitating signal detection of the more than three million reports in this database.

RISK MANAGEMENT GUIDANCES

The Prescription Drug User Fee Act of 2003 (PDUFA III) specifically addressed risk management, noting that efficient risk management as one of FDA's five strategic goals, including both the new drug review process and oversight after approval. Acknowledging that it is impossible at the time of approval to know everything about a medicine's safety, PDUFA III mandated that there be increased surveillance of the safety of medicines during their first 2 years on the market (or first 3 years for drugs with potentially serious safety concerns identified at the time of approval). The FDA also agreed to develop regulatory strategies and guidance documents on risk management. Three guidance documents were developed with input from the public and industry. These guidances, summarized below, were published as final documents in March 2005.

Due to its relevance to this chapter, the 'Guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment' is provided in full at the end of this chapter.

GUIDANCE ON PRE-MARKETING RISK ASSESSMENT

This regulatory guidance focuses on approaches a industry might consider throughout all stages of the clinical development of products. Some key components of the guidance include

1. specific recommendations to industry for improving the assessment and reporting of safety during drug development trials;
2. improving the assessment of important safety issues during registration trials and to provide best practices for analyzing and reporting data that are developed as a result of a careful pre-approval safety evaluation and
3. building on (but not superceding) a number of existing FDA and ICH (International Conference on Harmonisation of Technical Requirements

for Registration of Pharmaceuticals for Human Use) guidances related to pre-approval safety assessments.

GUIDANCE ON DEVELOPMENT AND USE OF RISK MINIMIZATION ACTION PLANS

This guidance provides a conceptual framework on the development, implementation and evaluation of risk minimization action plans for prescription drug and biological products. It focuses on (1) initiating and designing plans called risk minimization action plans or RiskMAPs to minimize identified product risks, (2) selecting and developing tools to minimize those risks, (3) evaluating RiskMAPs and monitoring tools, (4) communicating with FDA about RiskMAPs, and (5) the recommended components of a RiskMAP submission to FDA. Table 43.1 provides recent examples of drug RiskMAPs and tools to minimize risks.

GUIDANCE ON GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT

This guidance document focuses on pharmacovigilance activities in the post-approval period. Pharmacovigilance is defined to mean all scientific and data gathering activities relating to the detection, assessment and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency and potential risk factors.

CONCLUSIONS

Pharmaceutical risk management faces important challenges in addressing innovative therapies, public expectations of product safety and optimizing patient selection to better minimize adverse outcomes. Regulatory pharmacovigilance activities have a critical role in assuring product safety by means of proactively designing and implementing interventions to minimize a product's risks. Pharmacovigilance also provides a framework for evaluating these interventions in light of new knowledge that is

Table 43.1. Examples of drug RiskMAPs and tools to minimize risks.

Education	Reminder systems (e.g., limited supply of drug)	Pt-MD agreements/informed consent	Registration/enrollment of prescribers	Registration/enrollment of patients	Limits on dispensing or product administration
Medication Guide and targeted materials to patient and to health care provider					
Isotretinoin	Isotretinoin – 30 days	Alosetron	Bosentan	Bosentan	Dispensing by registered retail pharmacies
Mifepristone	Thalidomide and lenalidomide – 28 days	Isotretinoin	Clozapine	Clozapine	Isotretinoin
Actiq	Clozapine – 7 days, then 14 days, then 30 days	Lenalidomide	Isotretinoin	Isotretinoin	Clozapine
Revlimid	Lindane – maximum of 1 to 2 ounces	Mifepristone	Lenalidomide	Lenalidomide	Plenaxis (dispensed by registered hosp pharmacies)
Lindane	Xyrem – 30 day supply initially, no more than 3 month	Thalidomide	Lotronex	Thalidomide	Thalidomide
Symlin Exubera		Plenaxis	Mifepristone Plenaxis	Tikosyn Xyrem	Tikosyn Dispensing by specialty distributors/pharmacies
Tracleer			Thalidomide		Lenalidomide
Lotronex			Tikosyn		Bosentan
Xyrem			Xyrem		Xyrem
					Product administration in medical setting
					Plenaxis and mifepristone administered in medical setting (doctor's office)
					Tikosyn requires inpatient hospitalization for 3 days when initiating therapy

acquired over time and revising interventions when appropriate.⁴

APPENDIX: GUIDANCE FOR INDUSTRY – GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT⁵

INTRODUCTION

This chapter provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components).⁶ Specifically, this chapter provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation and (3) pharmacovigilance plan development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

⁴ Guidance for Industry: Development and Use of Risk Minimization Action Plans, March 2005, <http://www.fda.gov/cder/Guidance/6358fnl.htm>

⁵ This guidance has been prepared by the PDUFA III Pharmacovigilance Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the and Drug Administration.

⁶ For ease of reference, this guidance uses the term *product* or *drug* to refer to all products (excluding blood and blood components) regulated by CDER and CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.

Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0001 (until March 31, 2005) and 0910-0338 (until August 31, 2005).

BACKGROUND

PDUFA III's Risk Management Guidance Goal

On June 12, 2002, Congress reauthorized, for the second time, the PDUFA III. In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting pre-marketing risk assessment, (2) developing and implementing risk minimization tools and (3) performing post-marketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9–11, 2003, to discuss the concept papers. FDA considered all of the comments received in developing three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

1. Pre-marketing risk assessment (pre-marketing guidance).
2. Development and use of risk minimization action plans (RiskMAP guidance).
3. Good pharmacovigilance practices and pharmacoepidemiologic assessment (pharmacovigilance guidance).

Overview of the Risk Management Guidances

Like the concept papers and draft guidances that preceded them, each of the three final guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on pre- and post-marketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process for (1) assessing a product's

benefit–risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit–risk balance and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit–risk balance. This four-part process should be continuous throughout a product’s life cycle, with the results of risk assessment informing the sponsor’s decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

- Many recommendations in this guidance are *not* intended to be generally applicable to all products.

Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for *routine* risk assessment and risk minimization (see e.g. FDA requirements for professional labelling and adverse event monitoring and reporting). As a result, many of the recommendations presented here focus on situations when a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for all products or only this subset of products.

- It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy.⁷

⁷ See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness

- To the extent possible, this guidance conforms with FDA’s commitment to harmonize international definitions and standards as appropriate.

The topics covered in this guidance are being discussed in a variety of international forums. We are participating in these discussions and believe that, to the extent possible, the recommendations in this guidance reflect current thinking on related issues.

- When planning risk assessment and risk minimization activities, sponsors should consider input from health care participants likely to be affected by these activities (e.g. from consumers, pharmacists and pharmacies, physicians, nurses and third party payers).
- There are points of overlap among the three guidances.

We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, post-marketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product’s risk profile and for making informed decisions on risk minimization.

This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term *pharmacovigilance* to mean all

and safety of FDA-regulated products both to manufacturers and directly to FDA (45 CFR 164.512(b)(1)(i) and (iii), and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see <http://www.hhs.gov/ocr/hipaa>.

scientific and data gathering activities relating to the detection, assessment and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency and potential risk factors.

Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from post-marketing data and other sources, such as pre-clinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

Good Reporting Practice

Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the report is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and

subsequent follow-up, especially for serious events⁸ and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer, it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g. health care practitioner, patient and literature) and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

Characteristics of a Good Case Report

Good case reports include the following elements:

1. description of the adverse events or disease experience, including time to onset of signs or symptoms;
2. suspected and concomitant product therapy details (i.e. dose, lot number, schedule, dates and duration), including over-the-counter medications, dietary supplements and recently discontinued medications;
3. patient characteristics, including demographic information (e.g. age, race and sex), baseline medical condition before product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease and presence of other risk factors;
4. documentation of the diagnosis of the events, including methods used to make the diagnosis;

⁸ Good reporting practices are extensively addressed in a proposed FDA regulation and guidance documents. See (1) Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, 68 FR 12406 (March 14, 2003), (2) FDA guidance for industry on *Postmarketing Reporting of Adverse Experiences*, (3) FDA guidance for industry on *E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR)* and (4) FDA guidance for industry on *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

5. clinical course of the event and patient outcomes (e.g. hospitalization or death);⁹
6. relevant therapeutic measures and laboratory data at baseline, during therapy and subsequent to therapy, including blood levels, as appropriate;
7. information about response to dechallenge and rechallenge and
8. any other relevant information (e.g. other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, good case reports also include full descriptions of the following when such information is available:

1. products involved [including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration and type and size of container];
2. sequence of events leading up to the error;
3. work environment in which the error occurred and
4. types of personnel involved with the error, type(s) of error and contributing factors.

FDA recommends that sponsors capture in the case narrative section of a medication error report all appropriate information outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy.¹⁰ Although sponsors are not required to use the taxonomy, FDA has found the taxonomy to be a useful tool to categorize and analyze reports of medication errors. It provides a standard language and structure for medication error-related data collected through reports.

Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from post-marketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified

⁹ Patient outcomes may not be available at the time of initial reporting. In these cases, follow-up reports can convey important information about the course of the event and serious outcomes, such as hospitalization or death.

¹⁰ See <http://www.nccmerp.org> for the definition of a medication error and taxonomy of medication errors.

from the sponsor's global adverse event databases, the published literature and other available databases, such as FDA's AERS or vaccine adverse events reporting system (VAERS), using thorough database search strategies based on updated coding terminology [e.g. the Medical Dictionary for Regulatory Activities (MedDRA)]. When available, FDA recommends that standardized case definitions (i.e. formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series.¹¹ In general, FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabelled adverse events, although other events may warrant further investigation (see 'SAFETY SIGNALS THAT MAY WARRANT FURTHER INVESTIGATION' for more details).

As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness and follow-up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including

1. occurrence of the adverse event in the expected time (e.g. type 1 allergic reactions occurring within days of therapy and cancers developing after years of therapy);
2. absence of symptoms related to the event before exposure;
3. evidence of positive dechallenge or positive rechallenge;
4. consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
5. consistency of the event with the known effects of other products in the class;
6. existence of other supporting evidence from pre-clinical studies, clinical trials and/or pharmacoepidemiologic studies and

¹¹ See, for example Institute of Medicine (IOM) Immunization Safety Review on Vaccines and Autism, 2004.

7. absence of alternative explanations for the event (e.g. no concomitant medications that could contribute to the event and no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. They (i.e. cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke and pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA does not recommend any specific categorization of causality, but the categories *probable*, *possible* or *unlikely* have been used previously.¹² If a causality assessment is undertaken, FDA suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. Many references are available to assist sponsors in capturing a complete account of the event (Cohen, 1999). FDA recommends that sponsors follow-up to the extent possible with reporters to capture a complete account of the event, focusing on the *medication use systems* (e.g. prescribing/order process, dispensing process and administration process). This data may be informative in developing strategies to minimize future errors.

¹² See World Health Organization, the Uppsala Monitoring Center, 2000, *Safety Monitoring of Medicinal Products*, for additional categorizations of causality.

Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

1. the clinical and laboratory manifestations and course of the event;
2. demographic characteristics of patients with events (e.g. age, gender and race);
3. exposure duration;
4. time from initiation of product exposure to the adverse event;
5. doses used in cases, including labelled doses, greater than labelled doses and overdoses;
6. use of concomitant medications;
7. the presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;
8. the route of administration (e.g. oral vs. parenteral);
9. lot numbers, if available, for products used in patients with events and
10. changes in event reporting rate over calendar time or product life cycle.

Use of Data Mining to Identify Product–Event Combinations

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or the so-called *data mining*, can provide additional information about the existence of an excess of adverse events reported for a product. By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product–event combinations warranting further investigation. Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends and events associated with drug–drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event (e.g. liver failure) for a specific drug (i.e. the ‘observed reporting fraction’) with (2) the fraction of reports for the same particular event for all drugs (i.e. ‘the expected reporting fraction’) (Evans, 2000). This analysis can be refined by adjusting for aspects of reporting (e.g. the reporting year) or characteristics of the patient (e.g. age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease.

The score (or statistic) generated by data mining quantifies the disproportionality between the observed and expected values for a given product–event combination. This score is compared to a threshold that is chosen by the analyst. A potential excess of adverse events is operationally defined as any product–event combination with a score exceeding the specified threshold. When applying data mining to large databases (such as AERS), it is not unusual for a product to have several product–event combinations with scores above a specified threshold. The lower the threshold, the greater the likelihood that more combinations will exceed the threshold and will warrant further investigation.

Several data mining methods have been described and may be worth considering, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm (DuMouchel and Pregiborn, 2001; Szarfman *et al.*, 2002), the Proportional Reporting Ratio (PRR) method (Evans, 1998; 2000) and the Neural Network approach (Bate *et al.*, 1998). Except when the observed number of cases with the drug event combination is small (e.g. less than 20) or the expected number of cases with the drug event combination is <1, the MGPS and PRR methods will generally identify similar drug–event combinations for further investigation.¹³

Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the

same class or to all other products. FDA exercises caution when making such comparisons, because voluntary adverse event reporting systems such as AERS or VAERS are subject to a variety of reporting biases (e.g. some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other comorbidities or unrecorded confounders, may cause the events to be reported). In addition, AERS or VAERS data may be affected by the submission of incomplete or duplicate reports, under-reporting or reporting stimulated by publicity or litigation. As reporting biases may differ by product and change over time, and could change differently for different events, it is not possible to predict their impact on data mining scores.

Use of data mining techniques is not a required part of signal identification or evaluation. If data mining results are submitted to FDA, they should be presented in the larger appropriate clinical epidemiological context. This should include (1) a description of the database used, (2) a description of the data mining tool used (e.g. statistical algorithm, and the drugs, events and stratifications selected for the analyses) or an appropriate reference and (3) a careful assessment of individual case reports and any other relevant safety information related to the particular drug–event combination of interest (e.g. results from pre-clinical, clinical, pharmacoepidemiologic or other available studies).

Safety Signals that may Warrant Further Investigation

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably underreporting of some extent and incomplete information about duration of therapy, numbers treated and so on. Safety signals that may warrant further investigation may include, but are not limited to, the following:

1. new unlabelled adverse events, especially if serious;
2. an apparent increase in the severity of a labelled event;

¹³ This conclusion is based on the experience of FDA and of William DuMouchel, Ph.D., Chief Scientist, Lincoln Technologies, Wellsley, MA, as summarized in an email communication from Dr. DuMouchel to Ana Szarfman, MD., Ph.D., Medical Officer, OPaSS, CDER, on October 13, 2004.

3. occurrence of serious events thought to be extremely rare in the general population;
4. new product–product, product–device, product–food or product–dietary supplement interactions;
5. identification of a previously unrecognized at-risk population (e.g. populations with specific racial or genetic pre-dispositions or co-morbidities);
6. confusion about a product’s name, labelling, packaging or use;
7. concerns arising from the way a product is used (e.g. adverse events seen at higher than labelled doses or in populations not recommended for treatment);
8. concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g. reports of serious adverse events that appear to reflect failure of a RiskMAP goal)¹⁴ and
9. other concerns identified by the sponsor or FDA.

Putting the Signal into Context: Calculating Reporting Rates Versus Incidence Rates

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment. In pharmacoepidemiologic studies (see ‘PHARMAEOPIDEMOLOGIC STUDIES’), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate. Limitations in national denominator estimates arise because

1. accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available;

2. it may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low¹⁵ and
3. a product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator (Rodriguez *et al.*, 2001).¹⁶ FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes.

To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g. pre-menopausal women

¹⁴ For a detailed discussion of risk minimization action plan evaluation, please consult the *RiskMAP Guidance*.

¹⁵ See *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group V, Geneva, 2001.

¹⁶ In addition to U.S. reporting rates, sponsors can provide global reporting rates, when relevant.

and diabetics). These background rates can be derived from (1) national health statistics, (2) published medical literature or (3) ad hoc studies, particularly of subpopulations, using large automated databases or ongoing epidemiologic investigations with primary data collection. FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria and duration of time at risk.

Although the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g. publicity and newness of product to the market), and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES

FDA recognizes that there are a variety of methods for investigating a safety signal. Signals warranting additional investigation can be further evaluated through carefully designed non-randomized observational studies of the product's use in the 'real world' and randomized trials. The *Premarketing Guidance* discusses many types of randomized trials, including the large simple safety study, which is a risk assessment method that could be used either pre- or post-approval.

This document focuses on three types of non-randomized observational studies: (1) pharmacoepidemiologic studies, (2) registries and (3) surveys. By focusing this guidance on certain risk assessment methods, we do not intend to advocate the use of these approaches over others. FDA encourages sponsors to consider all methods to evaluate a particular

safety signal. FDA recommends that sponsors choose the method best suited to the particular signal and research question of interest. Sponsors planning to evaluate a safety signal are encouraged to communicate with FDA as their plans progress.

Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-crossover or other models.¹⁷ The results of such studies may be used to characterize one or more safety signals associated with a product or may examine the natural history of a disease or drug utilization patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests pre-specified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g. cohort studies) can also provide estimates of risk (incidence rate) for an adverse event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the pre-marketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated before marketing (e.g. to study the natural history of disease or patterns of product use or to estimate background rates for adverse events).

For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power. Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000–3000 (an exception may be larger trials conducted for some vaccines, which could move the threshold to 1:10 000). It may also be difficult to use clinical trials: (1) to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions or taking multiple

¹⁷ *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004, http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

concomitant medications or (2) to identify certain risk factors for a particular adverse event. On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials may be preferable to observational studies.

Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high.

Because different products pose different benefit-risk considerations (e.g. seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be made on a case-by-case basis. When an important adverse event-product association leads to questions on the product's benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest.

When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding. Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study (Strom, 2000). Because of the effects of bias, confounding or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different designs. Agreement of the results from more than one study helps to provide reassurance that the observed results are robust.

There are many references describing methodologies for pharmacoepidemiologic studies, discussing their strengths and limitations (Strom, 2000) and providing guidelines to facilitate the conduct, interpretation

and documentation of such studies.¹⁸ Consequently, this guidance document does not comprehensively address these topics. However, a protocol for a pharmacoepidemiologic study generally includes

1. clearly specified study objectives;
2. a critical review of the literature and
3. a detailed description of the research methods, including
 - the population to be studied;
 - the case definitions to be used;
 - the data sources to be used (including a rationale for data sources if from outside the United States);
 - the projected study size and statistical power calculations and
 - the methods for data collection, management and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such as data from previously conducted clinical trials or large databases. In recent years, many pharmacoepidemiologic studies have been conducted in automated claims databases (e.g. HMO and Medicaid) that allow retrieval of records on product exposure and patient outcomes. In addition, recently, comprehensive electronic medical record databases have also been used for studying drug safety issues. Depending on study objectives, factors that may affect the choice of databases include the following:

1. demographic characteristics of patients enrolled in the health plans (e.g. age and geographic location);
2. turnover rate of patients in the health plans;
3. plan coverage of the medications of interest;
4. size and characteristics of the exposed population available for study;
5. availability of the outcomes of interest;
6. ability to identify conditions of interest using standard medical coding systems [e.g. International

¹⁸ *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004, http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

Classification of Diseases (ICD-9)], procedure codes or prescriptions that could be used as markers;

7. access to medical records and
8. access to patients for data not captured electronically.

For most pharmacoepidemiologic studies, FDA recommends that sponsors validate diagnostic findings through a detailed review of at least a sample of medical records. If the validation of the specific outcome or exposure of interest using the proposed database has been previously reported, FDA recommends that the literature supporting the validity of the proposed study be submitted for review.

FDA encourages sponsors to communicate with the Agency when pharmacoepidemiologic studies are being developed.

Registries

The term *registry* as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is ‘an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that pre-disposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects’.¹⁹ Whenever possible, a control or comparison group should be included (i.e. individuals with a disease or risk factor who are not treated or are exposed to medical interventions other than the intervention of interest).²⁰

Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports or other sources and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure or

patient characteristics.²¹ Registries can be particularly useful for

1. collecting outcome information not available in large automated databases and
2. collecting information from multiple sources (e.g. physician records, hospital summaries, pathology reports and vital statistics), particularly when patients receive care from multiple providers over time.

A sponsor can initiate a registry at any time. It may be appropriate to initiate the registry at or before initial marketing, when a new indication is approved or when there is a need to evaluate safety signals identified from spontaneous case reports. In deciding whether to establish a registry, FDA recommends that a sponsor consider the following factors:

1. the types of additional risk information desired;
2. the attainability of that information through other methods and
3. the feasibility of establishing the registry.

Sponsors electing to initiate a registry should develop written protocols that provide (1) objectives for the registry, (2) a review of the literature and (3) a summary of relevant animal and human data. FDA suggests that protocols also contain detailed descriptions of (1) plans for systematic patient recruitment and follow-up, (2) methods for data collection, management and analysis and (3) conditions under which the registry will be terminated. A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity and validation of registry findings against a sample of medical records or through interviews with health care providers. FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study, and we encourage sponsors to discuss their registry development plans with FDA.

Surveys

Patient or health care provider surveys can gather information to assess, for example

¹⁹ See *Frequently Asked Questions About Medical and Public Health Registries*, The National Committee on Vital and Health Statistics, <http://www.ncvhs.hhs.gov/9701138b.htm>.

²⁰ See, for example *FDA Guidance for Industry: Establishing Pregnancy Exposure Registries*, August 2002, <http://www.fda.gov/cder/guidance/3626fnl.pdf>.

²¹ *Ibid.*

1. a safety signal;
2. knowledge about labelled adverse events;
3. use of a product as labelled, particularly when the indicated use is for a restricted population or numerous contraindications exist;
4. compliance with the elements of a RiskMAP (e.g. whether or not a Medication Guide was provided at the time of product dispensing) and²²
5. confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names.

Like a registry, a survey can be initiated by a sponsor at any time. It can be conducted at the time of initial marketing (i.e., to fulfill a post-marketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

FDA suggests that sponsors electing to initiate a survey develop a written protocol that provides objectives for the survey and a detailed description of the research methods, including (1) patient or provider recruitment and follow-up, (2) projected sample size and (3) methods for data collection, management and analysis.²³ FDA recommends that a survey-based monitoring system includes carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers, whenever possible. FDA recommends that survey instruments be validated or piloted before implementation. FDA suggests that sponsors consider whether survey translation and cultural validation would be important.

Sponsors are encouraged to discuss their survey development plans with FDA.

INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK

After identifying a safety signal, FDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also (1) employ data mining techniques and

(2) calculate reporting rates for comparison to background rates. Based on these findings and other available data (e.g. from pre-clinical or other sources), FDA suggests that a sponsor consider further study (e.g. observational studies) to establish whether or not a potential safety risk exists.

When evaluation of a safety signal suggests that it may represent a potential safety risk, FDA recommends that a sponsor submit a synthesis of all available safety information and analyses performed, ranging from pre-clinical findings to current observations. This submission should include the following:

1. spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;
2. background rate for the event in general and specific patient populations, if available;
3. relative risks, odds ratios or other measures of association derived from pharmacoepidemiologic studies;
4. biologic effects observed in pre-clinical studies and pharmacokinetic or pharmacodynamic effects;
5. safety findings from controlled clinical trials and
6. general marketing experience with similar products in the class.

After the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event. FDA suggests that the sponsor's submission provides an assessment of the benefit-risk balance of the product for the population of users as a whole and for identified at-risk patient populations and, if appropriate, (1) propose steps to further investigate the signal through additional studies and (2) propose risk minimization actions.²⁴ FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g. information on other products in the same class) and will communicate its

²² For a detailed discussion of RiskMAP evaluation, please consult the *RiskMAP Guidance*.

²³ See 21 CFR parts 50 and 56 for FDA's regulations governing the protection of human subjects.

²⁴ In the vast majority of cases, risk communication that incorporates appropriate language into the product's labelling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a RiskMAP. Please refer to the *RiskMAP Guidance* for a complete discussion of RiskMAP development.

conclusions to the sponsor whenever possible. Factors that are typically considered include:

1. strength of the association (e.g. relative risk of the adverse event associated with the product);
2. temporal relationship of product use and the event;
3. consistency of findings across available data sources;
4. evidence of a dose-response for the effect;
5. biologic plausibility;
6. seriousness of the event relative to the disease being treated;
7. potential to mitigate the risk in the population;
8. feasibility of further study using observational or controlled clinical study designs and
9. degree of benefit the product provides, including availability of other therapies.

As noted in ‘BACKGROUND’, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product’s benefit–risk balance and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps.²⁵ FDA recommends that assessment of causality and of strategies to minimize product risk occur on an ongoing basis, taking into account the findings from newly completed studies.

BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

For most products, routine pharmacovigilance (i.e. compliance with applicable post-market requirements under the FDCA and FDA implementing regulations) is sufficient for post-marketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance

plan describes pharmacovigilance efforts above and beyond routine post-marketing spontaneous reporting and is designed to enhance and expedite the sponsor’s acquisition of safety information.²⁶ The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor’s decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. the likelihood that the adverse event represents a potential safety risk;
2. the frequency with which the event occurs (e.g. incidence rate, reporting rate or other measures available);
3. the severity of the event;
4. the nature of the population(s) at risk;
5. the range of patients for which the product is indicated (broad range or selected populations only) and
6. the method by which the product is dispensed (through pharmacies or performance linked systems only).²⁷

A pharmacovigilance plan may be developed by itself or as part of a RiskMAP, as described in the *RiskMAP Guidance*. Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product’s pharmacovigilance plan.

²⁶ As used in this document, the term ‘pharmacovigilance plan’ is defined differently than in the ICH draft E2E document (version 4.1). As used in the ICH document, a ‘pharmacovigilance plan’ would be routinely developed (i.e. even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks. This ICH guidance is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November, 2004.

²⁷ For a detailed discussion of controlled access systems, please consult the *RiskMAP Guidance*.

²⁵ For additional discussion of the relationship between risk assessment and risk minimization, please consult the *RiskMAP Guidance*.

FDA believes that for a product without safety risks identified pre- or post-approval and for which at-risk populations are thought to have been adequately studied, routine spontaneous reporting will be sufficient for post-marketing surveillance. On the other hand, pharmacovigilance plans may be appropriate for products for which (1) serious safety risks have been identified pre-or post-approval or (2) at-risk populations have not been adequately studied. Sponsors may discuss with the Agency the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

1. submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e. as 15-day reports);
2. submission of adverse event report summaries at more frequent, pre-specified intervals (e.g. quarterly rather than annually);
3. active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be (1) drug based: identifying adverse events in patients taking certain products; (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g. emergency departments etc.) or (3) event based: identifying adverse events that are likely to be associated with medical products (e.g. acute liver failure);
4. additional pharmacoepidemiologic studies (e.g. in automated claims databases or other databases) using cohort, case-control or other appropriate study designs (see 'BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES');
5. creation of registries or implementation of patient or health care provider surveys (see 'BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES') and
6. additional controlled clinical trials.²⁸

As data emerges, FDA recommends that a sponsor re-evaluate the safety risk and the effectiveness of its pharmacovigilance plan. Such re-evaluation may result in revisions to the pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions on potential safety risks and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee or the FDA Advisory Committee dealing with the specific product in question. Such committees may be convened when FDA seeks (1) general advice on the design of pharmacoepidemiologic studies, (2) comment on specific pharmacoepidemiology studies developed by sponsors or FDA for a specific product and safety question or (3) advice on the interpretation of early signals from a case series and on the need for further investigation in pharmacoepidemiologic studies. Although additional information is being developed, sponsors working with FDA can take interim actions to communicate information about potential safety risks (e.g. through labelling) to minimize the risk to users of the product.

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Risk Management – a European Regulatory View

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INTRODUCTION

In the decade since the European regulatory systems were fully implemented in 1995, the concepts of risk management have developed and evolved in the light of growing knowledge and experience. The term ‘risk management’ may be broadly defined as the identification and implementation of strategies to reduce risk to individuals and populations, while a risk management plan in relation to a particular medicine has a specific interpretation set out in European guidance.

The principles of risk management informed the ‘2001 review’ of European Legislation, which was adopted in 2004 and was subsequently the subject of detailed guidelines. It is often said that regulation follows science; in the case of risk management, regulation has followed not only scientific and technical progress, but growing public expectations that the systems for monitoring the safety of medicines are optimally effective.

Risk management in Europe faces particular challenges. The regulatory systems depend on the collective functioning of a network which now comprises 26

national agencies (2 in Germany), with the European Medicines Agency (EMEA) performing a supervisory and co-ordinating role. This chapter therefore has two interrelated themes: the scientific and regulatory basis for risk management in Europe, and the organisational and operational delivery of this approach to pharmacovigilance.

Much remains to be done to maximise the benefit of the new legislative basis for risk management in Europe, and yet additional options to further strengthen pharmacovigilance systems are already under examination. Several initiatives are in hand involving a range of stakeholders, and the way forwards is a matter of wide debate. Judging by the number of initiatives and discussion fora, the further development of European risk management may be long term.

BACKGROUND

The test of the effectiveness of regulatory systems is their performance in responding to emerging drug

safety hazards to identify, evaluate, manage and communicate risk in the context of benefit. Recent significant drug safety issues handled in the European regulatory framework and the evidence which triggered them are shown in Table 44.1.

The withdrawal of cerivastatin in 2001 following spontaneous reports of cases of serious and fatal rhabdomyolysis represented a regulatory milestone. The extent of use of cerivastatin in Europe meant that wide public debate ensued. This debate was reignited on an international scale in September 2004, when Merck withdrew rofecoxib, a selective cyclo-oxygenase 2 inhibitor widely used in the treatment of arthritic pain, because of clinical trial evidence of an increased risk of heart attack and stroke.

While high-profile drug withdrawals have been the focus of detailed public scrutiny, evidence has continued to gather of the general burden of adverse drug reactions in public health terms. Research conducted in the United States by Lazarou concluded that adverse drug reactions in 1994 were between 4th and 6th leading cause of death (Lazarou *et al.*, 1998). A recent prospective analysis in the United Kingdom by Pirmohamed *et al.* gave a similar estimate; about 6.5% of hospital admissions were related to an adverse

drug reaction (ADR) with a 0.15% incidence of fatal ADRs (Pirmohamed *et al.*, 2004).

EUROPEAN FOCUS ON ADRs

In 2002 the public health importance of adverse drug reactions was recognised by the European High-Level Group on Innovation and Provision of Medicines (the so-called 'G10 group') comprising health ministers, patient representatives and industry leaders. The G10 report recommended that 'industry and national regulatory authorities should undertake regular monitoring to ensure that medicines once authorised meet the required standards of safety... systems for post marketing surveillance should be optimised to ensure co-ordinated processes are in place to gather data' (European Commission G10 Medicines, 7 May 2002).

Following publication of the G10 report, in 2002 the heads of the European national medicines agencies set up an ad hoc Working Group on establishing a Risk Management Strategy (European Risk Management Strategy (ERMS) Working Group) to take stock of the current status of pharmacovigilance in Europe and explore how it could be strengthened. The EMEA had at that time presented proposals for a

Table 44.1. Drug safety issues and their evidence.

Drug	Safety Concern	Key evidence	Regulatory action
Trovofloxacin	Hepatotoxicity	Spontaneous ADRs	Withdrawn
Tolcapone	Hepatotoxicity	Spontaneous ADRs	Suspended
Cisapride	QT prolongation cardiac arrhythmias	Spontaneous ADRs	Patient registration – licences subsequently cancelled
Bupropion	Seizures drug interactions	Spontaneous ADRs	Posology change warnings
Cerivastatin	Rhabdomyolysis	Spontaneous ADRs	Withdrawn
Hormone replacement therapy	CVS risk and cancer long term	Epidemiological studies	Warnings and restriction of indication
SSRIs	Suicidal behaviour in children	Clinical trials	Warnings accompanied by clinical guidance
COX IIIs	CVS risk	Clinical trials	Warnings and clinical guidance
Topical macrolide immunosuppressants	Risk of cancer	Spontaneous reports	Restriction of use risk management plan

risk management strategy concentrating on centrally authorised products, and it was accepted that the future strategy should be applicable to all medicines on the European market, including those authorised nationally and by mutual recognition. An initial report of the ERMS Working Group published in January 2003 set out priorities for action and subsequently led to a programme of work published in May 2005 encompassing a range of operational improvements.

EXCELLENCE IN PHARMACOVIGILANCE MODEL

The ERMS Working Group adopted an approach to establishing a European Risk Management Strategy based on the model for delivering effective pharmacovigilance known as ‘Excellence in Pharmacovigilance’. This was the result of a project set up by the then UK Medicines Control Agency and published in 2003. It is a conceptual framework for achievement of demonstrable effectiveness in terms of public health protection, comprising the following components: (Figure 44.1).

- Best evidence, moving up the ‘evidence hierarchy’ away from spontaneous ADR reports to more reliable evidence, from observational studies and clinical trials.
- Robust decision-making, including analysis of potential impact of signals on risk–benefit balance.
- ‘Tools’ to protect public health including effective communication mechanisms as well as action to update the marketing authorisation.



Figure 44.1. Working model for excellence in Pharmacovigilance.

- Routine outcome measures and audit of regulatory action.
- A culture of scientific development which keeps pace with new developments and maximises opportunities for improving pharmacovigilance offered by new scientific and technological advances.

The so-called ‘Excellence’ model not only defined the prerequisites for an effective pharmacovigilance system, but argued for a change in mindset, a shift from searching for evidence of harm to demonstrating safety, and a capability to demonstrate that serious adverse reactions are rare in the long term. This in turn requires a consideration at the time of licensing a new medicine of the level of safety already demonstrated, any possible concerns which need further investigation and appropriate strategies by which further evidence is to be gathered.

This proactive approach to demonstrating safety merited wider debate, and the International Conference on Harmonisation presented an opportunity to gain the perspective of the United States and Japan. The outcome was the harmonised tripartite guidelines E2E on Pharmacovigilance Planning, adopted in November 2004. This guideline sets out the elements of the safety specification and provides guidance on the structure of the pharmacovigilance plan and appropriate methodologies to generate information on known risks as well as what is not known.

EUROPEAN PHARMACEUTICAL LEGISLATION

In November 2005 new European legislation came into force including a number of provisions aimed at strengthening pharmacovigilance. Specifically, Article 8(3) (ia) of Directive 2001/83/EC requires applicants for marketing authorisations to submit ‘a detailed description of the pharmacovigilance and where appropriate, of the risk management systems which the applicant will introduce’. The description of the pharmacovigilance system is company-specific, encompassing *inter alia* pharmacovigilance databases, and systems for collecting and reporting ADRs. The requirement for submission of a description of the risk management system is in contrast product-specific.

EUROPEAN RISK MANAGEMENT PLANS

A European Guideline on Risk Management for Medicinal Products for Human Use, also published in November 2005, sets out in detail the situations when a risk management plan is required. In brief, a risk management plan is required for all new active substances, significant changes to marketing authorisations such as new indications (unless the competent authority agrees it is unnecessary), and when an unexpected hazard is identified.

The EU Risk Management Plan contains 2 parts:

1. Part I

- A safety specification
- A pharmacovigilance plan.

2. Part II

- An evaluation of the need for risk minimisation activities, and if there is need for additional (i.e., non-routine) activities
- A risk minimisation plan.

The sections of the guideline dealing with the safety specification and pharmacovigilance plan build on the relevant text from ICH E2E.

SAFETY SPECIFICATION

The starting point for proactive pharmacovigilance, the safety specification, summarises what is known and what is not known about the safety of the product. This encompasses the important identified risks and any important information and outstanding safety questions which warrant further investigation, in order to refine understanding of benefit:risk during the post-authorisation period. The epidemiology of the indication is to be included, together with background incidence rates of events of interest for further investigation. Additional EU requirements for inclusion in the safety specification are potential for overdose, potential for transmission of infectious agents and potential for misuse for illegal purposes. The safety specification also forms the basis for the risk minimisation plan if this is required.

PHARMACOVIGILANCE PLAN

The purpose of the pharmacovigilance plan is not to replace but to complement procedures in place to detect safety signals. For medicines with important identified risks, important potential risks or important missing information, additional pharmacovigilance activities to address these concerns should be considered. The EMEA Guideline describes a range of study designs (e.g., active surveillance, comparative observational studies) and data sources. An inventory of European pharmaco-epidemiology centres and healthcare databases is to be created by EMEA to facilitate the implementation of pharmacovigilance plans.

RISK MINIMISATION PLAN

A risk minimisation plan is only required in circumstances where standard information provision via the medicine's summary of product characteristics, patient information leaflet and label is not considered adequate to address identified safety concerns. Where a risk minimisation plan is considered necessary, both routine and additional activities are to be included. Some safety concerns may have more than one risk minimisation activity, each of which should be evaluated for effectiveness.

IMPLEMENTATION OF RISK MANAGEMENT PLANS

The need for agreement of risk management plans for new medicines, and when an unexpected new hazard has been identified, has been rapidly incorporated into regulatory procedures as a matter of routine. This includes Opinions of the Committee for Human Medicinal Products and the Coordinating Group. Around 50 risk management plans were reviewed in the first 6–9 months. The early experience has suggested a need for appropriate pharmaco-epidemiology and biostatistics expertise to be available, and this has also been co-opted into the membership of the Pharmacovigilance Working Party from March 2006. There has also been discussion about wider public access to risk management plans. To date, this has been limited to isolated examples such as the risk management plan for lumiracoxib,

a Cox II inhibitor published in December 2005 (Medicines and Healthcare Products Regulatory Agency).

FUTURE DEVELOPMENT OF EUROPEAN RISK MANAGEMENT STRATEGIES

The focus on delivering risk management plans in practice which followed the implementation of new European Legislation did not curtail the wider debate about future development of European risk management.

THE ERMS ACTION PLAN

The development and population of EudraVigilance by the member states, enabling signal detection from a substantial European database is a major strategic objective. The advantage for rapid, robust signal detection from a population base of over 450 million people is clear. The ‘downstream’ work of impact analysis and risk assessment would also benefit from collaborative working, following the pilot study by a small group of member states sharing the evaluation of periodic safety update reports. This pilot study was triggered by the results of a high-level survey of member states resources for pharmacovigilance conducted in 2003–04, which found that the total number of staff engaged in pharmacovigilance in Europe was only around 340 full-time equivalents with around 40% involved in data management.

EUROPEAN COMMISSION

On 15 March 2006, the European Commission (DG Enterprise) published an independent assessment of the European Community system of pharmacovigilance. This broad-ranging assessment based on the results of a questionnaire and interviews with pharmacovigilance staff in national authorities highlighted the strengths and weaknesses of the European system of pharmacovigilance as operated by the network of member state agencies. The report’s recommendations focussed on: the breadth and variety of data sources; the proactive use of the legislation; the speed of decision-making; the impact of regulatory action

and communication; compliance by marketing authorisation holders; and general principles of quality management and continuous quality improvement.

INNOVATIVE MEDICINES INITIATIVE

In July 2005, the European Commission (DG Research) published the Innovative Medicines Initiative Strategic Research Agenda whose objective is to accelerate the development of safe and more effective medicines by joint public and private collaborations. The main recommendations concerning safety evaluation include the creation of a European Centre of Drug Safety Research (ECDS) to identify and co-ordinate research needs in safety sciences. The ECDS as envisaged would cover issues of non-clinical safety as well as pharmacovigilance and risk management. Priority areas for research in pharmacovigilance and risk management include development of methodologies and networks, and novel methods of risk prediction and benefit–risk assessment, including decision analysis tools. The establishment of the proposed ECDS will depend on availability of funding.

CONCLUSION

In conclusion, the new European legislative provision requiring risk management systems to be in place for particular medicines signals a change in regulation from a largely reactive to a proactive approach to pharmacovigilance. The focus on regulators approving risk management plans, utilising appropriate expertise and data resources, needs to shift to monitoring their effectiveness in practice. A climate of greater transparency and openness about risk management plans would help manage public expectations and foster greater understanding of the fact that no medicine is risk-free. Finally, the case for risk management to begin early in drug development, in the form of a Development Risk Management Plan (DRMP) has been well set out in the Report of the CIOMS Working Group VI. The worldwide alarm at the life-threatening reaction in health volunteers receiving the monoclonal antibody TGN 1412 first in man studies in the United Kingdom in March 2006 can only strengthen this case.

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The Efficacy and Safety of Selective Serotonin Reuptake Inhibitors for the Treatment of Depression in Children and Adolescents

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ABSTRACT

Much confusion has been generated by the sharply differing perspectives of the various stakeholders on the benefit to risk assessment of selective serotonin reuptake inhibitors (SSRIs). To make these issues clearer, this chapter aims to provide a review and critique of the following topics: (1) published randomized clinical trials on the efficacy of SSRIs for the treatment of major depressive disorder (MDD); (2) meta-analysis of related published and unpublished trials; (3) safety of SSRIs from clinical trial analyses and published clinical trial reports; (4) safety of SSRIs from observational studies; (5) suggestions for new studies to assess suicidality and related treatment-emergent adverse drug events, for example hostility,

aggression and activation; (6) improving the safety infrastructure to assess drug safety in children and adolescents and (7) recent consequences of Food and Drug Administration (FDA) black box warnings. From this review, the reader should have a more detailed knowledge base from which to assess clinical decisions related to the safety of the SSRIs for the treatment of depression in youth and to build consensus on future research and policy.

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 behaviour

in depressed adults (Teicher, Glod and Cole, 1990) and 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 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, Warner and Brown, 2000). However, in June 2003, the suicidality issue began to draw renewed media attention following the publication from the United Kingdom (UK) drug regulatory agency (MHRA) of a preliminary report on paroxetine clinical trial data which revealed that children receiving this SSRI experienced more suicidality than randomly assigned children receiving placebo (3.7% vs. 2.5%, respectively) (Medicines and Healthcare products Regulatory Agency, 2004). FDA hearings on this subject in February 2004 and September 2004 reviewed 25 US pediatric trials of ATDs with respect to the risk of suicidality (defined as suicidal ideation or attempts). These industry-conducted registration trials were submitted to FDA, many in response to the FDA Pediatric Rule, which extended patent exclusivity for 6 months regardless of 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 (defined as ideation, attempts or completed suicides) based on depression trial data for youth exposed to SSRIs relative to placebo. Recommendations from MHRA in the United Kingdom and the European agency (European Medicines Agency, 2005) contrast with US drug regulators (FDA, 2004) and have led to confusion and limited, often misleading interpretations of the pertinent scientific information. Although no completed suicides occurred in the trials, the FDA pediatric panel of reviewers recommended caution, and in October 2004, the FDA announced that a black box warning would be added to the official label for all ATDs, stressing the risk of treatment-emergent suicidality. In contrast to UK announcements restricting the use to fluoxetine, no contraindication for SSRI use to treat depression in children and adolescents was recommended except to discourage use of paroxetine. Also in 2004, the European drug safety

agency (EMEA) issued similar warnings for SSRIs and like the United Kingdom also prohibited prescription of SSRIs to treat depression in youths (European Medicines Agency, 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 on the efficacy) of SSRIs for the treatment of depression in children and adolescents in the United States. 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 TRIALS

Table 45.1 describes the major published SSRI efficacy studies conducted in US youth. The studies used many outcome measures including (1) symptom rating scale score change from baseline (intent to treat model); (2) symptom rating scale score change at final endpoint (completers model); (3) percent improved and (4) clinical global impression (CGI) rating score change. Two of the fluoxetine studies did not meet the *a priori* primary endpoint of symptom score reduction from baseline (Emslie, Rush and Weinberg, 1997; Emslie *et al.*, 2002) causing a FDA statistical expert to reject the efficacy claim (Shen, 2003). For the studies including both children and adolescents, Wagner (sertraline) and Emslie (fluoxetine), 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 by Keller *et al.* (2001). The authors therefore based the conclusion of paroxetine efficacy on a relatively modest difference in the percent improved (63 vs. 46). The NIMH-funded treatment of adolescent depression study (TADS) was added to the list of registration trials for the FDA safety analysis (see below 'SAFETY FROM CLINICAL TRIAL DATA'). The TADS study 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 behaviour therapy (CBT)] and

Table 45.1. 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)	Adolescents (12–17/18 or 13–17)
Wagner (2003), MDD, Sertraline	% improved (69 vs. 59), 40% drop in CDRS-r, $p = .05$	Mean change from baseline CDRS-r (-24.05 vs. -22.20), ns; at 10 weeks (-31.44 vs. -27.56), $p < .05$	Group diff mean CDRS-r (-21.55 vs. -18.20), $p = .01$; at 10 weeks (-28.95 vs. -24.11), $p = .01$
Emslie (1997), MDD, Fluoxetine	% improved (29 vs. 19), ns; remission, ns; CGI improvement (56% vs. 33%), $p = .02$	8–12 y/o 30% reduction from baseline, ns	13–17 30% reduction from baseline, $p = .075$
Emslie (2002), MDD, Fluoxetine	% improved (65.1 vs. 53.5), $p = .09$	8–12 CDRS-r 30% reduction ns	13–17 CDRS-r 30% reduction ns
TADS, 2004, MDD, Fluoxetine Keller (2001), MDD, Paroxetine			Fluox + CBT > Fluox > CBT > Placebo unblinded HAM-D 50% reduction ns; week 8 endpoint % improved (63 vs. 46), $p = .02$

MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitors.

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. The data do not support efficacy in children although published clinical interpretations suggest moderate overall effectiveness (Vitiello and Swedo, 2004), are silent on this important distinction (Cheung, Emslie and Mayes, 2005) and focus on the weak safety evidence in the face of the serious risks of the failure to treat depression irrespective of efficacy in children compared with adolescents (Brent, 2004; Cheung, Emslie and Mayes, 2005; Mann *et al.*, 2006).

META-ANALYSIS OF PUBLISHED AND UNPUBLISHED STUDIES

In addition to individual published trial analysis, there has been a meta-analysis of registration studies from the United Kingdom (Whittington *et al.*, 2004). The authors divided the studies into peer-reviewed published and unpublished studies residing with the

Committee on Safety of Medicines (CMS). Efficacy measures included remission, response to treatment and depression symptom scores. Safety measures included serious adverse events (AEs), suicide-related behaviours and discontinuation of treatment because of AEs. 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 major depressive disorder (MDD) in youth: fluoxetine use was supported but one paroxetine and two sertraline trials had equivocal or weak positive risk–benefit profiles. However, in these two cases, the addition of unpublished data shifted the results to an unfavourable risk–benefit profile. Data from citalopram and venlafaxine showed unfavourable 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 suicidality.

From a research methodology perspective, unpublished trial data are a source of publication bias and render meta-analytic approaches virtually meaningless. Demands for an end to tolerate unpublished

studies based on the 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 (<http://www.clinicaltrials.gov>). Thus far, database compliance has been increasing but is in need of substantial improvement especially regarding completion of the field for recording the primary outcome measurement (Zarin, Tse and Ide, 2005).

SAFETY FROM CLINICAL TRIAL DATA

Before 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 suicidality conducted by Andrew Mosholder was removed from the agenda. Subsequently, a reclassification of the AEs reported in the trials was conducted by Columbia University epidemiologists. After the revised data were available, the Mosholder analytic design [Office of Drug

Safety (ODS)] and a second analysis conducted by Turek Hammad for the Division of Neuropharmacological Drug Products (DNDP) were compared (Shen, 2003; Hammad, 2004; Mosholder, 2004). The analyses differ in that person-years was the unit of analysis used in ODS and persons was the unit of analysis in DNDP. This results in incident rate ratios for the former and relative risk estimates for the latter. The studies also differ in the definition of suicidality AEs that were captured in each study.

Table 45.2 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) compared with the risk of serious suicide-related events according to the standard regulatory definition: that is, life-threatening adverse drug experience, in-patient hospitalization or prolongation of hospitalization, or disability/incapacity (column 4). There is little overall difference between the two results for outcome 3 and serious suicide-related events. Both show an increased risk for all MDD studies. 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

Table 45.2. Comparison of risk of serious suicide-related events and outcome 3 in two distinct analytic approaches (ODS and DNDP).

Category of trial	Total N drug	Total N placebo	ODS analysis (incidence rate ratios, serious suicide-related events)	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	*	1.58 (0.06–38.37)
Nefazodone	279	189	*	**
Fluvoxamine	57	63	*	5.52 (0.27–112.55)
Bupropion	71	36	**	**
All MDD trials	1586	1299	1.95 (1.19–3.21)	1.71 (1.05–2.77)
SSRI*** 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)

MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitors.

* Ratio undefined because of zero events in the placebo group.

** No events in either arm.

*** Includes paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine.

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 suicide-related events 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 behaviour ($n = 33$) in the risk estimates of suicidality was shown to dilute the risk [1.00 (0.52–1.94) vs. 1.83 (0.89–3.77)], respectively (Hammad, 2004, Table 5.10.36, p. 38). 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 behaviour, 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 behaviour 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 [2.34 (1.24–4.41)]. Overall, patients with symptoms of activation or hostility were up to 6.6 times more likely to have suicidality than those without such activation (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 behaviours 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 suicidality. In addition, age may be crucial to further understanding AEs in relation to SSRI use. Using published trials in which child and adolescent data were recorded separately, an analysis of AEs, for example activation was two to three times more prevalent in children than adolescents and accounted for more discontinuations than in adults (Safer and Zito, 2006).

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 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 alternative interpretation, that is the adverse symptoms may be indicative of treatment-emergent activation rather than true mania.

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 proposed inpatient hospitalization as an outcome. Hospitalizations might shed light on the general problem of behavioural toxicities (new psychiatric or behavioural 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 that ‘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.

A number of limitations of these FDA-sponsored analyses should be considered:

First, searching clinical trial data restricts the assessment to a very small drug-exposed population. In

this case, there were approximately 2000 youths with major depressive disorder, mainly adolescents who were exposed to an SSRI. Since suicide events in a lifetime estimate for adolescents were estimated at 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 the assessment of suicidality from clinical trial data particularly troubling. The positive gain from having youths randomized to drug and placebo conditions to avoid channelling or other treatment bias found in community-treated populations is offset by the selection biases produced by the use of trial data (e.g. exclusion of suicidal behaviour and volunteer bias). Third, measurement bias may further limit the analysis, because the overwhelming proportion of suicidal events in the DNDP outcome 3-analysis relied on suicidal ideation reports which resulted in a weak non-significant risk estimate. The prediction of completed suicide from suicide attempts for 15–19 year old boys is 400:1 and 3000:1 for girls, whereas for suicidal ideation it is 9000:1 for boys and 19 000:1 for girls. Such ratios in children and adolescents are lower than that for adults (Mann, 2006) 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 4–6 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, 2006). It is also instructive 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 (*community*

treated individuals), many ecological studies on suicidality in relation to SSRI use have been performed. In these studies, temporal trends in completed suicides in relation to trends in SSRI utilization within specific countries were analyzed statistically. The findings, strengths and weaknesses of each of these studies will be reviewed.

Observational studies on the relationship between adult suicide and exposure to ATDs have been conducted on the Swedish population (Isacsson, Boethius and Bergman, 1992; Isacsson *et al.*, 1997). These studies conclude that adult suicides are associated with little or no ATD use at the time of death and suggest 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 antidepressants (TCAs) ($p < .001$). They infer that changing to an ATD class that is safer in over-dosage (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 persons.

In the United States where the recent concern has been on the risk for youth treated with SSRIs, administrative reimbursement claims for prescription use in an insured population were collected for 1 month in 1989 and a corresponding 1 month period in 2001 (Olfsen *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, Center 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 presented 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 percentage white population, median income and number of physicians per capital. 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).

Several study limitations are prominent: The total sample size of exposed youths in 1 month window is very small to link with very rare events occurring at the population level, the assumption that prescriptions dispensed were consumed and the theoretical model suggesting that suicide and ATD use are strongly negatively correlated ignores many non-pharmacologic factors known to influence suicide rates, for example firearms reduction, non-pharmacologic therapies and the broad national trend for suicide reduction going back years before ATDs were being used. Also, it is difficult to interpret the data when the denominator is composed of youths 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 suicide events representing population data. 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. A similar analysis focused on the association of prescriptions dispensed within a county and the suicide rate but found no association for total ATDs but a significantly higher rate for TCAs and 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. 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 have been obtained by Jick, Kaye and Jick (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 and 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 non-fatal suicidal behaviour 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 before the index date for suicidal behaviour 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 3-fold higher for youth in the United States than in the United Kingdom (Delate *et al.*, 2004; Murray, de Vries and Wong, 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 United Kingdom 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 non-fatal self-harm relative to TCA use ($p < .05$). However, the possibility of channelling of SSRIs to patients at higher risk of suicidal behaviour 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 ($n = 24\,110$), 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 a health maintenance organization (HMO) population in the northwest region of the country (Simon *et al.*, 2006) and studied 82,285 ATD use episodes ($n = 65$ 103 patients, mainly 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). During the 6 months following the start date of the dispensed prescription, the risk of serious suicide attempts was 1 in 1000 and the risk of suicide during acute-phase ATD treatment was 1 in 3000. The authors concluded that the data do not indicate a significant increase in 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 (odd ratio = 1.2, 95% 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 findings, there was a higher risk of suicide attempt in the first week of ATD treatment than in subsequent weeks. The authors suggest that a causal model would require a randomized study and for single drug comparisons to placebo samples on the order of 300 000 to detect a 2-fold 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.

NEW STUDIES TO ADDRESS THE RESEARCH QUESTION

The main FDA clinical trial analysis (DNDP) 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 psychiatric-related hospitalizations and emergency department (ED) visits.

Survey data shed some light on the scope of the suicide-related medical service utilization. The self-reported suicide attempts and those resulting in medical attention for adolescents (14–17 year olds) in the 2003 population-based high school CDC survey was 8.5% and 2.9%, respectively. Medical attention was not defined in the survey and presumably refers to outpatient care as well as hospitalization or ED visits (Grunbaum *et al.*, 2004). By self-report then, approximately 1.3 million US high school students have 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) 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 multi-state 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 per 100,000 for those less than 15 years and 259 per 100,000 among 15–19 year olds. Overdoses and cutting accounted for 85%–90% of attempts.

Estimates of the frequency of ED use for intentional self-injury by youths suggest that it is relatively low. In the state of Oregon from 1988 through 1993, suicide attempts by youths aged 10–17 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, Graham and Flowers,

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 came 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 records data are likely to be a feasible approach to patient-level assessment of the association of psychiatric-related AEs 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 AEs 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 data set prior and ongoing medication patterns of those admitted. Unfortunately, this is not generally recorded. Using a community-based data set 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 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 study is essentially that youth rather than adults would be studied; youth and not episodes would be the unit of analysis; and 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 suicidality in youth requires a prospective randomized cohort study design in a large 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 is 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 placebo control. Following the cohort forward for 6 months would allow information to be collected on the effectiveness

of treatment and reasons for discontinuation of 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, behavioural toxicity.

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 (Ray and Stein, 2006; Wood, Stein and Woosley, 1998; Avorn, 2005a) 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 AEs. 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.

AE 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 AEs.

RECENT FDA ACTIONS AND CONSEQUENCES

Drug exposure data are typically based on prevalence estimates which are based on *exposed youth rather than prescription sales*, and this distinction is critical to a refined understanding of the impact of warnings on the use of prescribed ATDs in youth. Since the heightened media coverage of treatment-emergent suicidality – which began in June 2003 – the prescription sales of SSRIs for the treatment of youth have dropped (Elias, 2005; Rosack, 2005).

The drop in prescription sales varied sizably with the age of the youth. In the Medco Health Systems report on prescription rate analyses from 2003–05 ATD prescriptions dropped 32% for youth under age 12 and 18% for youth aged 12–18 (Elias, 2005). Among youth with a diagnosis of depression, there was a 23% decrease in ATD prescriptions for those less than 18 in 2004 compared with the previous year (Pomerantz, 2005).

In a South Carolina Medicaid youth population ATD assessment covering the period May 2004 through April 2005, SSRI use decreased but TCAs and other ATDs increased (Narasimhan *et al.*, 2005). In addition, the methodology for assessing change is critical. A recent study using Canadian insurance data defined new onset (incident) users of ATDs as those with a prescription following the diagnosis of depression. In this cohort of youth initially identified as *diagnosed with depression*, SSRI treatment varied by race, gender, age, ATD subclass and medical provider (primary care or psychiatry). Being female, having a diagnosing general practitioner or pediatrician and having the same diagnosing and prescribing physician were associated with higher odds of receiving a SSRI (Sewitch *et al.*, 2005). 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 prescription sales.

CONCLUSIONS

This 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 raise serious concerns that youth outcomes are different, particularly in children. Data have been presented and their findings have been critiqued. Suggestions for further research are posed. Many publicized interpretations of the existing studies suggest that 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 clinical readers’ perspective, wisdom and FDA warnings demand caution and close monitoring.

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Pharmacoepidemiology of Hormone Therapy: An Evolving Picture*

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When the FDA first approved menopausal hormone replacement therapy (Emmenin) in 1933, the formulation was not easy to mass-produce (Rothenberg, 2005). In 1942, Premarin, a more easily manufactured estrogen, was introduced to the US mass market (CDER, 1997). At that time, Premarin was known to contain two main oestrogens, estrone and equilin, and some additional oestrogens in smaller amounts. It was approved primarily for the short-term treatment of postmenopausal symptoms – for relief of vasomotor symptoms associated with menopause. According to the FDA website,

the drug's approval in 1942 predicated the current requirements for such comprehensive analysis of products under review for marketing approval. At that time, Premarin's approval was based on acceptable chemistry, manufacturing, and controls information and a showing, from reports of clinical investigations, that the drug was safe for its intended use in the treatment of menopausal symptoms and related conditions (CDER, 2005).

Over the years, however, many US women began to use the product off label for prevention of certain diseases such as coronary heart disease (CHD) or osteoporosis and for much longer periods of times than first envisioned. By the mid-1960s, about 12% of all postmenopausal women were taking oestrogen (Harvard, 2003). Eventually, in 1986, the FDA

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approved the drug for prevention of osteoporosis. By the time WHI was initiated in 1993, progestins had been added to protect the endometrium and most postmenopausal women in the US had been prescribed hormone therapy (HT). In addition, most, if not all of these women, had used HT in a way not originally approved by the FDA. A study by Hersh, Stefanick and Stafford (2004) estimated that from 1999 to June 2002, approximately 15 million postmenopausal women per year were taking HT. This figure was up substantially from earlier years primarily due to an increase in oral oestrogen/progestin combinations. It is of interest to note that more than one-third of patients who were prescribed HT were older than 60 years and thus several years post menopause.

There is a long history of observational studies of HT, starting shortly after the drug's approval to treat menopausal symptoms in 1942. Epidemiological studies, animal studies and studies of surrogate biomarkers of CHD, as well as clinical studies such as angiography and bone mineral density studies, all pointed in the direction that HT was beneficial for the prevention of CHD and osteoporosis. Some of the larger, and more influential, observational HT studies, such as the Million Women Study (MWS) and Nurses' Health Study (NHS), are listed and described in Table 46.1 (Banks *et al.*, 2004; Beral, 2003; Beral, Bull and Reeves, 2005; Grodstein, Manson and Stampfer, 2001). In general, these observational studies, as well as several clinical trials, showed the efficacy of oestrogen, and later a combination of oestrogen and progestin, for treating menopausal symptoms (NIH, 2005; Rothenberg, 2005). Most observational studies also indicated that HT conferred a protective effect on CHD and was associated with a decreased risk of fractures, higher bone mineral density (BMD) and a lower colorectal cancer risk than women of the same age and menopausal status who were not receiving therapy (Banks *et al.*, 2004; Beral, 2003; Grodstein *et al.*, 1999; Komulainen *et al.*, 1999; Lufkin *et al.*, 1992; Speroff *et al.*, 1996).

In addition to demonstrating benefits of HT, early studies demonstrated several risks. The main risk was an increased risk of venous thromboembolic events (VTEs), or blood clots, in women on HT, a finding that has been borne out over time (BCDSP, 1974; Grady *et al.*, 2000; Hulley, 2002; Nachtingall *et al.*,

1979; PEPI, 1995; Petitti *et al.*, 1979; WHI, 2002, 2004). Results of observational research studies were less conclusive about HT's risks or benefits related to CHD, breast cancer and uterine cancer, though the results trended towards showing a benefit of HT on CHD risk and an increased risk of breast and uterine cancer (Beral, 2003; Grodstein, Manson and Stampfer, 2001; Lerner, 1986; Speroff *et al.*, 1996; Wilson *et al.*, 1985). The addition of progestins to the HT formulations in the mid-1980s was thought to be protective of the uterus, and some studies, though not all, demonstrated a decrease in the risk of uterine cancer in those women with a uterus who were taking combination oestrogen progestin therapy (Beral, Bull and Reeves, 2005) (Figure 46.1)

Though these observational studies were helpful for evaluating some of the risks and benefits of HT, they had known biases that could impact the observed benefits and risks of HT (Grodstein, Clarkson and Manson, 2003). In general, women who are prescribed oestrogen are leaner, less likely to smoke, less likely to eat a high fat or high salt diet, more physically active, more highly educated, and more likely to visit physicians regularly and take part in recommended screenings than women who are not prescribed hormones (WHI, 1998). These factors in and of themselves tend to decrease the risk of both CHD and some cancers. Also, though not well documented, women taking HT and the physicians who prescribe it may be less likely to attribute ischaemic symptoms to CHD if they believe *a priori* that HT reduces CHD risk (Col and Pauker, 2003). This makes it difficult to draw conclusions about the effects of HT separate from the effects of these socio-behavioural factors.

In addition to the previously mentioned biases that make interpreting the results of observational trials of hormone replacement difficult, additional interpretability issues arise due to major differences between the studies. The age ranges of individuals in the various observational studies mentioned previously and their racial and socioeconomic makeup differed greatly from study to study. Major differences in these factors make comparing results (both within and across different observational studies) difficult, especially since these factors have been shown to be related to CHD development. In addition to these population differences, observational studies of HT differed in how they defined CHD and other

Table 46.1. Major HT study description and results

Study	Treatment(s)	Study type/follow-up	Study Population Characteristics	Primary Results
Coronary Drug Project	E, placebo	Randomized controlled trial. Stopped after 2.5 years	Men with previous heart attacks	Slightly higher risk of death from all causes (19.9 in E group, 18.8 in placebo); equivalent risk of heart attack; and increased risk of VTE (1.5% in men taking E vs. 0.8% in men taking placebo)
Framingham Heart Study	E, none	Prospective cohort study. 8 years of follow up at time of first HT results	1234 postmenopausal women over age 50 from Framingham, MA who were free of CHD at baseline	Women who used E had increased risk of cardiovascular morbidity (adjusted RR = 1.76) and cerebrovascular events (adjusted RR = 2.27); no major benefits noted. Risk of CHD was shown to be higher in E users who smoked than in non-smoking E users
Nurses' Health Study (NHS)	E, E + P	Prospective cohort study with 20 years of follow up	70,533 postmenopausal nurses on HT followed by periodic surveys. Substudy of 2489 women with previous MI	Current users of HT (E alone or E + P) were found to be at increased risk of breast cancer and decreased risk of CHD compared to those not taking HT. Women with previous MI who took HT for a long duration had lower rates of recurrent CHD events than women who never used HT (RR = 0.65). In this subset, CHD events increased slightly with short-term use of HT
Uppsala Sweden study	Medium potency or low-potency/short acting E with or without P	Prospective cohort study (survey + registry) started in 1987. 8 years follow-up	9236 women in Uppsala Sweden with a mean age of 61 who had received at least 1 prescription for HT between 1977–80	Decreased MI (RR = 0.75) and hip fracture risk (RR = 0.65) with medium-potency E or E + P compared to low potency E
Million Women Study	E, E + P in various formulations	Prospective cohort study	320,953 postmenopausal women (age 50–64) in the UK without history of hysterectomy or cancer	Risk of endometrial cancer varied by HT formulation. Compared to those who never used HT, users of continuous combined

(continued)

Table 46.1. *Continued.*

Study	Treatment(s)	Study type/follow-up	Study Population Characteristics	Primary Results
Postmenopausal Oestrogen/ Progestin Interventions Trial (PEPI).	CEE, CEE + MPA, CEE + MP, or placebo over various spans of a 28-day cycle	Randomized, controlled trial. 3-year follow-up	Recruited 1996–2001, mean follow-up 3.4 years 875 postmenopausal women age 45–64, 596 with and 279 without a uterus. Eligibility criteria included cessation of menses for 1–10 years, FSH level of > 40 IU/L, normal or atrophic endometrial biopsy results at baseline, and no history of breast or endometrial cancer or of other cancer within 5 years	E & P had a RR of 0.71; e alone RR of 1.45; and users of cyclic combined had a RR of 1.05. Users of any HT formulation had reduced risk of fracture and increased risk of breast cancer Those on E alone were more likely to have endometrial hyperplasia compared to E+P and placebo groups. In women taking E alone, simple endometrial hyperplasia was noted in 27.7%, complex in 22.7%, and atypical in 11.8% compared to 0.8%, 0.8%, and 0% in placebo, respectively. All HT groups had lowered LDL and Lp (a) and increased triglyceride levels compared to placebo (PEPI, 1995, 1996)
Heart and oestrogen/progestin replacement study (HERS).	E, E + P, placebo	Randomized, controlled trial. Mean follow-up 4.1 years	2763 postmenopausal women age < 80 years with a history of CAD	No significant differences between treated and placebo groups on death, MI, or secondary cardiovascular outcomes (RR = 0.99). VTE (RR = 2.89) and gall bladder disease (RR = 1.38) were increased in the HT groups
Heart and oestrogen/progestin replacement study II (HERS II). Women's Health Initiative (WHI)	E, E + P, placebo	Open-label follow-on study to HERS	2321 postmenopausal women with history of CAD who participated in HERS	No cardiovascular benefit of HT observed after following the HERS I cohort for additional time
		Randomized Controlled Trial	For the E + P component, the population is 16,608 postmenopausal US women aged 50–79 with an intact uterus at baseline. For the E alone, it is 10,739 postmenopausal US women, age 50–79 with prior hysterectomy.	Neither E alone nor E + P reduced CHD risk (RR for E and E & P vs. placebo = 0.91 and 1.29 respectively). Risks of E + P (including breast cancer, VTE and stroke) shown to outweigh benefits

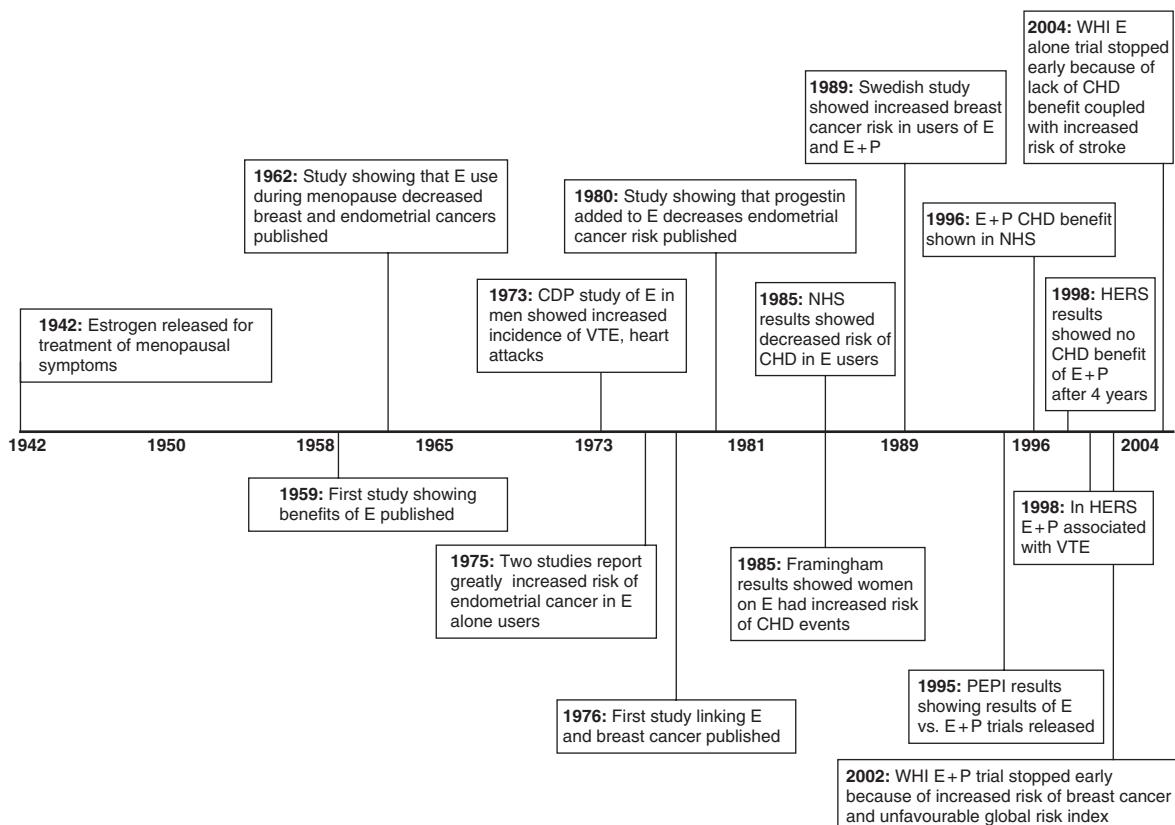


Figure 46.1. Hormone therapy timeline of major events: 1942–present.

endpoints. For example, some studies, such as the Framingham Heart Health Study, that examined the relationship between HT and CHD included angina as part of the constellation of conditions that comprise CHD while others, such as the Nurses Health Study, did not. This makes comparison of the results of these studies difficult at best.

In part because of these difficulties in interpreting data from observational studies (given the potential biases mentioned previously), a number of randomized controlled clinical trials (RCTs) of HT were initiated in an attempt to definitively answer questions about the risks and benefits of HT (Therapeutic Letter, 1999). These studies were conducted first in highly selected populations with trials such as the Coronary Drug Project (CDP) and the Heart and Estrogen/Progestin Replacement Study (HERS), and then in the more general population, with studies such as the Postmenopausal Estrogen/Progestin

Interventions (PEPI) and the much larger, and more comprehensive, Women's Health Initiative (WHI). The first RCT relating to this question – the HERS trial – was published in 1998 (Hulley *et al.*, 1998; Petitti, 1998). Several additional small, short-term RCTs were also conducted. One of these trials, The Coronary Drug Project, was actually conducted in men (The Coronary Drug Project Research Group, 1973), though the others were conducted in women (Hall *et al.*, 1998; Komulainen *et al.*, 1999; Lufkin *et al.*, 1992; Speroff *et al.*, 1996). These trials sought more conclusive evidence of the relationship between HT and CHD, uterine cancer, or other endpoints and all seem to corroborate evidence from the earliest published RCTs on HT. Table 46.1 summarizes the study populations and results from some of these randomized clinical trials as well as several of the larger, more influential observational studies.

It was clear from the findings from these small, short-term trials that a larger, longer-term randomized clinical trial with a greater diversity of post-menopausal women and 'hard' disease endpoints needed to be undertaken to definitively answer these questions. And so, the timing was right for the Women's Health Initiative, which was made possible because of the efforts of the NIH's first female director, cardiologist Bernadine Healy, the Women's Health Caucus, and other groups who successfully lobbied for a line item in congress' budget to try to erase a 25-year gender gap in our knowledge of diseases which affect women in their later years. In addition, the FDA would not approve a statement in the HT label claiming a benefit for heart disease until a definitive clinical trial was conducted. This was the state of the field when the WHI was first proposed.

Flash ahead to 2002, when the WHI oestrogen plus progestin trial was stopped early because of an increased risk of breast cancer ($HR = 1.26$; $CI = 1.00\text{--}1.59$), CHD ($HR = 1.29$; $CI = 1.02\text{--}1.63$), Stroke ($HR = 1.41$; $CI = 1.07\text{--}1.85$), and PE ($HR = 2.13$; $CI = 1.39\text{--}3.25$) (WHI Writing Group, 2002). Immediately following the publication of these trial results in July of that year, oral HT prescriptions began a steady decline, while a slight increase was seen in the use of vaginal formulations. In 2003, the FDA, in conjunction with some members of Congress, launched a national campaign to provide information and increase awareness about the recent findings on menopausal use of HT (FDA, 2003). In April 2004, the results of the WHI oestrogen-alone trial were published (WHI Writing Group, 2004). The investigators noted an increased risk of fatal and non-fatal strokes ($HR = 1.39$; $CI = 1.10\text{--}1.77$) and venous thrombosis ($HR = 1.47$; $CI = 1.04\text{--}2.08$); no significant difference in risk of CHD ($HR = 0.91$; $CI = 0.75\text{--}1.12$), colorectal cancer ($HR = 1.08$; $CI = 0.75\text{--}1.55$), total cancer ($RR = 0.93$; $CI = 0.81\text{--}1.07$), or all cause ($HRR = 1.04$; $CI = 0.91\text{--}1.12$).

The effect on breast cancer was uncertain ($HR = 0.77$; $CI = 0.59\text{--}1.01$) and there was an increased benefit on bone fractures ($HR = 0.70$; $CI = 0.63\text{--}0.79$).

In March of 2005, an NIH State-of-the-Science Conference on the Management of Menopause-

Related Symptoms took place to discuss and form consensus on menopause-related symptoms and preventive and treatment modalities. The report discusses HT as 'menopause hormonal therapy', reflecting the belief that menopause is a natural state of being for women of a certain age and not a disease state (NIH, 2005). After the release of results from the WHI, a black box statement pertaining to cardiovascular risks was added to the label for oestrogen. This statement read 'The Women's Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.' The warning goes on to state that the FDA assumes these findings will hold for all HT formulations containing oestrogen and suggests that HT drugs should be used in the lowest doses necessary for the shortest duration possible (FDA, 2003).

CONTROVERSY OVER WHI RESULTS

There is some controversy in the medical community about whether or not the results of the WHI were 'valid' or 'relevant', particularly in the context of divergent findings from earlier observational work and smaller clinical trials. Like most trials, the WHI may have had some minor limitations, which have been examined in an attempt to ascertain whether such problems might have biased the results sufficiently to change the direction of the effect of HT on CHD and on the global risk/benefit assessment. One of these limitations was the relatively high dropout and crossover rates that the study had. If dropouts and cross-over are differential, they would have had potential to bias the results of the study, particularly if dropouts or crossover occurred differentially based on women's health status, which is plausible. However, these issues should not have biased the 'intention-to-treat' analyses.

Another concern voiced in the literature was the age of the WHI participants in the hormone trials compared with the average age of menopause. In most observational studies, HT is started at, or close to, the time of menopause. In WHI, as in most other

clinical trials, the therapy was often initiated more than a decade, on average, after menopause, with an average age of women in the E & P trial of 63.2 years and of 63.6 years in the E-alone trial (WHI, 1998, 2002, 2004). If the effects, both positive and negative, of HT vary depending on the age of the women (or the duration of time since menopause), as has been suggested, conducting the study in older women may have biased it away from seeing favourable effects and towards seeing increased risks associated with HT in high-risk women. Also, baseline absolute rates of disease are much lower in recently menopausal women than in older women, so the absolute number of excess events will also differ by age.

One issue that spurred much debate was the use of what the WHI investigators termed a 'global index' – a composite measure consisting of the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture and death due to other causes – which was used to quantify the overall risk associated with the drug (WHI Writing Group, 2002). Issues raised regarding the global index include the criticism that it was not validated (Goldman, 2004); the selection of events to be included in the global index; and the index's apparent lack of weighting of treatment types (despite very different health, quality of life, and economic impacts of each type of event).

Whatever the concerns, however, the findings (which seemed to contradict long-standing dogma), caused the medical and lay communities to express dismay and disbelief. As Elias Zerhouni, director of NIH, said about the HT controversy when WHI results were first published in 2002 – 'Often in science the reaction to a new finding is directly proportional to the strength of the dogma it overturns. People are still in denial of the theory of relativity, too' (Rothenberg, 2005; Spake, 2002). The way in which some of the WHI data was presented in the media may also have increased the concern expressed by some. There was an emphasis on Relative Risk (RR) versus rate difference (RD), which may have served to magnify the risks observed and led to misinterpretations of the results. For example, while the relative hazard of CHD was elevated by 29% for women taking E & P, in absolute terms this equates on only an additional 7 cases of CHD per 10 000 women per year (WHI, 2002). Regardless of these concerns, however, the

fact remains that WHI is still the largest randomized clinical trial of HT to date, with the best ascertainment of outcomes. As such, the results of this landmark study should not be dismissed. As noted by the European Menopause and Andropause Society (EMAS) and by S. Barton, 'it is not an easy task to opt between results of observational and clinical trials. High-quality observational studies may extend evidence over a wider population and are likely to be dominant in the identification of harms', but the 'best RCT still trumps the best observational study' (Barton, 2000; Neves-e-Castro *et al.*, 2002).

DISCUSSION

The evolving attitude towards HT, from a treatment many believed unethical *not* to prescribe to post-menopausal women to one associated with negligible benefit and moderate risk, is a good example of how scientific thinking about a drug may change over time. The HT debate illustrates the various scientific methods used to understand drug safety and how each can either increase understanding or produce confusion. While it is difficult to make decisions on HT use now because of uncertainty, the evolution of knowledge about HT provides a good example of current thinking about the tradeoffs of using data from observational studies or clinical trials to understand the population impact of drug treatment. Some of these principles are discussed below using examples from the study of HT.

STRENGTHS OF CLINICAL TRIALS COMPARED TO OBSERVATIONAL EPIDEMIOLOGY STUDIES

Despite their strengths, which make them valuable tools in attempting to determine relationships between drugs and outcomes, observational epidemiologic studies have a number of limitations. These limitations are a large part of the reason that clinical trials remain the gold standard for evaluating drug-outcome relationships.

A major concern with observational studies is that they are not randomized and treatment may well vary according to characteristics linked to the disease process. This could occur through selective

prescribing or through issues related to medical care access. Confounding by demographics, socio-economic status, and variables related to health, as described previously, can be a substantial problem in observational studies.

A second problem with observational epidemiology studies, especially the larger ones, is that they tend to have less robust ways of evaluating endpoints than clinical trials, relying on self-report or simple clinical reports, rather than a methodical AE reporting system. Short-term effects of treatment may be particularly difficult to 'capture' in observational settings. There may also be inconsistent endpoint definitions between studies, making comparability difficult. This problem may have contributed to the divergent estimates of CHD in women taking HT in the NHS and Framingham studies, which defined CHD differently.

In addition to problems ascertaining outcomes, observational studies also frequently have poor or limited characterization of health status or lifestyle factors, particularly those that change over time. For example, over-the-counter medications that can affect outcomes are not always ascertained and variables such as physical activity levels and diet are often not measured as often or with as much precision as would be desirable. Because of potential differences in these factors between those prescribed and those not prescribed drugs, residual confounding is likely to be present in observational studies. If some of the relevant confounding variables are measured at baseline (and, if possible, throughout the study), adjustment for some confounding is certainly possible, but residual confounding remains likely.

Another potential limitation of observational studies is assessment of drug exposure, in terms of both dose and duration. The duration of use of a drug is sometimes poorly defined in observational studies. Often treatment use is measured at the beginning of the study or only at irregular periods throughout the study, and constant use is assumed, whether this is valid or not. Observational studies often have poor information on the dose or particular formulation of a drug that is being used. Strategies, including having patients bring all of their medicines with them to intake visits, have been developed to help with this problem, but many studies, particularly those that are survey-based, have limitations related to exposure assessment. Clinical trials, on the other hand, frequently employ systems

such as pill counts or blood level monitoring that allow researchers to monitor actual dose received on an ongoing basis.

Finally, in observational studies, particularly cross-sectional, case-control and prevalence studies, it is often not possible to establish a temporal relationship between drug and disease, which is crucial to establishing cause-and-effect relationships, rather than simple associations. This limitation can impede interpretation, such as when a drug improves survival with a condition or increases its latency period, both benefits, rather than causing the condition itself.

STRENGTHS OF OBSERVATIONAL EPIDEMIOLOGY STUDIES COMPARED TO CLINICAL TRIALS

As shown by some of the analyses from the WHI, confounding can be a problem even in clinical trials, especially when the blind is imperfect. This can lead to some problems of differential follow-up and ascertainment, but these are usually less prominent than those seen in observational epidemiologic studies. Critics cite this as a potential flaw of the WHI that may, in addition to other factors (such as the age structure of the population the trial was conducted in), have biased the results.

Though the WHI looked at hard outcomes, many clinical trials use surrogates as their primary outcomes of interest. This can cast doubt about whether the results of such trials are clinically meaningful. By contrast, observational epidemiologic studies can, and usually do, look at 'real' events (such as MI) rather than their surrogates (e.g., cholesterol). This is due in part to the fact that, unlike clinical trials, they can be retrospective (mitigating the need for costly follow-up) or long-term prospective follow-up of a large-scale cohort may be feasible.

The WHI, which looked at actual events in a large population of women over a long time period, had many of the advantages of a large-scale prospective follow-up usually associated with observational studies rather than with clinical trials, but duration of follow-up tended to be shorter than in many observational studies. However, some of the earlier, smaller clinical trials that form an important part of the evidence base about the risks and benefits of HT used surrogate endpoints and were limited to very

short-term follow-up. Thus, the duration of observational studies is frequently longer than is feasible for clinical trials, which allows evaluation of 'hard' outcomes instead of surrogates and of rare or time-delayed effects. Part of the controversy following the results of the early, short-term randomized controlled trials of HT stemmed from their short duration (especially compared to some of the observational studies) and, in some trials, use of surrogate markers rather than clinical disease states for some outcomes.

Another strength is that observational studies occur in 'real life', using drugs in the particular dose and schedule used by patients in the field. This may more appropriately represent usage patterns than more controlled studies. One criticism of the WHI is that only one combination of oestrogen and progestin was evaluated, though other doses and formulations exist. Arguably, the effects of a drug, in terms of both risks and benefits, may vary by the dose, duration of exposure and route of administration, as well as the demographics and health status of those treated. Thus, an observational study may be better equipped to evaluate several factors that are relevant to usage of the drug in 'real life'.

Finally, because of their decreased demands in terms of cost, observational studies, particularly large simple studies, often allow for larger sample sizes and longer duration of follow-up than clinical trials. Although some consider observational studies more 'cost-effective', tradeoffs related to confounding and selection biases must be given careful consideration, as discussed above.

THE FUTURE

There is no doubt that future drugs being developed for postmenopausal prevention and treatment of disease will be undergoing intense scrutiny by the FDA, the medical community and consumers. Each of these groups is better informed now than in the mid-1990s, and as new replacements for oestrogen therapy (such as new oestrogen receptor modulators or SERMS) are explored, the lessons of HT will remain in the forefront, influencing the way future drugs are developed, approved, marketed and prescribed.

Several professional societies have weighed in on these issues (and continue to do so). The American

College of Obstetricians and Gynecologists (ACOG), for example, formed a task force to examine the evidence from WHI and other studies and in 2004 issued the following statement: 'The risks of HT exceed the benefits for the prevention of chronic diseases in postmenopausal women. Hormone therapy remains an effective therapy for treating women with vasomotor symptoms and vaginal atrophy.' The ACOG task force went on to state that

The use of HT for specific indications, for example, treatment of menopausal symptoms or treatment of osteoporosis, will require balancing the known benefits of HT in treating these conditions with the known or potential risks of HT, as well as balancing the benefits and risks of alternatives to HT. Clearly, healthy symptomatic women who choose to use the most effective treatment for menopausal symptoms, that is, HT, should not be denied this option based on available data regarding health risks (ACOG, 2004).

The EMAS has also carefully weighed the risk/benefit ratio of HT and has revised their earlier recommendation statements for clinical practitioners regarding peri- and postmenopausal HT to reflect the changing state of research following WHI (EMAS 2005; Neves-e-Castro *et al.*, 2002).

As noted by the ACOG HT Task Force (2004) and by others, 'Virtually all medications carry risks as well as benefits, and as detailed in the preceding chapters, HT is no exception. Balancing these beneficial and harmful effects is a challenging but important task for making informed decisions about the prescribing and use of HT.' Despite the many questions answered by WHI and the even more questions raised by this study, it is clear that professional societies in both Europe and the US feel that there is no one solution for all postmenopausal women. It is also true that one piece of clarity in all of this controversy is that the WHI has paved the way for more open communication between the postmenopausal women and her health care provider. *That* is most certainly a good thing.

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NSAIDs – COX-2 Inhibitors – Risks and Benefits

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INTRODUCTION

The worldwide market withdrawal of rofecoxib in September 2004 was a major lesson in pharmacovigilance (Edwards, 2005). Sales of rofecoxib in US increased substantially after licensure in 1999 and, due to its extensive use, even a moderate increase in the risk of serious adverse reactions among rofecoxib users would have major public health implications. This chapter is a review of the cardiovascular safety signal detection and safety assessment process for the cyclo-oxygenase-2 (COX-2) inhibitors in chronological order after their market approval. As safety assessment of any drug should not be isolated from potential benefits of the drug, we conclude the chapter with a succinct risk–benefit assessment for non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors.

* The points of view expressed in this chapter are solely those of the authors and do not reflect the official opinions of their respective employers.

Several non-scientific events after the market withdrawal of rofecoxib were widely reported in the press and generated much public attention and debate. They include financial impact on pharmaceutical companies, congressional hearings in the US, product liability litigations, the role of direct-to-consumer advertisement, promotional activities of pharmaceutical companies, and calls for overhaul of post-approval drug safety review system in the US (Ray and Stein, 2006; Strom, 2006). These are important questions for the society in general but are beyond the scope of this chapter and are not covered.

NSAIDs for symptomatic relief of pain and inflammation comprise one of the most widely used group of drugs in the industrialized world. Gastrointestinal toxicity of NSAIDs is associated with substantial morbidity and mortality (Wolfe, Lichtenstein and Singh, 1999). Advances in pharmacologic knowledge about prostaglandins that mediate inflammatory reactions and the discovery of two isoforms of cyclooxygenase (COX-1 and COX-2) have led to development of promising new drugs. Traditional

NSAIDs are non-selective with regards to inhibition of COX-1 and COX-2 and are now referred to as non-selective NSAIDs. While inhibition of the inducible COX-2 results in anti-inflammatory effects, inhibition of the constitutive COX-1 increases the risk of gastrointestinal toxicity (Warner *et al.*, 1999). Drugs that selectively inhibit COX-2 but have minimal effect on COX-1 would theoretically result in targeted anti-inflammatory actions and reduced gastrointestinal toxicity. The COX-2 inhibitors, as a subclass of NSAIDs, were developed to achieve this favorable risk–benefit profile (FitzGerald, 2003). In the US, the first COX-2 inhibitor, celecoxib, was approved at the end of 1998 and the second, rofecoxib, was approved in May 1999.

POST-MARKETING CARDIOVASCULAR SAFETY SIGNAL

LARGE-SCALE CLINICAL TRIALS

At the time of market approval of celecoxib and rofecoxib, upper gastrointestinal safety information of these two drugs was based on endoscopy studies. As the reduced frequency of mucosal injury in the upper gastrointestinal tract may not correlate well with incidence of serious gastrointestinal events that include ulcer, perforation, obstruction, or bleeding, manufacturers of celecoxib and rofecoxib sponsored large-scale clinical trials that were powered to provide definitive evidence on upper gastrointestinal safety for these drugs.

The Celecoxib Arthritis Safety Study (CLASS) was the first large-scale randomized trial of a COX-2 inhibitor (Silverstein *et al.*, 2000). Patients with osteoarthritis or rheumatoid arthritis were randomly assigned to receive celecoxib, ibuprofen, or diclofenac for more than six months (Table 47.1). Approximately 20% of the study subjects took low dose aspirin (325 mg a day or less) for cardiovascular disease prevention during the study. There was no significant reduction of risk of upper gastrointestinal ulcer complications within the first 12 months of therapy (Hrachovec and Mora, 2001). Among patients who did not use aspirin, risk of upper gastrointestinal ulcer complication was reduced by approximately 50%. In the first published report of CLASS results, incidence

of stroke, myocardial infarction, and angina was virtually the same in the celecoxib group and in the ibuprofen/diclofenac group during the first six months of therapy. No cardiovascular safety signal was observed in this study.

The first cardiovascular safety signal of a COX-2 inhibitor came from the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) (Bombardier *et al.*, 2000), which was another large trial that evaluated the risk of adverse upper gastrointestinal outcomes among patients on COX-2 inhibitor or non-selective NSAID. Patients with rheumatoid arthritis were randomly assigned to receive rofecoxib 50 mg once per day or naproxen 500 mg twice per day, 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, reported incidence of myocardial infarction was higher among the rofecoxib group (relative risk, 5.0; 95% confidence interval [95% CI], 1.68–20.13) (Curfman, Morrissey and Drazen, 2005). The VIGOR investigators hypothesized that the increased relative risk among the rofecoxib users could be a result of inherent cardiovascular risk of rofecoxib, cardio-protective effect of naproxen, or both.

SPONTANEOUS REPORTS

The spontaneous adverse drug reaction reporting system is usually the first line of defense in the detection of adverse drug effects that may not be apparent during pre-marketing studies, but the cardiovascular safety signal for rofecoxib was not detected by the Adverse Event Reporting System in the US. After the VIGOR results were reported in professional 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 US.

In the US, Mukherjee and colleagues conducted a search for thrombotic or embolic events associated with celecoxib and rofecoxib in the US Adverse Event Reporting System in October 2000 (Mukherjee, 2001).

Table 47.1. Large-scale clinical trials of selective cyclooxygenase-2 inhibitors that reported cardiovascular outcomes in chronological order of publication.

Acronym (Reference)	Study population/ Disease	Drug regimens	Duration of treatment	Primary end point	Findings for CV outcomes
CLASS (Silverstein <i>et al.</i> , 2000; White <i>et al.</i> , 2003)	Rheumatoid arthritis and osteoarthritis	Celecoxib 400 mg twice a day, ibuprofen 800 mg three times a day, or diclofenac 75 mg twice a day; 22% used low dose aspirin	Six months in the first report, data for more than one year available afterwards	Upper gastrointestinal ulcer and complications	Relative risk (celecoxib versus ibuprofen/ diclofenac combined) of serious CV events was 1.1 (95%, 0.7–1.6)
VIGOR (Bombardier <i>et al.</i> , 2000; Curfman Morrissey and Drazen, 2005)	Rheumatoid arthritis	Rofecoxib 50 mg once a day or naproxen 500 mg twice a day; no aspirin allowed	Median of 9 months, longest was 13 months	Upper gastrointestinal ulcer and complications	Relative risk (rofecoxib versus naproxen) of 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 per day, naproxen 500 mg twice a day, or ibuprofen 800 mg three times a day; 24% used low dose aspirin	One 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)	Patients with history of colorectal adenoma removal	Rofecoxib 25 mg per day or placebo; 17% among the rofecoxib group and 16% among the placebo group used low dose aspirin	Average of 2.4 years (rofecoxib) and 2.6 years (placebo)	Recurrence of colorectal adenoma	Relative risk of thrombotic CV events for rofecoxib versus placebo was 1.92 (95% CI, 1.19–3.11)

(continued)

Table 47.1. *Continued.*

Acronym (Reference)	Study population/ Disease	Drug regimens	Duration of treatment	Primary end point	Findings for CV outcomes
APC (Solomon <i>et al.</i> , 2005; Bertagnolli <i>et al.</i> , 2006)	Patients with history of colorectal adenoma removal	Celecoxib 400 mg twice a day, celecoxib 200 mg twice a day, or placebo; 30% of patients used low dose aspirin	3 years	Recurrence of colorectal adenoma	Based on an adjudicated composite CV end point and comparing with placebo, relative risk was 3.4 (95% CI, 1.5–7.9) for celecoxib 400 mg twice a day and 2.6 (95% CI, 1.1–6.1) for celecoxib 200 mg twice a day
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	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 to 3.2) for the two COX-2 inhibitors arms combined versus placebo
PreSAP (Arber <i>et al.</i> , 2006)	Patients with history of colorectal adenoma removal	Celecoxib 400 mg per day or placebo; 17% used low dose aspirin	3 years	Recurrence of colorectal adenoma	For the same CV end point as the APC study, relative risk was 1.3 (95% CI, 0.65–2.62) for celecoxib when compared with placebo

The number of cases that could possibly be associated with celecoxib and rofecoxib were 99 and 102 respectively. Of the 99 patients who used rofecoxib, there were 26 cases of myocardial infarction, 43 cases of stroke, 19 cases of pulmonary embolism or venous thrombosis, and 14 cases of miscellaneous thrombotic

events. Given the millions of doses of rofecoxib and celecoxib that had been dispensed in the US by then, the small number of reported adverse cardiovascular events did not represent a strong numeric signal.

Aside from the spontaneous reporting system, there was no case report in clinical journals on a suspected

association between rofecoxib and myocardial infarction. A simple PUBMED search by one of the authors (KAC) in December 2005 using the search term ‘rofecoxib case reports’ identified 119 publications, which included case reports of hepatitis, interstitial nephritis, colitis, angioedema, anaphylactic shock, gynecomastia, acute renal failure, delirium, Stevens–Johnson syndrome, congestive heart failure, and transient visual impairment and potential drug–drug interactions in MEDLINE-indexed journals. Not a single case of myocardial infarction was reported in these peer-reviewed journals.

CARDIOVASCULAR SAFETY SIGNAL EVALUATION

As results from VIGOR indicated that rofecoxib was associated with increased risk of myocardial infarction, a Food and Drug Administration (FDA) advisory committee meeting was convened in February 2001 to review gastrointestinal and cardiovascular safety data of rofecoxib and celecoxib. These data are available from the FDA website (FDA, 2001) and some were subsequently published in peer-reviewed journals. In the US, revised package insert of rofecoxib with updated safety information was released in April 2002 (Kweder, 2004).

BIOLOGICAL MECHANISM

As the COX-2 inhibitors have minimal effects on COX-1 in gastric epithelium, they have more favorable gastrointestinal safety profile than the non-selective NSAIDs. However, at the time of approval of celecoxib and rofecoxib, pharmacologic studies indicated that selective inhibition of COX-2 may contribute to imbalance in the prostacyclin (prostaglandin I₂) to thromboxane ratio and result in 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. On the other hand, the COX-1 in platelets, which is not affected by the COX-2 inhibitors, is responsible for thromboxane A₂ synthesis, and thromboxane A₂ 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 (FitzGerald, 2003).

The VIGOR investigators cited a study in healthy volunteers that showed different effects on thromboxane A₂ production and platelet aggregation associated with different non-selective NSAIDs (Van Hecken *et al.*, 2000). Ibuprofen 800 mg three times a day and sodium naproxen 550 mg twice a day in healthy volunteers showed substantial inhibition effects on thromboxane A₂ production and platelet aggregation, but how these pharmacologic findings translate to prevention of myocardial infarction by naproxen needed to be verified in clinical studies. The cardio-protective effects of naproxen would have to be very powerful in order to result in the VIGOR findings and support the hypothesis that rofecoxib 50 mg per day was not associated with increased risk of myocardial infarction.

CLINICAL TRIALS OF CELECOXIB AND ROFECOXIB

After the results of clinical trials discussed during the February 2001 FDA advisory committee meeting were made public, a group of independent investigators reviewed cardiovascular events observed in CLASS, VIGOR, and two unpublished clinical trials of rofecoxib (Mukherjee, Nissen and Topol, 2001). The review covered more cardiovascular data than that was published in the original CLASS and VIGOR reports in 2000 as patients contributed more follow-up time and cardiovascular events were independently adjudicated. Reviews of cardiovascular safety data in the clinical development programs of celecoxib and rofecoxib were also published by manufacturers of the drugs from 2001 through 2003.

Celecoxib

No increased risk of myocardial infarction, stroke, or death was found in the celecoxib group in CLASS. The same finding was observed in patients who received aspirin and those who did not receive aspirin during the trial (Mukherjee, Nissen and Topol, 2001).

The CLASS investigators carried out a safety analysis and evaluated the risk of cardiovascular outcomes, cerebrovascular outcomes, and peripheral vascular outcomes (White *et al.*, 2002). No increased risk of thromboembolic events was found among the celecoxib group (Table 47.1). White and colleagues combined data from 15 trials of celecoxib and used the Anti-Platelet Trialists' Collaboration (APTC) definition of adverse cardiovascular outcomes (Antiplatelet Trialists' Collaboration, 1994), including cardiovascular, hemorrhagic and unknown death, myocardial infarction, and cerebrovascular accident, as the end point of interest (White *et al.*, 2003). A relative risk of 1.06 (95% CI, 0.70–1.61) was found for the celecoxib (all doses) versus non-selective NSAID comparison.

Rofecoxib

Two unpublished studies, 085-2001 and 090-2001, of rofecoxib reported by Mukherjee and colleagues in 2001 were three-arm trials of rofecoxib 12.5 mg per day, nabumetone 1000 mg per day, and placebo for six weeks among patients with osteoarthritis. Using low dose aspirin was not an exclusion criterion in both trials. No difference in cardiovascular events was found between the rofecoxib- and nabumetone-treated groups in 085-2001 and there was a non-significant increase in the incidence of cardiovascular events in the rofecoxib versus nabumetone comparison (1.5% versus, 0.5%) in 090-2001.

For VIGOR, Mukherjee and colleagues reported incidence of serious thrombotic cardiovascular events, including myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attacks in the treatment groups (Mukherjee, Nissen and Topol, 2001). In addition, more adjudicated cases of serious cardiovascular events were reported at the February 2001 FDA advisory committee, which did not appear in the original VIGOR publication (Curfman, Morrissey and Drazen, 2005). The VIGOR study protocol stated that history of cerebrovascular events in the two years before the study, history of myocardial infarction or coronary bypass in the year before the study, and requirement for or ongoing treatment with aspirin, ticlopidine, or anticoagulants were exclusion criteria. However, 'requirement

for aspirin treatment' was not objectively defined and was subjectively assessed by the physicians who enrolled the patients. Mukherjee and colleagues reported a post-hoc stratification of study subjects according to cardiovascular indication for aspirin use, which was operationally defined as prior history of stroke, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions. Only 321 (4%) of the 8076 enrolled subjects were aspirin-indicated and no myocardial infarction occurred among aspirin indicated patients. Relative risk of serious cardiovascular events was 4.89 (95% CI, 1.41–16.88) among the rofecoxib (50 mg per day) group in the full cohorts and for the non-aspirin indicated subjects, the relative risk was 1.89 (95% CI, 1.03–3.45).

Scientists from the manufacturer of rofecoxib and academic investigators analyzed the safety database of clinical trials of rofecoxib and published three safety reports after VIGOR. In the first report, Konstam and colleagues reviewed combined data of more than 28 000 patients from 23 trials and used the APTC definition for cardiovascular end point (Konstam *et al.*, 2001). Rofecoxib was associated with increased risk of APTC events when compared with naproxen (relative risk, 1.69, 95% CI, 1.07–2.69) but there was no increased risk when rofecoxib was compared with placebo or non-naproxen NSAIDs. Stratifying the rofecoxib group by dose and compared with all NSAIDs, relative risk was 2.08 (95% CI, 0.57, 7.51) for rofecoxib 50 mg per day and was 1.16 (95% CI, 0.25, 7.18) for rofecoxib 25 mg per day. Reisin and colleagues reported results from pooled data from eight phase IIB or III trials of rofecoxib, ibuprofen, diclofenac, nabumetone, or placebo for osteoarthritis, with a total of 5435 patients (Reisin *et al.*, 2002). Using the APTC end point and any arterial or venous thrombotic cardiovascular adverse event as the outcome of interest, no significantly increased cardiovascular risk was observed in the rofecoxib–non-selective-NSAID and rofecoxib–placebo comparisons. However, statistical power was limited to detect a modest increase in cardiovascular risk among a dataset of this size and these trials were short-term studies with no information on potential effects among long-term use. In 2003, Weir and colleagues reported safety data from the rofecoxib development

program that included short-term trials, long-term studies like VIGOR, and placebo-controlled studies for the prevention of Alzheimer's disease (Weir *et al.*, 2003). The results confirmed the increased cardiovascular risk for the rofecoxib–naproxen comparison, with a relative risk of 1.61 (95% CI, 1.04–2.50) in pooled analysis for trials among patients with rheumatoid arthritis and/or osteoarthritis. No increased cardiovascular risk was found for the rofecoxib–non-naproxen-NSAID comparison or the rofecoxib–placebo comparison. These data pooling exercises were helpful in the safety assessment of drugs, but the heterogeneity of the study populations and treatment periods are major limitations. In the report by Weir and colleagues, there were no stratified results based on dose and duration of use for rofecoxib.

CARDIOPROTECTIVE EFFECTS OF NAPROXEN IN EPIDEMIOLOGY STUDIES

While there has been pharmacologic basis for cardioprotective effects of naproxen (Van Hecken *et al.*, 2000), there has been no reported clinical trial that specifically evaluated the risk of adverse cardiovascular outcomes in a naproxen versus placebo comparison before VIGOR or through 2005. The VIGOR results prompted more than 10 reports of observational studies that evaluated the association between naproxen use and myocardial infarction, all of them were included in a meta-analysis conducted by Jüni and colleagues (Jüni *et al.*, 2004). Reduced risk of myocardial infarction associated with naproxen was reported in three case-control studies; reduced but non-significant risk was reported in four studies; and small increased risk associated with naproxen was reported in three studies. All these data taken together suggested a small reduced risk, on the order of 15%, of myocardial infarction associated with naproxen use. However, these findings did not support the hypothesis that rofecoxib 50 mg per day did not increase risk of myocardial infarction, as the small reduction in risk associated with naproxen use could not adequately explain the more than fourfold increase in risk of myocardial infarction in the rofecoxib–naproxen comparison observed in VIGOR.

OBSERVATIONAL STUDIES OF CELECOXIB AND ROFECOXIB

After VIGOR, important information about population-based cardiovascular risk associated with rofecoxib and celecoxib came from large observational studies with sufficient numbers of COX-2 inhibitors users in a real life setting. Ray and colleagues reported that new users of high dose rofecoxib (more than 25 mg per day) had an almost twofold increase in the risk of hospital admission for acute myocardial infarction or death from coronary heart disease when compared with those who did not receive any non-selective NSAID or COX-2 inhibitor (Ray *et al.*, 2002; Table 47.2). No statistically significant increased risk was observed among new users of lower dose rofecoxib (25 mg or less per day), celecoxib, naproxen, or ibuprofen.

Three other observational studies, one each from Canada, the UK, and the US, were published before the market withdrawal of rofecoxib in September 2004 and are summarized in Table 47.2. Mamdani compared new users of COX-2 inhibitors or non-selective NSAIDs with subjects who did not use any COX-2 inhibitors or non-selective NSAID and reported no increased risk in acute myocardial infarction in new users of celecoxib or rofecoxib (Mamdani *et al.*, 2003).

The UK study was based on the Prescription-Event Monitoring system and was reported as two companion articles in the same journal in 2003 – one was a comparison between celecoxib and meloxicam (Layton *et al.*, 2003a) and the other was a comparison between rofecoxib and meloxicam (Layton *et al.*, 2003b). Outcomes of interest were cardiovascular, cerebrovascular, and peripheral venous thrombotic events. Comparing with meloxicam, a preferential but not selective COX-2 inhibitor, and only adjusted for age and sex, celecoxib and rofecoxib were both associated with increased risk of cerebrovascular events. Age-sex-adjusted relative risk for cardiovascular events suggested an increased risk for both drugs but the 95% confidence intervals for both relative risks included one.

The manufacturer of rofecoxib funded a case-control study among members of state-sponsored pharmacy benefit programs for residents aged 65 or older of New Jersey and Pennsylvania in the US (Solomon *et al.*, 2004). Comparing rofecoxib with no

Table 47.2. Observational studies of selective COX-2 inhibitors, non-selective NSAIDs, and adverse CV outcomes in chronological order of publication.

Reference	Data source	Study design and data collection	CV Outcomes of interest	Selected comparison groups from published reports	Adjusted relative risk (95% CI)
Ray <i>et al.</i> (2002)	Administrative data from Tennessee Medicaid in the United States and vital statistics	Retrospective cohort with new users design based on automated data	Hospital discharge diagnosis of myocardial infarction or death from coronary heart disease	Rofecoxib more than 25 mg per day versus no NSAID use Rofecoxib 25 mg or less per day versus no NSAID use Celecoxib versus no NSAID use	1.93 (1.09–3.43) 1.02 (0.76–1.37) 0.88 (0.67–1.16)
Mamdani <i>et al.</i> (2003)	Administrative data from Ontario, Canada	Retrospective cohort with new users design based on automated 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 United Kingdom	Cohort study based on mailed surveys to general practitioners	CV, cerebrovascular, and peripheral vascular events	Celecoxib versus meloxicam Cerebrovascular events CV events Rofecoxib versus meloxicam Cerebrovascular events CV events	1.66 (1.10–2.51) 1.72 (0.87–3.40) 1.68 (1.15–2.46) 1.38 (0.71–2.67)
Solomon <i>et al.</i> (2004)	Administrative data from Pennsylvania and New Jersey drug assistance program for the elderly in the United States	Nested case-control study based on automated data and review of medical records of selected subjects	Hospitalized cases of myocardial infarction	Rofecoxib versus no NSAID use Celecoxib versus no NSAID use Rofecoxib (all doses) versus celecoxib	1.14 (1.00–1.31) 0.93 (0.84–1.02) 1.24 (1.01–1.46)
30 September 2004	Worldwide market withdrawal of rofecoxib				
Shaya <i>et al.</i> (2005)	Administrative claims data from Maryland Medicaid program in the United States	Retrospective cohort study	Thrombotic events as defined by the Antiplatelet Trialists' Collaboration	Celecoxib versus non-naproxen NSAIDs Rofecoxib versus non-naproxen NSAIDs	0.99 (0.76–1.30) 1.19 (0.93–1.51)

Table 47.2. *Continued.*

Reference	Data source	Study design and data collection	CV Outcomes of interest	Selected comparison groups from published reports	Adjusted relative risk (95% CI)
Kimmel et al. (2005)	Patients admitted to 36 hospitals in five counties in the Philadelphia area in the United States	Case-control study with community-based controls, exposure history, and confounder information obtained through telephone interview	First non-fatal myocardial infarction	Celecoxib versus no NSAID use Rofecoxib versus no NSAID use	0.43 (0.23–0.79) 1.16 (0.70–1.93)
Graham et al. (2005)	Administrative data from Kaiser Permanente, California	Nested case-control study with automated data and telephone survey of a random sample of subjects	Coronary heart disease (myocardial infarction or sudden death)	Celecoxib versus no NSAID use during previous 60 days ^a Rofecoxib (25 mg per day or less) versus no NSAID use during previous 60 days ^a Rofecoxib (more than 25 mg per day) versus no NSAID use during previous 60 days ^a	0.84 (0.67–1.04) 1.23 (0.89–1.71) 3.00 (1.09–8.31)
Levesque, Brophy and Zhang (2005)	Administrative claims data from Quebec, Canada	Nested case-control study with automated data	First hospitalized myocardial infarction during the study period	Celecoxib versus no NSAID use within the previous year Rofecoxib (more than 25 mg per day) versus no NSAID use within the previous year	0.99 (0.85–1.16) 1.73 (1.09–2.76)
Hippisley-Cox and Coupland (2005)	Electronic medical record database in the United Kingdom (QRESEARCH)	Retrospective cohort and nested case-control study	First acute myocardial infarction	Rofecoxib (25 mg or less per day) versus no NSAID use within the previous year Celecoxib versus no use Rofecoxib versus no use	1.21 (1.02–1.43) 1.21 (0.96–1.54) 1.32 (1.09–1.61)
Johnsen et al. (2005)	Danish National Patient Registry in Denmark and the Danish Civil Registration System	Population-based case-control study	First time hospitalization for acute myocardial infarction	Current celecoxib versus no use Current rofecoxib versus no use	1.25 (0.97–1.62) 1.80 (1.47–2.21)

(continued)

Table 47.2. *Continued.*

Reference	Data source	Study design and data collection	CV Outcomes of interest	Selected comparison groups from published reports	Adjusted relative risk (95% CI)
Huang et al. (2006)	Administrative data from National Health Insurance in Taiwan	Retrospective cohort study for subjects with more than 180 days of continuous drug exposure	Acute myocardial infarction, angina, stroke, and transient ischemic attacks	Celecoxib versus meloxicam Acute myocardial infarction Stroke Rofecoxib versus meloxicam	0.78 (0.63–0.96) 0.81 (0.70–0.93) No increased risk of CV outcomes
Gislason et al. (2006)	Danish National Patient Registry, Danish Registry of Medicinal Product Statistics, and vital statistics	Retrospective cohort study	Reinfarction or death after post-myocardial infarction discharge	Any use of celecoxib versus no use Any use of rofecoxib versus no use	1.50 (1.10–2.05) for reinfarction 1.63 (1.27–2.10) for reinfarction
Velentgas et al. (2006)	Administrative data from large US health plans and manual review of medical records	Retrospective cohort study	Acute coronary syndrome and sudden cardiac death	Current celecoxib use versus ibuprofen or diclofenac Current rofecoxib use versus ibuprofen or diclofenac	1.03 (0.83–1.27) 1.35 (1.09–1.68)
Andersohn et al. (2006)	Electronic medical record system in the United Kingdom (General Practice Research Database)	Nested case-control study	Ischemic stroke	Celecoxib versus no NSAID use Rofecoxib versus no NSAID use Etoricoxib versus no NSAID use	1.07 (0.79–1.44) 1.71 (1.33–2.18) 2.38 (1.10–5.13)
McGettigan, Han and Henry (2006)	Three hospitals in New South Wales, Australia	Hospital-based case-control study	Acute coronary syndrome	Current celecoxib use versus no use Current rofecoxib use versus no use	1.11 (0.59–2.11) 0.63 (0.31–1.28)

^a No NSAID use represents no use of COX-2 inhibitors or non-selective NSAIDs throughout this table.

^b Remote NSAID use in the Graham study was operationally defined as drug supply from the most recent dispensing ended 60 days or more ago.

use of non-selective NSAIDs or COX-2 inhibitors, naproxen, ibuprofen, or other NSAIDs, relative risk estimates for developing acute myocardial infarction were 1.14, 0.95, 1.21, and 1.17 respectively. Comparing celecoxib against the same drug groups, the relative risk estimates ranged between 0.93 and 0.98. 95% CIs for these eight relative risks all included one. Consistently higher relative risk of acute myocardial infarction was associated with the use of more than 25 mg per day of rofecoxib than that for the use of 25 mg per day or less of rofecoxib when compared with the same groups. No dose-dependent finding was observed

for celecoxib. Rofecoxib was associated with a 24% increased risk of hospitalized myocardial infarction when compared with celecoxib (Table 47.2).

NON-THROMBOEMBOLIC ADVERSE CARDIOVASCULAR EVENTS

Other adverse cardiovascular effects of COX-2 inhibitors have also been reported after their approval. Whelton and colleagues conducted a 6-week clinical trial of COX-2 inhibitors among patients 65 years or older with osteoarthritis and stable

medication-controlled hypertension and showed that the incidence of increased systolic blood pressure was higher among patients randomly assigned to receive 25 mg of rofecoxib per day than among those who received celecoxib 200 mg per day (Whelton *et al.*, 2002). Using automated administrative data from Ontario, Canada, Mamdani and colleagues reported an increased risk of congestive heart failure among rofecoxib users but not celecoxib users (Mamdani *et al.*, 2004).

SUMMARY OF SAFETY INFORMATION OF CELECOXIB AND ROFECOXIB THROUGH JULY 2004

Results from VIGOR clearly indicated that rofecoxib 50 mg per day was associated with higher risk of adverse cardiovascular thrombotic events. Epidemiology studies reported by Ray and colleagues in 2002 and by Solomon and colleagues in 2004 corroborated this finding. Whether the use of rofecoxib 25 mg or less per day increased the risk of serious cardiovascular thrombotic events was less certain. On the other hand, no compelling evidence suggested that celecoxib use was associated with increased risk of adverse cardiovascular outcomes and as of mid-2004 these results did not support a class effect of adverse cardiovascular effects for the COX-2 inhibitors. In the label revision for rofecoxib in 2002, increased cardiovascular risk observed from the VIGOR trial was noted and recommendation that high dose rofecoxib not to be used chronically was added (Kweder, 2004).

LARGE TRIALS OF COX-2 INHIBITORS IN DISEASE PREVENTION (TABLE 47.1)

COX-2 INHIBITORS AND PREVENTION OF COLORECTAL ADENOMA

Rofecoxib in APPROVe

The study that prompted the market withdrawal of rofecoxib was the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial (Bresalier *et al.*, 2005). The trial was funded by the manufacturer of rofecoxib and the primary objective of the trial was to evaluate the efficacy of long-term rofecoxib

use in the prevention of adenomatous polyps recurrence among patients with a history of colorectal adenomas. Patients who had history of removal of histologically confirmed colorectal adenoma were randomly assigned to receive rofecoxib 25 mg per day or placebo for three years. Exclusion criteria included patients who had prior history of coronary heart disease and need for long-term NSAID therapy. Patient enrollment started before the adverse cardiovascular outcomes from VIGOR became available and patient enrollment completed in November 2001. The original protocol specified that patients on low dose aspirin (less than 100 mg per day) would be excluded, but after the VIGOR results became available, enrolled patients were allowed to take aspirin less than 100 mg per day. A committee blinded to treatment assignment evaluated all cardiovascular events and the composite cardiovascular 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 when 72 patients (46 among the rofecoxib group and 26 among the placebo group) had confirmed thrombotic events, the data and safety monitoring board found an increased risk of cardiovascular events among the rofecoxib arm, with a relative risk of 1.92 (95% CI, 1.19–3.11). The same conclusion could be reached if the APTC definition for cardiovascular end point was used. Although the Kaplan–Meier curves of adverse cardiovascular outcomes for the two treatment arms did not diverge after 18 months, there was insufficient statistical power to evaluate the risk difference during the first 18 months of treatment and no definitive conclusion could be made about when the risk might increase after initiation of rofecoxib therapy (Lagakos, 2006). APPROVe was terminated on 30 September 2004 and rofecoxib was withdrawn from the worldwide market on the same day.

Celecoxib in APC and PreSAP

Results of the APPROVe trial prompted the National Cancer Institute to carry out a cardiovascular safety analysis to evaluate the cardiovascular effects of

celecoxib in the Adenoma Prevention with Celecoxib (APC) study (Solomon *et al.*, 2005). Similar to APPROVe, APC was a chemoprevention trial that evaluated the efficacy of a COX-2 inhibitor in the prevention of recurrence of colorectal polyp. It was co-sponsored by the National Cancer Institute and the manufacturer of celecoxib. Subjects were randomly assigned to receive celecoxib 400 mg two times per day, celecoxib 200 mg two times per day, or placebo. Prior history of cardiovascular disease was not an exclusion criterion. Subject enrollment was completed in March 2002 and the treatment phase of the trial was terminated on 16 December 2004 because of cardiovascular safety concerns. The safety committee evaluated a composite cardiovascular end point of myocardial infarction, stroke, congestive heart failure, and death due to cardiovascular disease during the three-year follow-up period. An increased cardiovascular risk was found among patients who received celecoxib 800 mg per day when compared with the placebo arm (relative risk 3.4; 95% CI, 1.5–7.9). For the comparison between the groups who received celecoxib 400 mg per day and placebo, the relative risk was 2.6 (95% CI, 1.1–6.1) (Bertagnolli *et al.*, 2006).

The manufacturer of celecoxib funded another chemoprevention trial of colorectal polyps called Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial that compared the efficacy of celecoxib 400 mg daily and placebo in the prevention of colorectal adenoma recurrence. Preliminary findings were reported at the FDA advisory committee meeting in February 2005 (Levin, 2005) and the final report showed that for the same composite end point used in APC, relative risk for use of celecoxib 400 mg per day as compared with placebo was 1.3 (95% CI, 0.65–2.62) (Arber *et al.*, 2006).

Due to the cardiovascular safety signals discovered from preliminary analysis of APC and PreSAP, the National Cancer Institute commissioned a cardiovascular safety committee to combine cardiovascular safety data from APC and PreSAP and use a single set of criteria to blindly adjudicate cardiovascular end points (Solomon *et al.*, 2006). The overall relative risk was 1.9 (95% CI, 1.1–3.1) for all celecoxib doses when compared with placebo in these two colorectal adenoma prevention trials.

CELECOXIB AND NAPROXEN IN AN ALZHEIMER'S DISEASE PREVENTION TRIAL

The US National Institute of Aging sponsored the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) that began patient recruitment in 2001. Subjects of age 70 or older, but who did not have symptoms of dementia, were randomly assigned to receive long-term use of celecoxib 200 mg twice a day, naproxen 220 mg twice a day, or placebo. At an interim cardiovascular safety analysis conducted in December 2004, naproxen use was found to be associated with increased risk of adverse cardiovascular or cerebrovascular events when compared with the placebo group. No increased risk in the celecoxib group in comparison with placebo was found. The National Institute of Health announced that the trial was suspended, but no data were reported in peer-reviewed journals (NIH News Release, 2004).

META-ANALYSIS OF COX-2 INHIBITORS AND CARDIOVASCULAR OUTCOMES

Meta-analysis of clinical trials involving COX-2 inhibitors and cardiovascular outcomes conducted by investigators not associated with the pharmaceutical manufacturers were published after the market withdrawal of rofecoxib. Jüni and colleagues abstracted reported frequency of fatal or non-fatal myocardial infarction from 18 clinical trials of rofecoxib among patients with rheumatoid arthritis, osteoarthritis, or back pain (Jüni *et al.*, 2004). Rofecoxib dosage ranged from 12.5 to 50 mg per day and treatment duration ranged from 4 to 56 weeks. The comparison groups received either placebo or a non-selective NSAID. Approximately a third of the 25 573 patients in the 18 trials were enrolled in VIGOR. In 10 of the 18 trials, myocardial infarction was more common among the rofecoxib arm, but the difference only reached statistical significance in VIGOR. The combined odds ratio for the rofecoxib versus non-selective NSAID or placebo comparison was 2.24 (95% CI, 1.24–4.02).

Kearney reviewed 138 randomized trials of either a COX-2 inhibitor versus placebo or a COX-2 inhibitor versus non-selective NSAIDs and evaluated a range of cardiovascular end points, including vascular events, myocardial infarction, stroke, and vascular death (Kearney *et al.*, 2006). For all COX-2

inhibitors (celecoxib, etoricoxib, lumiracoxib, rofecoxib, and valdecoxib) as a group and compared with placebo, relative risk of developing serious vascular events was 1.42 (95% CI, 1.13–1.78). Heterogeneous results were observed when COX-2 inhibitors were compared with different non-selective NSAIDs. COX-2 inhibitors were associated with increased vascular risk when compared with naproxen (relative risk 1.57; 95% CI, 1.21–2.03) and were not associated with increased vascular risk when compared with non-naproxen NSAIDs (relative risk 0.88; 95% CI, 0.69–1.12).

For other adverse cardiovascular outcomes, Aw and colleagues reviewed 19 clinical trials involving COX-2 inhibitors and reported that use of COX-2 inhibitors was associated with increased blood pressure when compared with placebo or non-selective NSAIDs (Aw *et al.*, 2005). The effect on blood pressure was more pronounced among rofecoxib users than among celecoxib users. Zhang and colleagues reviewed 114 clinical 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 events (Zhang, Ding and Song, 2006).

OBSERVATIONAL STUDIES PUBLISHED AFTER THE WITHDRAWAL OF ROFECOXIB

Eleven observational studies on COX-2 inhibitors and adverse cardiovascular outcomes were reported after the withdrawal of rofecoxib and major findings are summarized in Table 47.2. Reports in abstract form or conference proceedings are not included in this review. The results were heterogeneous as there was much variation in study design, study populations, comparison groups, and outcomes of interest. Four reports were based on administrative data of private or public health insurance data in North America. Shaya and colleagues compared incidence of APTC events among users of COX-2 inhibitors and non-selective NSAIDs and found no increased risk among users of rofecoxib or celecoxib when compared with users of non-selective NSAIDs (Shaya *et al.*, 2005).

Graham and colleagues evaluated the risk of myocardial infarction and sudden cardiac death among users of non-selective NSAIDs and COX-2 inhibitors in a nested case-control study (Graham *et al.*, 2005). Comparing with those who were unlikely to have used a prescription non-selective NSAID or COX-2 inhibitor during the last 60 days, the adjusted odds ratio was 0.84 (95% CI, 0.67–1.04) for celecoxib. Adjusted odds ratio was higher for high dose rofecoxib (more than 25 mg per day) than for low dose rofecoxib (25 mg per day or less). Levesque and colleagues compared current use of COX-2 inhibitors, non-selective NSAIDs, and no use of either COX-2 inhibitors or non-selective NSAIDs and found that high dose rofecoxib (more than 25 mg per day) and low dose rofecoxib (25 mg per day or less) were both associated with increased risk of hospitalized myocardial infarction when compared with no use (Levesque, Brophy and Zhang, 2005). There was no increased risk among celecoxib users. Velentgas and colleagues reported an increased risk of acute coronary syndrome among current rofecoxib users compared with ibuprofen or diclofenac users (relative risk 1.35; 95% CI, 1.09–1.68) and no increased risk among current celecoxib users for the same comparison drugs (relative risk 1.03; 95% CI, 0.83–1.27) (Velentgas *et al.*, 2006). Huang and colleagues used national health insurance data from Taiwan and reported no increased risk of myocardial infarction, angina, stroke, or transient ischemic attack when rofecoxib or celecoxib was individually compared with meloxicam among an ethnic Chinese population (Huang *et al.*, 2006).

Two studies were based on electronic medical record systems in the UK. Hippisley-Cox and Coupland found that rofecoxib use was associated with myocardial infarction (adjusted odds ratio 1.32; 95% CI, 1.09–1.61) and celecoxib use showed similar level of increased risk, but the lower bound of the 95% CI was 0.97 (Hippisley-Cox and Coupland, 2005). Andersohn studied stroke as an outcome interest and found increased risk of stroke among rofecoxib and etoricoxib users but not celecoxib users (Andersohn *et al.*, 2006).

Two studies were based on population-based registries in Denmark. Johnsen and colleagues studied the risk of first myocardial infarction and reported increased risk among rofecoxib users and non-statistically-significant increased risk among

celecoxib users (Johnsen *et al.*, 2005). Gislason and colleagues studied re-infarction and death after post-myocardial infarction discharge and found increased risk for both celecoxib and rofecoxib (Gislason *et al.*, 2006).

The two other studies were case-control studies with patients identified from hospitals. Kimmel and colleagues in the US compared the use of COX-2 inhibitors with no NSAID use and reported adjusted odds ratio of 0.43 (95% CI, 0.23–0.79) for celecoxib and 1.16 (95% CI, 0.70–1.93) for rofecoxib (Kimmel *et al.*, 2005). McGettigan and colleagues in Australia studied acute coronary syndrome and did not find increased risk among celecoxib users or rofecoxib users (McGettigan, Han and Henry, 2006).

McGettigan and Henry combined data from 12 observational studies involving COX-2 inhibitors and found that celecoxib was not associated with increased cardiovascular risk, with a combined relative risk of 1.06 (95% CI, 0.91–1.23) (McGettigan and Henry, 2006). Both high dose rofecoxib (more than 25 mg per day) and lower dose rofecoxib (25 mg or less per day) were associated with increased cardiovascular risk. Combined relative risk for high rofecoxib was 2.19 (95% CI, 1.64–2.91) and it was 1.33 (95% CI, 1.00–1.79) for lower dose rofecoxib.

CARDIOVASCULAR SAFETY OF OTHER COX-2 INHIBITORS

VALDECOXIB AND PARECOXIB

Parecoxib is the only COX-2 inhibitor available for intravenous or intramuscular administration and is indicated for post-operative pain. Parecoxib is a prodrug of valdecoxib, which is available in oral form. Cardiovascular safety profiles of the two drugs are assumed to be the same. Ott and colleagues reported general safety information from a placebo-controlled trial of parecoxib and valdecoxib in patients after coronary artery bypass graft (CABG) surgery, in which patients assigned to the active treatment group received intravenous parecoxib 40 mg every 12 hours during the first 3 days, followed by oral valdecoxib 40 mg every 12 hours for up to 11 days (Ott *et al.*, 2003). All serious adverse events occurred more frequently among the parecoxib–valdecoxib group

than among the placebo group (19 versus, 9.9%), but the difference in cardiovascular adverse events did not reach statistical significance.

White and colleagues reviewed cardiovascular safety data from 10 clinical trials of oral valdecoxib in approximately 8000 patients with osteoarthritis or rheumatoid arthritis and found no increased risk of thrombotic events among the valdecoxib users when compared with patients who used non-selective NSAIDs or placebo (White *et al.*, 2004).

Nussmeier and colleagues reported a larger trial of parecoxib–valdecoxib among CABG patients than that reported by Ott and colleagues (Nussmeier *et al.*, 2005). In the three-arm study, one group of patients was randomly assigned to receive one dose of intravenous parecoxib 40 mg followed by 20 mg every 12 hours for 3 days and oral valdecoxib 20 mg once-daily for up to 10 days; the second arm of patients received intravenous placebo for three days followed by the same regimen of oral valdecoxib as in the first arm; the third arm received both intravenous and oral placebo. Increased frequency of thromboembolic events was found in the active drug groups (Table 47.1). Data from the two post-CABG trials clearly showed an increased cardiovascular risk for parecoxib–valdecoxib if used for post-CABG pain management, therefore this regimen is contraindicated for use in CABG patients in countries where the regimen is available.

In addition to increased cardiovascular risk, reporting rates of Stevens–Johnson syndrome and toxic epidermal necrolysis were higher for valdecoxib than that for other COX-2 inhibitors or NSAIDs (La Grenade *et al.*, 2005). The increased risk of cutaneous toxicity led to the market suspension of valdecoxib in the US in April 2005.

LUMIRACOXIB

A large-scale randomized trial, the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), was conducted to evaluate the efficacy and safety of lumiracoxib (Schnitzer *et al.*, 2004 and Farkouh *et al.*, 2004; Table 47.1). During one year of follow-up, risk of upper gastrointestinal ulcer complications was substantially lower in the lumiracoxib group when compared with patients on naproxen or ibuprofen (relative risk 0.34; 95% CI, 0.22–0.52). The risk reduction was more pronounced among

patients not receiving low dose aspirin (relative risk 0.21; 95% CI, 0.12–0.37), but the 95% CI of the relative risk estimate for patients who received low dose aspirin included one. Cardiovascular outcomes of interest were defined by the APTC criteria. In the primary analysis of all subjects, lumiracoxib–naproxen and lumiracoxib–ibuprofen comparisons, and subgroups stratified by low dose aspirin use, 95% CIs of the relative risk estimates for adverse cardiovascular events all included one. Scientists from the manufacturer of lumiracoxib combined data from all lumiracoxib trials of duration between one week and one year and reported the cardiovascular safety information in 2005 (Matchaba *et al.*, 2005). For APTC end points, relative risk was 1.08 (95% CI, 0.41–2.86) for the lumiracoxib–placebo comparison, 0.83 (95% CI, 0.46–1.51) for the lumiracoxib–non-naproxen NSAIDs comparison, and 1.49 (95% CI, 0.94–2.36) for the lumiracoxib–naproxen comparison. Twelve and six trials involving lumiracoxib were included in the meta-analysis reports by Kearney and colleagues and Zhang and colleagues, respectively, but the number of adverse cardiovascular events reported in the trials was not large enough to provide definitive inference (Kearney *et al.*, 2006; Zhang, Ding and Song, 2006).

ETORICOXIB

Etoricoxib is developed by the same manufacturer of rofecoxib. At the time of market withdrawal of rofecoxib, a large trial by the name of Etoricoxib versus Diclofenac sodium Gastrointestinal Tolerability and Effectiveness (EDGE) was ongoing to evaluate the tolerability and efficacy of etoricoxib 90 mg daily versus diclofenac sodium 50 mg three times a day in patients with osteoarthritis. Some results have been reported in professional society meetings and an FDA advisory committee meeting, but the results have not been published in peer-reviewed journals (Schiffenbauer, 2005). Seventeen and fifteen trials involving etoricoxib were included in the meta-analysis reports by Kearney and colleagues (Kearney *et al.*, 2006) and Zhang and colleagues (Zhang, Ding and Song, 2006), respectively. Aldington and colleagues independently reviewed cardiovascular safety information from five published etoricoxib trials (Aldington *et al.*, 2005), but the number of adverse cardiovascular events reported

in the trials in these three meta-analysis reports was not large enough to provide definitive inference.

As etoricoxib is already available in some countries, it is anticipated that more safety reports based on observational studies will be available in the near future. For example, Andersohn reported that etoricoxib was associated with an increased risk of stroke when compared with no NSAID use (relative risk 2.38; 95% CI, 1.10–5.13).

COMMENTS

LIMITATIONS OF SPONTANEOUS REPORTS SYSTEM

The post-marketing safety assessment of COX-2 inhibitors and market withdrawal of rofecoxib provided important lessons but left some unanswered questions as of the writing of this chapter. Perhaps the most important lesson is the limitation of spontaneous adverse drug reactions reporting system in the detection of safety signals with a high background rate in a population using a drug of interest. In the US where millions of patients have used celecoxib or rofecoxib in 1999 and 2000, there has been no cardiovascular safety signal identified in the Adverse Event Reporting System. The safety signal report from the Netherlands was not widely publicized in the US. If there was no VIGOR or APPROVe, the cardiovascular risk of rofecoxib might not be recognized until much later. It is understandable that the traditional spontaneous reporting system did not detect the cardiovascular safety signal of rofecoxib. For rare outcomes that have been previously reported as drug-induced adverse events, such as Stevens–Johnson syndrome, liver failure, or agranulocytosis, the prescribing physician'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 risk factors are well characterized, the prescribing physician may not readily attribute the myocardial infarction in a patient to the rofecoxib that the patient was using. For example, an overweight 59-year-old male smoker who had poorly controlled blood pressure and serum cholesterol started rofecoxib for his knee pain and then developed acute myocardial infarction in early 2000. Results from VIGOR were not yet available, the event could be explained by the

patient's existing cardiovascular risk factors (smoking, hypertension, and hypercholesterolemia), and the event would not be reported as an adverse drug reaction. This example illustrates the importance of additional safety signal detection scheme to complement the existing spontaneous reporting system.

PRE-MARKETING AND POST-MARKETING TRIALS

According to current regulatory requirement, clinical trials of new NSAIDs like the COX-2 inhibitors only need to demonstrate short-term efficacy and safety. The study populations are usually relatively healthy and free from major comorbidity. However, once the drug is on the market, it is used in patients with a wide range of chronic diseases and concomitant medications and the new drug is used for periods much longer than the study period of the pre-marketing trials. In all observational studies of COX-2 inhibitors that evaluated baseline comorbidity of study subjects, a substantial proportion had cardiovascular risk factors at baseline. Pooling data from multiple clinical trials (Konstam *et al.*, 2001; Weir *et al.*, 2003; White *et al.*, 2003; White *et al.*, 2004; Matchaba *et al.*, 2005) to increase statistical power to evaluate risk of rare events is an important tool in safety assessment, but it does not address the issue of limited trial duration and non-generalizability to patients with cardiovascular comorbidity and concomitant medications. Moreover, not all relevant safety information is included in published reports. Zhang and colleagues identified 502 reports involving COX-2 inhibitors and 331 had no event data on the occurrence of arrhythmia or renal complications (Zhang, Ding and song, 2006).

Sample sizes of the post-marketing trials of celecoxib (CLASS), rofecoxib (VIGOR), and lumiracoxib (TARGET) were much larger than that of the pre-marketing trials and had larger statistical power to evaluate less common adverse events. Even so, they were not powered to precisely estimate relative risk associated with serious cardiovascular outcomes. Moreover, low dose aspirin was allowed in only two of the three trials and provided limited information on potential interaction between COX-2 inhibitors and aspirin on gastrointestinal and

cardiovascular outcomes. Placebo-controlled trials of COX-2 inhibitors and non-selective NSAIDs would provide the most compelling evidence on the safety of these drugs, but these trials are ethically infeasible. For the active-control trials, long-term cardiovascular safety of the commonly used comparator drugs, ibuprofen, naproxen, and diclofenac, has not been evaluated in clinical trials. Placebo-controlled results would have to come from study populations who did not require NSAID therapy, and APPROVe, APC, and PreSAP were such studies which demonstrated the increased cardiovascular risk among users of rofecoxib and celecoxib. Not surprisingly, incidence of adverse cardiovascular events was much lower in these three trials than that observed among CLASS, VIGOR, and TARGET, raising questions about the generalizability of these results to patients who need NSAIDs. Trials need to be conducted among patients with coronary heart disease or cardiovascular risk factors to provide the most valid and generalizable answer to address the cardiovascular safety questions of the COX-2 inhibitors. The Multinational Etoricoxib and Diclofenac Arthritis Long-Term program sponsored by the manufacturer of etoricoxib (Merck News Release, 2006) and the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen sponsored by the manufacturer of celecoxib (Cleveland Clinic Press Release, 2005) will provide more definitive answers.

Lastly, while the analgesic and anti-inflammatory effects of the non-selective NSAIDs may be similar at optimal doses, their cardiovascular safety profiles may not be the same. The meta-analysis of clinical trials involving NSAIDs by Kearney and colleagues and the meta-analysis by McGettigan and colleagues clearly indicated that the NSAIDs are not the same with regards to adverse cardiovascular effects (Kearney *et al.*, 2006; McGettigan and Henry, 2006). This heterogeneity of cardiovascular effects has major implications in the selection of comparison groups in large safety trials.

THE ROLE OF OBSERVATIONAL STUDIES

As large-scale clinical trials are costly and time-consuming, evaluation of cardiovascular safety of COX-2 inhibitors with existing automated data has

been an efficient way to provide important safety information on a timely basis. Thirteen of the fifteen studies summarized in Table 47.2 are based on automated data sources, further demonstrating the utility of these data systems in rapid response to drug safety signals. The observational studies on the COX-2 inhibitors did suggest increased risk of serious cardiovascular thrombotic events among rofecoxib users, especially at dosages higher than 25 mg per day. However, the study designs for these reports were not the same, the comparator drugs were different, and important confounders, including smoking, body mass index, and use of non-prescription low dose aspirin, were not accounted for in the analysis in several studies.

RISK–BENEFIT ASSESSMENT OF THE COX-2 INHIBITORS AND NSAIDS

The therapeutic role of COX-2 inhibitors needs to be interpreted in the context of the risk–benefit profiles of the agents. Difficulties experienced by regulators are discussed by a senior FDA officer (Kweder, 2004) and by the director of the Uppsala Monitoring Center (Edwards, 2005). For both the COX-2 inhibitors and non-selective NSAIDs, their principal anticipated beneficial effects are the analgesic and anti-inflammatory effects, and no single agent or class of agent has been shown to have superior efficacy than others. The risks may involve multiple organ systems and are not restricted to the gastrointestinal and cardiovascular systems. Liver, renal, cutaneous, and hematologic toxicities are important issues to consider in the risk–benefit calculus. While the COX-2 inhibitors are associated with less gastrointestinal complications than selected NSAIDs for patients not taking aspirin, how they compare against the combination of NSAID and a proton pump inhibitor or an H₂ blocker or misoprostol is not known.

Another factor that may affect the risk–benefit profile of NSAIDs and COX-2 inhibitors is the development of new indication. Celecoxib has already been shown to decrease the development of rectal polyp among patients with familial polyposis and it has been shown to decrease the recurrence of colorectal adenoma among those who had a history

of adenoma removal (Arber *et al.*, 2006; Bertagnolli *et al.*, 2006). The efficacy results of APPROVE will provide more information on the potential use of COX-2 inhibitors in the prevention of colorectal adenoma.

In addition to overall risk–benefit assessment, regulators and clinicians need to carry out the assessment among subgroups of patients defined by specific risk factors, including those for gastrointestinal complications and cardiovascular disease. For example, the risk–benefit 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. Another issue that has not been adequately addressed in the large COX-2 inhibitor trials is the effect of duration of treatment, which has major clinical implications. More systematic synthesis of data and quantitative risk–benefit assessment for the non-selective NSAIDs and COX-2 inhibitors are needed.

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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 steroidal 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 vs. non-response as diagnostic information. A still further change, which will foreseeably continue, has been increasingly ability to see disease in its earliest stages, thus moving backwards the somewhat fuzzy boundary between prophylaxis of disease 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 of various lipids in blood, steadily lowering the risk of coronary arterial disease.

In the arena of infectious disease, the period 1945–2005 have seen an intense race between the emergence of micro-organismal 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 micro-organisms. Most infectious disease experts recognize that either form of under-treatment can drop the concentrations of anti-infective agents in blood or tissues to a point low enough to allow high rates of micro-organismal replication, whilst still being high enough to exert so-called 'selection pressure'. Thus, mutant micro-organisms, carrying mutations that confer drug resistance, are selected for, as they are believed to thrive better in an environment of partial exposure to anti-microbial drug action than wild-type micro-organisms, 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 micro-organisms? 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. *Treponema 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 as the leading infectious disease and cause of mortality and major morbidity at all ages

of human life. In contrast, other micro-organisms, for example *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 micro-organisms involved. Such detail goes beyond the scope of this chapter, but suffice it to say that erratic exposure of infecting micro-organisms 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 micro-organismal resistance to anti-microbial 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 United States, have risen steeply since the early 1990s.

Thus the advent of medicines with unprecedented therapeutic power and economic cost, some of which are indicated for multi-year 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), which concerns itself with learning what patients actually do with prescribed drugs and analysing 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 analysing 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. 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 line labelled ‘persistence’ in Figure 48.1. These are patients who never start the dosing regimen, though have enrolled in the treatment programme. They may take an initial dose or two, but most of them take none, and then disappear from the treatment programme. There may be a time that they come back to treatment, but it does not

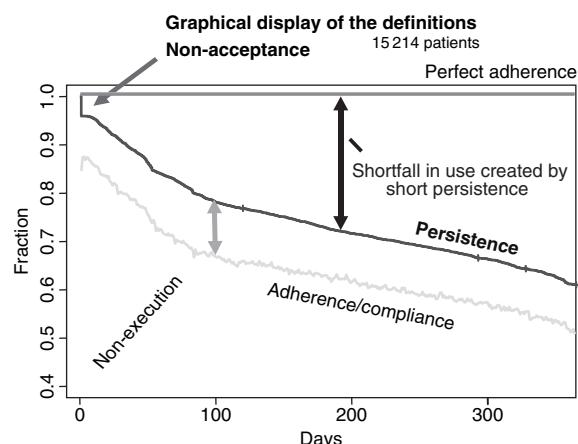


Figure 48.1. Fractions of 15 214 patients, whose electronically compiled drug dosing histories have been compiled in 14 different therapeutic fields, ranging in duration from 30 days to 4 years, as a function of time in days since the start of their course of ambulatory pharmacotherapy. The meaning of the terms and the interpretation of the data are discussed in the text. (Copyright Pharmionic Systems Ltd, 2006. Reproduced with permission.)

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 Figure 48.1, between the ‘persistence’ line and the lower, somewhat irregular line, labelled ‘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 of the gap arises from dose omissions made by about a third of ambulatory patients (Urquhart, 1997), 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 non-acceptors, we are left with patients who engage with the dosing regimen. They dwindle in numbers throughout the one-year period shown in Figure 48.1. By the end of the first year, in the 15 214-patient cohort represented by Figure 48.1, about a third had discontinued what was meant to be multi-year, 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 non-persisters, 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 non-acceptance, incomplete execution and early discontinuation are pervasive in long-term ambulatory pharmacotherapy. To illustrate one end of the range of variation, Catalan and LeLorier 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, which means that economic obstacles to continuity of treatment were nullified. Switches between one drug and another within the 'statin' class were considered to represent continuity of statin treatment. 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–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 minimus 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; Catalan and LeLorier, 2000; Benner *et al.*, 2002).

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 recently published, 392-patient, one-year study (Vrijens *et al.*, 2005a), 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 programme 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 his/her interventional manoeuvres.

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, execution 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.

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, for example 24 hours for once-daily dosing. Aggregate figures across long periods of time hide informative time-variations in dose-taking behaviour. For example, there is a marked ‘weekend effect’ frequently evident, by which substantially and significantly more doses are missed on weekends than on weekdays. Another time-dependency is the tendency for the quality of regimen execution to decline gradually over long periods of time.

The choice of limits on the dosing interval should ideally relate to the pharmacometric properties of the drug in question, for example bendroflumethiazide, the diuretic widely used in the United Kingdom for hypertension treatment, has a 3-hour plasma half-life (Jack-

son, 1995), but a 6.3-day duration of anti-hypertensive action after a last-taken dose; if one considers only the pharmacokinetic properties of that drug, the range would be set quite narrowly, perhaps ± 1.5 hours, 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 ± 2 days.

In the known pharmacometric properties of bendroflumethiazide, 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 pharmacodynamic 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 naive notion.

Contrasting Dynamics of Acceptance, Execution, Discontinuation: why no Single Parameter can Encompass all Major Dosing Errors and Support 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 non-acceptance, poor execution

and early discontinuation. As a concrete example, consider the following statement by the 6th Joint National Commission on High Blood Pressure (The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997): ‘Poor adherence to anti-hypertensive 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 non-acceptance, 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 anti-hypertensive drug treatment. As the Belgian atorvastatin study illustrates, a programme of measurement-guided medication management can not only 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, it probably means attacking specifically each of the three major errors: non-acceptance, poor execution, early discontinuation.

The Importance of Distinguishing Early Discontinuation and Poor Execution in Analysing Drug Dosing History Data

A common manner of expressing adherence/compliance data goes as follows:

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 (Osterberg and Blaschke, 2005).

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 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 his intention to quit, versus a careful review with the patient of his day-to-day dosing patterns, with assistance in finding robust routines in his daily life to which his daily dosing can be linked, as suggested by Cramer and Rosenheck (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 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’ self-evidently relates to what happens while the patient is engaged with the dosing regimen; when that engagement halts, execution 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 vs. intervening to prolong persistence, 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 executor will, for as long as he persists, continue to generate revenues, albeit at a rate reduced by the extent of his 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 executor 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 the best 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).

Note that Figure 48.1 is a very simple, straightforward summary of pharmionic 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 can not only 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 re-formulation 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). 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 correlates 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.

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, Urquhart and Leufkens, 2002), hazardous rebound effects (Urquhart, 1997) and recurrent first-dose effects (Urquhart, 1997). 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 compliance (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 to automatically compile complete records of electrophysiological activity throughout multi-week 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.

METHODOLOGICAL ISSUES IN COMPILING DRUG DOSING HISTORIES OF AMBULATORY PATIENTS

Until the later 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 towards over-estimation of the patient's adherence to the prescribed dosing regimen. What patients tell their physician or other health care personnel is strongly coloured 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. Recent work with a special diary that captured and stored 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, Schiffman, Schwartz, 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 3–4 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 hours or less (Benet, Oie and Schwartz, 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, that is 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). 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 use-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 oestrogen–progestin, oral contraceptives. As the UK labelling indicates, being more than 12 hours 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 (Guillebaud, 1993). Thus, a patient who routinely takes a daily ‘pill’, but wobbles in dose-taking between doing so at the usual 7 AM or, exceptionally, at bed-time, creates intervals between doses that exceed 36 hours, which would appear to be the mean point at which the risk of breakthrough ovulation starts to rise. (Note that the 36-hour mean implies that half the patients can be expected to have an even shorter margin for dose-timing error than 36 hours.) Clearly, then, in the case of these most widely used products, the

‘80% is OK’ criterion, which means missing one dose in 5, and thus a series of 48-hour 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 bendroflumethiazide, a thiazide diuretic widely used in the treatment of hypertension in the United Kingdom, and which has a once-daily dosing regimen, though it is able to maintain anti-hypertensive 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 oestrogen/progestin oral contraceptives, with their minuscule average of 12 hours of safety margin beyond the recommended 24-hours 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 anti-hypertensive 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 1989. This product inferentially compiled drug intake by detecting, time-stamping and storing time 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. Recently this surrogate measure was 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 time (Vrijens *et al.*, 2005b).

Prior to this validation, electronic monitoring had already been in use between 1989 and 2005, giving rise to approximately 250 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, analysed 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 regarding details of product use. Some users of MEMS have opted to have their data analysed at the recently established AARDEX Statistical Research Centre in Visé, Belgium, done on a fee for service basis.

Many commentators or reviewers of the field of patient adherence have described the MEMS Monitors as ‘expensive’ (see, e.g., Osterberg and Blaschke, 2005), leaving it to the reader to infer: (a) the costs of the various pre-electronic techniques of compiling drug dosing histories in ambulatory patients; (b) the values of having reliable data on ambulatory patients’ drug dosing histories.

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 infectious diseases, public health consequences. There are, in the history of this field three landmarks 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 analysing ambulatory patients’ dosing histories.

The three areas are (a) tuberculosis 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 clinical consequences of variable underdosing by ambulatory patients.

CASE 1: POOR ADHERENCE IN TUBERCULOSIS (TB) TREATMENT – CONSEQUENCES AND COUNTER-ACTIONS

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 endeavours 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 multi-drug resistant (MDR) tubercle bacilli were 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 HIV is the opposite, in that the multi-drug resistant 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 tuberculosis were required, if necessary by force of law, to attend the TB clinic the specified number of times per week, usually 3 or 4, at which times the clinic staff observed their taking of the requisite doses of anti-TB medicines (<http://www.nyc.gov/html/doh/html/tb/tb2a.shtml>).

This manoeuvre required that individual administered doses of anti-TB drugs be considerably increased, compared to 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 3–4-times weekly dosing mode appears to be virtually unique to the field of tuberculosis. In contrast, it would be impossible, for example, to make a comparable escalation in administered doses of the present group of anti-retroviral drugs used to treat patients infected with HIV. Nor could one give the usual once-daily doses of anti-retroviral drugs on only 4 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 pre-market 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, Urquhart and Leufkens, 2002).

Directly observed therapy has turned out to be a remarkably successful addition to the treatment of tuberculosis (Weis *et al.*, 1994; <http://www.who.int/mediacentre/factsheets/fs104/en/>). It has worked so well that it has been widely adopted, including by the World Health Organization (<http://www.who.int/mediacentre/factsheets/fs104/en/>). 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 3–4 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 New York City Department of Public Health and Mental Hygiene 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 programme depends not only on the medicines used, but also on the quality of management of the programme, 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 programme.

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 4 to 2 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 – 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 works

and what does not work when deviations occur from the currently recommended dosing regimen.

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CASE 2: ADHERENCE TO VERY UNFORGIVING ORAL CONTRACEPTIVE DOSING REGIMENS – CONSEQUENCES AND COUNTER-ACTIONS

The original oral contraceptive ‘pill’, the combination of an oestrogen 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 by 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 latter 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 pre-menopausal women, which facilitated recognition of their increased incidence among oral contraceptive users. After due consideration, the decision was made to reduce the oestrogen 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 to the prior experience with the original, high-dose ‘pill’. It was correctly hypothesized at the time that the low-dose, combined oestrogen–progestin oral contraceptive ‘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 ‘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 AM, and who, on a particular day misses the usual 7 AM dose, will begin to incur elevated risk of ovulation by 7 PM in the evening of the same day. It is therefore possible that ‘breakthrough’ ovulation might have occurred in a patient who missed her usual 7 AM dose, but at 11 PM 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.

CASE 3: PREVENTION OF RECURRENT ACUTE RHEUMATIC FEVER.

Towards 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 auto-immune phenomenon, without evident bacterial involvement. This sequence suggested a pathway to eliminating acute rheumatic fever and its malign sequelae: 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.

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 under-exposure 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 three 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 non-contracepting, 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, is 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 vs. 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 under-usage 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, for example syphilis, acute rheumatic fever as a sequel to streptococcal infections, trachoma, malaria and others. Prevalent under-use creates conditions that nullify the effectiveness of anti-infective or anti-parasitic drugs and open the door to emergent drug-resistant micro-organisms, 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 tuberculosis 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. This field of study is called *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.

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Part V

LESSONS AND DIRECTIONS

Teaching and Learning Pharmacovigilance

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INTRODUCTION

There are two closely connected primary 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 learn to continually discriminate benefits and risks associated with the pharmacotherapies they are supervising. On the other hand, the professional pharmacovigilist needs to develop and maintain the same fundamental clinical knowledge and discriminatory skill as well as mastery of 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 here as learners and teachers of pharmacovigilance.

In recent years, two significant political undercurrents have powerfully influenced the field of pharmacovigilance: these currents have created a notable undertow that has magnified interest in and extended the scope of teaching in this field. Additionally, these forces have resulted in a more lively interest in the communication of findings from the field of pharmacovigilance to those engaged in overseeing pharmacotherapy in practice.

The first of these currents derives from publicity and revitalized public interest in mistakes and mishaps in conventional healthcare provisions. The second has emerged from concerns about medicinal drug therapy, and the contemporary expectation that available therapies should be uniformly 'safe' in customary use. 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 the care of their patients and also for training

health professionals in pharmacovigilance management techniques.

CURRENT INFLUENCES ON PHARMACOVIGILANCE EDUCATION

The 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 has 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 (Edwards, Faich and Tilson, 2005): *A general effort to improve risk communication both in particular instances and in the general education of the public, should be a high priority.*

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

Well-publicized studies of mistakes and mishaps in care of hospitalized patients in both the United States (Brennan *et al.*, 1991) and Australia (Wilson *et al.*, 1995) led to substantially heightened levels of public interest in achieving less harm from customarily delivered health care. In the United States, a landmark Institute of Medicine report *To err is human* (Kohn *et al.*, 2000) acted as a platform to launch a range of initiatives to draw attention to and improve patient safety.

Parallel action was taken in the United Kingdom 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 United Kingdom, a pivotal report from the NHS chief medical officer (Donaldson, 2000) led to the establishment of a

National Patient Safety Agency that was tasked with reporting, analysing and disseminating the lessons of adverse events and 'near misses' involving British NHS patients.

Embedded within reports associated with this movement are the documentation of significant numbers of incidents associated with medication use, and by implication, unsafe healthcare practice. Recently, in the United Kingdom, 9% of reported patient safety incidents in acute hospitals and 21% of such incidents in general practice were noted to be associated with medications (Scobie *et al.*, 2005). The relationship between medication errors and adverse drug events is complex, with medication errors being generally more common than adverse drug events. 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).

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, 1995), and other respected 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 propose a comprehensive system for detecting and classifying medication-related incidents and suggest 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 (Figure 49.1).

There are clearly important implications for use of the term 'error' when applied to medication use. As an absolute term, the implication that such incidents must be preventable defies the logic of what is known about pharmacotherapy. 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

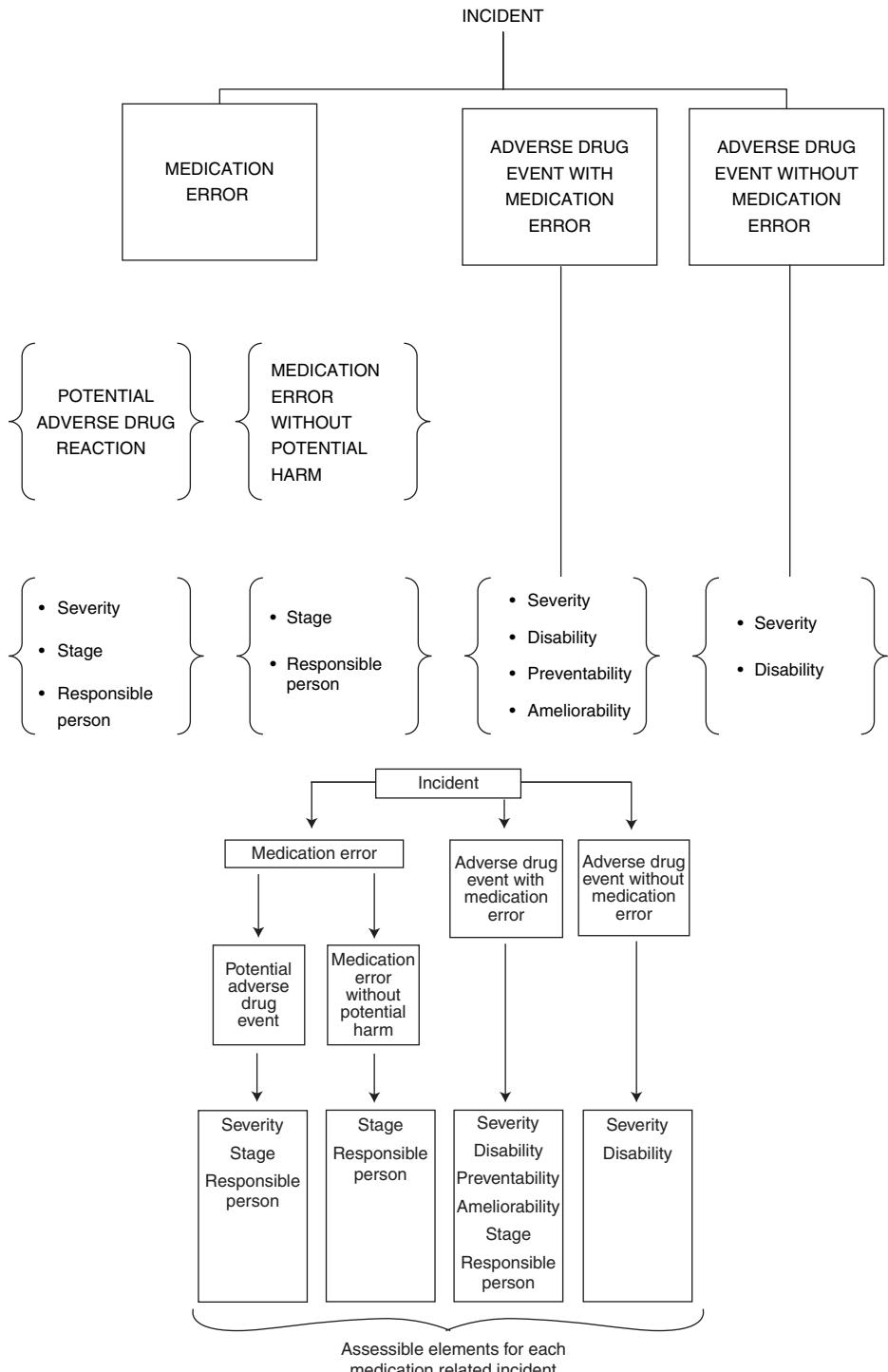


Figure 49.1. Flow diagram for the classification of adverse drug events and medication errors and identifiable incident characteristics. Source: Morimoto et al. (2004). Reproduced with permission from the BMJ Publishing Group.

appears to be an error may well prove to have been a conscious judgement of perceived relative benefit and risk on the part of an individual prescriber.

'Error' may have occurred in such circumstances solely insofar as the decision to use a drug was not openly shared between prescriber and patient, with both parties being properly informed about potential benefits and risks associated with treatment. For the pharmacovigilist, whether an 'error' actually occurred often remains uncertain, depending on the distance in time and space from the event and its specific circumstances.

'SAFETY' AS A CONSTRUCT IN HEALTHCARE

This 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 also 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 health care. At present, the quality-in-healthcare movement is gaining considerable currency, with countries such as the United States pouring very substantial resources into Quality Improvement Organisations as part of their publicly funded Medicare system. The benefits from such systems at present remain controversial (Marciniak *et al.*, 1998; Snyder and Anderson, 2005).

These 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 contribute to mistakes within the healthcare system, but they are also equally aware of their responsibilities to achieve healthcare quality and, in particular, to strive for the best balance between risk and benefit in all that they do to assist restoration of health to 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 recent years, the highly publicized withdrawal from sale of many extensively used drugs has elicited wide but shallow public debate about risks and benefits associated with use of pharmaceuticals. Regrettably, this discussion has been confounded by increasingly prevalent perceptions of an unsupportable rapacity of the global pharmaceutical industry. In addition, in some countries such as the United States, there has been a growing belief that existing regulatory systems designed to evaluate relative risks and benefits of individual products, both before and after licensure for sale, have been compromised by inappropriately structured public administration.

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 increasingly 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 licensure. The implications of past failure to make such post-marketing assessments has been analysed, and the need for decisive action has been comprehensively justified by

Dr Jerry Avorn (2004) in his pivotal book: 'Powerful medicines – the benefits, risks and costs of prescription drugs'.

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 (p. 383).

Additionally, beyond licensure for marketing, there is also a need for comparative studies assessing both pharmaceutical risks and benefits at different dosing levels between drugs of the same class (or drugs used for the same purpose) across broad end-user populations.

This has been perhaps a key conclusion after recent controversies surrounding negative cardiovascular effects associated with the non-steroidal anti-inflammatory class of drugs. It has been the failure to recognize differential levels of benefits and adverse effects amongst members of this class that has resulted in precipitate drug withdrawals (Edwards, 2005). Why retain relatively more hazardous forms of these drugs on the market, when beneficial effects can be achieved from other members of the class with lower levels of negative cardiovascular effects? This is a question that is increasingly being asked. Regrettably the information that might allow some degree of certainty about these relative benefits and risks in actual practice is not currently available.

Failure to require such post-marketing studies remains therefore perhaps the single biggest deficiency in public regulation of drug 'safety' at present.

Global movements are now starting to at least partially address these deficiencies in contemporary systems of pharmaceutical regulation. These movements are highlighting and deepening the field of pharmacovigilance and leading to learning needs far from traditional pharmacovigilance activities of past decades. The study and classification of ADRs remains a core activity for pharmacovigilance, but study of and communication about risks as well as benefits of pharmaceuticals in whole user populations is now confronting pharmacovigilance educators as a further key contemporary challenge.

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 European Union, Japan and the United States. The ICH has developed significant new guidelines for pharmacovigilance planning that are currently under active consideration for adoption in each of the major developed world jurisdictions of the pharmaceutical market (ICH, 2004). These guidelines suggest that marketing licensure might become conditional upon pharmacovigilance planning.

Actions in these pharmacovigilance plans are foreshadowed as extending well into, if not throughout the period of patent protection for pharmaceutical proprietors. 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.

It is to be hoped that these moves will be followed with steps to incorporate collection of the needed intra-class drug hazard/effectiveness data that will assist in colouring a more complete picture of key issues in pharmacovigilance.

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.

In this regard, a recent summary of 26 systematic reviews of the effects of continuing medical education on improving physician clinical care and patient health (Bloom, 2005) has 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 therefore need to constitute a new foundation for communication of the fruit of ongoing pharmacovigilance alongside 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, discussion of, and interaction about ADR reports becomes a matter of routine. Such arrangements need to be purposefully fostered. Multi-disciplinary 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 catalyse 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. In particular, such multidisciplinary groups have been in place amongst community-based practitioners in the Netherlands for more than 25 years and have proven themselves to be effective in gaining changes in history taking, communication with patients, follow-up decisions and drug prescribing (van Eijk *et al.*, 2001; Beyer *et al.*, 2003).

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. In particular, interactive audit and feedback requirements within continuing medical education programmes 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 PROGRAMMES

After many years as a concept being subjected solely to research, a considerable number of countries have now begun developing interactive, one-on-one public

interest-oriented academic detailing programmes for primary care practitioners. Such programmes 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 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 United Kingdom, Belgium, Canada and Australia. Generally speaking, these programmes have fostered supportive relationships with primary care practitioners, which have then spear-headed application of additional educational and behaviour-changing initiatives.

In Australia, a National Prescribing Service has been extending academic detailing-led programmes throughout the Australian continent. These programmes have aimed for the improvement of general practitioner (GP) discrimination in their use of pharmacotherapies as well as for overall better health outcomes (NPS, 2005). The GP-academic-detailer relationships have then been used to increase credibility and uptake of a range of other NPS-initiated practice improvement programmes.

The central approach taken in these service-oriented programmes has often been to deliver key clinical behaviour-change messages targeting achievement of the most judicious balance of benefit and risk associated with pharmacotherapies (May and Rowett, 2000). In this context, these public interest programmes 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 for the placement of constantly evolving evidence about risks and benefits of pharmaceuticals into a context of uncertainty. This context of scientific uncertainty then joins seamlessly with the professional's daily experience of uncertainty in their own clinical practice (McWhinney, 1997). Another of the central tenets of the academic detailing model is the acknowledgement

of both sides of controversial issues (Soumerai and Avorn, 1990).

This interactive presentation of pharmacovigilance messages stands in contrast with 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 reliably modulates individual clinical practice.

REMINDERS

The use of reminders was also characterized by Bloom as an additional effective interactive technique for achieving clinical practice professional behaviour 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 generally effective in issues such as drug dosage selection and also for providing general triggers for prudent monitoring of ongoing pharmacotherapies (Hunt *et al.*, 1998). An increasingly broad understanding is being gained of barriers to the use of such systems in routine clinical care: further improvement of their dovetailing into operational patterns of clinical care will increase their usefulness over time.

The potential for the integration of electronic cautionary notes into such systems offers a further 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). Such 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 deterministic nature 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 behaviour 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 subspecialisation.

Building onto these basic health sciences, pharmacotherapeutics education needs to be solidly grounded on principles of benefit and risk from drug therapies. This paradigm of benefit and risk 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 differing health professions in different settings will have different roles to play in this management process, the concept of benefit/risk management is fundamental to sound preparation 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 unexpurgated fashion. The real benefits to humanity from this enterprise need to be projected clearly in the context of the inevitable risks to health, which also accompany the benefits.

Coupled with the paradigm of benefits and risks of drug therapies, the undergraduate health professional needs to be instructed at the outset in the realities of both error and uncertainty in health care. Techniques for purposefully dealing with error and personally managing the breadth of uncertainty involved in ongoing healthcare practice need to be instilled 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 risks of medicines will always be viewed.

In this context, each of the professions participating in pharmacotherapy needs 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 benefits and risks from pharmacotherapy can 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 programmes for professionals working within the discipline of pharmacovigilance itself.

The International Society of Pharmacovigilance (ISOP: <http://www.isoponline.org>) is a non-profit organization whose stated aims are *to foster Pharmacovigilance both scientifically and educationally, and enhance all aspects of safe and proper use of medicines, in all countries*. Educational courses in pharmacovigilance principles are periodically available through ISOP, which acts as a key global meeting place for those specifically engaged in collecting, assessing and disseminating information about risks of medicines in broad use in whole populations.

Another organization having a rather broader remit for the evaluation of both benefits and risks of pharmacotherapies is the International

Table 49.1. Main content of the training programme developed by the Uppsala Monitoring Centre – WHO Collaborating Centre for International Drug Monitoring.

The aims and content of pharmacovigilance
Clinical aspects, pharmacology and epidemiology of ADRs
The practice of spontaneous reporting and running a pharmacovigilance centre
Use of the WHO database and other Uppsala Monitoring Centre resources
Connections with drug regulation, international harmonization and standardization
Principles of pharmacoepidemiology and the practice of other methods of research
Special fields such as vaccines, herbal remedies, dependence and quality defects
Literature sources
Benefit/harm assessment
Communication
Crisis management

Source: Adapted from Olsson S. (ed.) (1999). National Pharmacovigilance Systems. Uppsala: The Uppsala Monitoring Centre – WHO Collaborating Centre for International Drug Monitoring; 1999. Reproduced by permission of the Uppsala Monitoring Centre – WHO Collaborating Centre: Viewpoint: Watching for safer medicines Part 2. <http://www.who-umc.org/publ.html>.

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 and for the development of policy; education; and advocacy for the fields of pharmacoepidemiology and therapeutic risk management. ISPE has developed important guidelines for good pharmacoepidemiological practice (Epstein, 2005). Greater confidence can be placed in inferences drawn from observational studies of drug benefit and risk when such studies conform to these guidelines. The guidelines are now formally recognized in many countries by reference in Government regulatory requirements. International Society for Pharmacoepidemiology also provides periodic training courses and educational programmes both in sound pharmacoepidemiological methods and, more recently, in therapeutic risk management.

There are many other authorities that provide disciplined training for professionals who work specifically in the fields of pharmacovigilance and therapeutic risk management: e.g. the Drug Information Association (DIA: <http://www.diahome.org>); The United Kingdom Drug Safety Research Unit (DSRU: <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 (EMEA: <http://eudravigilance.emea.eu.int>) in collaboration with the DIA is now also providing train-

ing for pharmacovigilance professionals. These DIA programmes are particularly relevant for pharmacovigilance professionals who work 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 centre now located in Uppsala, Sweden, has since the 1960s been active in setting global operational standards for public health-oriented pharmacovigilance activities (WHO, 2004). Staff from this centre have developed benchmark training programmes, which since 1993 have inspired and fed the development of many national spontaneous ADR reporting systems around the world (Table 49.1).

Table 49.1 provides a summary of curricular materials included in training programmes of the Uppsala Monitoring Centre. These programmes are regularly delivered both in Sweden and also periodically in different parts of 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 and benefits of pharmaceuticals in individual patient care.

These developments have been propelled by the recent elaboration of significant harms that can be caused by health services in general and pharmaceuticals in particular.

The Erice Declaration of 1997 by the most respected figures associated with the field of pharmacovigilance clearly enunciated international aspirations for more effective communication of drug 'safety' information (Anon, 1998). However, as has been shown through expressions of deep public concern about recent 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 both risks 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 uncovered through good pharmacovigilance practice, it is necessary to place these messages within a framework acknowledging 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 pharmacotherapy) is especially relevant in this regard. A clear understanding of the nature and direction of the quality-in-healthcare field is going to become increasingly 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 aggregate clin-

ical 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 which 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.

It is notable that despite the fact that so many patient–physician interactions conclude with a prescription for pharmacotherapy being handed to the patient, relatively little attention is generally paid to sound training for this key clinical function. Prescribing of course is an action that prefigures the discipline of pharmacovigilance itself. Scrutiny of the conventional healthcare literature of the past 15 years reveals very little systematic investigation of the educational needs or determinants for the act of prescribing.

Whilst at least two published curricula are available for training prescribers (de Vries *et al.*, 1995; NPS, 2002), the systematic investigation of whether presumed 'appropriate' prescribing results in better or safer care remains in its infancy (Kazandjian, 2004; Paton and Lelliott, 2004). Indeed a persuasive case has been made by Dowie that the lack of an infallible, 'if–then' prescriptive basis for specific clinical decision-making will always confound attempts to associate better care with particular patterns of pharmacotherapy usage (Dowie, 2004).

However, it is clear that the paradigm of benefit and risk from pharmaceuticals, and the prudent management of these dimensions of drug effect now needs 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 risks from drug therapies.

Keeping or establishing pharmacovigilance education on these lines will enhance the impact that can be achieved by the discipline on the health of the public.

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Practical Experience in Teaching Pharmacovigilance

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PRACTICAL EXPERIENCE IN TEACHING PHARMACOVIGILANCE

A short course in Pharmacoepidemiology and Pharmacovigilance at the London School of Hygiene and Tropical Medicine was started in 1997, and the tenth course has just begun in 2006.

There are only a limited number of university-based examined courses in Europe in which pharmacovigilance is a major component. Another example is a flexible Masters course in Pharmacovigilance taught at the UK University of Hertfordshire, which can have components used to have diploma or certificate courses. This course largely uses external teachers.

The London School of Hygiene & Tropical Medicine (LSHTM) is Britain's national school of public health and a leading postgraduate institution in Europe for public health and tropical medicine. Part of the University of London, the London School is an internationally recognized centre of excellence in public health, international health and tropical medicine with a remarkable depth and breadth of expertise.

The LSHTM course is part-time and comprises 190 h (approximately 1 day per week) that are spent as follows: 70 h formal teaching and contact time, 70 h self-directed study and 50 h project work. Formal teaching takes place as three sessions of 3 or 4 days in a week (total 11 days) spread over 5 months. Examinations and a project are used to assess students, and there is a high, but not 100%, pass rate.

While LSHTM has a sizable active group of researchers studying adverse effects of medicines (over 30 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. Part of the course covers the historical and legal background of pharmacovigilance and pharmacoepidemiology, pharmacological basis of adverse drug reactions and the application of pharmacoepidemiological principles and methods to practical drug issues.

The experience of both teachers and participants seems to have been generally very positive. Students have come from a wide variety of backgrounds and

European countries, with numbers per year generally being about 10–20. In recent years, an increase in people coming from outside Europe, especially Africa, has been seen.

There is a need for more courses of this type, which give a recognized qualification, targeted at the special problems seen in areas like Africa.

A short ‘commentary’ was published in 2002 (Dunn and Thorogood, 2002) describing the

course, though it has developed further since that publication.

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Fatal Medication Errors and Adverse Drug Reactions – Coroners’ Inquests and Other Sources

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INTRODUCTION

Adverse drug events are harmful consequences from the therapeutic use of drugs. They include adverse consequences from reactions to drugs, adverse interactions between drugs and the harm that comes from medication errors. Some ambiguity arises from the term ‘adverse drug event’, as it is sometimes used to represent an adverse drug reaction (ADR).

The widely accepted definition of an ADR is ‘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’ (World Health Organization, 1972). Medication errors, i.e. errors in prescribing, drawing up and administering drugs, are a particularly important group of adverse drug events, because they are potentially preventable. The precise definition has

proved difficult, but we have previously suggested 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). ‘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 categorised as ‘preventable’ represent medication errors.

THE CONSEQUENCES OF ADVERSE DRUG EVENTS

Adverse drug events can cause considerable harm to a patient. They can even be fatal. However, fatal adverse events are relatively rare, and the proportion

of fatal cases in most spontaneous reporting schemes and post-marketing studies 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, health care providers and the health care 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 United States, which extrapolated from information obtained in two relatively restricted hospital surveys, excited a lot of media attention in 2000 when it suggested that as many as 98 000 deaths a year in the United States were because of 'medical error' (Kohn, Corrigan and Donaldson, 1999). Cases such as those of the young man Wayne Jowett, who died after the erroneous administration of intrathecal vincristine in place of intrathecal methotrexate, have also received wide press coverage and stimulated careful enquiry (Woods, 2001). In addition, the doctors who committed the medication error were charged with manslaughter, and one was convicted. This outcome is not unique, as the past decade has seen a marked increased in the number of legal proceedings being brought against doctors when their patients die because of a medical error (Ferner, 2000; Ferner and McDowell, 2006). Paradoxically, this censoriousness has come at the same time as a realisation 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). These views should lead to 'an open culture', where those who make errors readily admit to them, so that they can be avoided in future. Openness is a distant goal when doctors face conviction for manslaughter after errors lead to a patient's death.

Adverse events can also result from negligence, where medical staff clearly fall below the standards expected of them. 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 (Brennan *et al.*, 2004). One quarter of the patients who suffered an adverse event due to negligence died.

THE LITERATURE RELATING TO FATAL ADVERSE DRUG EVENTS

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 adverse drug events] 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, Pomeranz and Corey (1998) examined the evidence from 16 studies published between 1964 and 1995 and concluded that ADRs accounted for over 100 000 deaths in the United States in 1 year. This would mean that doctors and their treatments caused about 4% of all deaths. This study has, however, been criticised because there was a high risk of publication bias and a large amount 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 United States. He compared death certificates and the Food and Drug Administration's (FDA) spontaneous post-marketing 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 as because of 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 100-fold less than values based on extrapolations of data from surveillance programmes. His conclusion was that better and more comprehensive data are needed to develop appropriate health care 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 United Kingdom 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 1964–65, and 1% in 1981–85, 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 paediatric patients with epilepsy, the data are hard to interpret.

In Canada, Liu and colleagues (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, Furhoff and Holmberg (1979) scrutinised 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 sulphonamides.

Data from spontaneous ADR reporting schemes do, however, have manifold disadvantages when used to assess rates of fatal ADRs – a task they are not designed to perform. Usually the diagnostic criteria for an ADR are at the discretion of the reporter, who will rarely have assessed causality in a formal way. A small but variable proportion of reactions is 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 because of ADRs. Of the total cohort, 0.15% were adjudged to be admitted with an ADR of which they died (Pirmohamed *et al.*, 2004). In France, a multi-centre study by the French pharmacovigilance centres 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 computerised pharmaco-epidemiological surveillance system in Zurich was used to record adverse drug events prospectively and to categorise 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 generally suffer from several 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 publicised. 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, which does not prove a causal association in the specific instance. This is underlined by the fact that treatment with low-dose aspirin doubles the rate of gastro-intestinal haemorrhage. Put inversely, half of the episodes of gastrointestinal haemorrhage occurring in patients taking aspirin would have occurred even without the drug treatment.

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 adverse reactions, 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 in which the risks occur. 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. When the population incidence of a fatal reaction can be estimated, some idea of the community burden of deaths from adverse reactions can be gained. However, doctors and patients are more interested in the risk of a fatal reaction with a specific medicine. This risk cannot be estimated without data on the number of persons taking the medicine. Even then, the risk of an adverse reaction may be very different in subsets of the patient

population. For example, the risk of angioedema with an angiotensin-converting enzyme inhibitor is substantially greater in Afro-Caribbean patients than in Europid patients (McDowell, Coleman and Ferner, 2006).

STUDIES INVESTIGATING MEDICATION ERRORS AND ADVERSE DRUG EVENTS

The designs of the studies investigating ADRs varies and so too do those investigating adverse drug events 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 homes (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, Fleming and Whittington, 1987; Whittington, 1991), and the medical defence societies (Ferner, 1995) have alerted doctors to some of the dangers.

More recent systematic studies of medication errors have examined the incidence in various settings. Some studies have examined the overall incidence of adverse drug events and determined how many might have been prevented by judicious prescribing or administration of medicines. A systematic review of 10 studies of adverse drug events 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 adverse drug events (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 a 9-month study of 1247 residents of two long-term care facilities, Gurwitz and colleagues (2005) identified 815 adverse drug events, of which 338 (41%) were judged to be preventable. Four residents who suffered an adverse drug event died as a result. An examination of 447 fatal adverse drug events published in the pharmacy journal *Clin-Alert* defined 58% as ADRs and 17% as medication errors (Kelly, 2001). The American study by Gurwitz *et al.* (2003) investigated the incidence of ADEs 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 ADE and 0.022% died because of an ADE over the course of 1 year.

Numerous studies of different design and length, and in various different populations, have reported a considerable variation in the incidence of fatal adverse drug events. One additional source of information that is potentially useful for investigating the epidemiology of adverse drug events is the records kept by Coroners in England and Wales.

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 centre 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). Here, we present further data from the Birmingham and Solihull Coroner's Court for the period November 2001–June 2005.

There were significant differences in the collection and analysis of the data, most notably because Dr Richard Whittington, who was medically qualified, retired before the start of this third period, and Mr Aidan Cotter, a solicitor, became Coroner. Moreover, some of the processes have changed, as explained below. There also exists the possibility that the two Coroners might differ in their verdicts on the same set of facts, so that one might categorise a case as because of an adverse drug event, 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.

SEARCH STRATEGIES

In the first series, we searched a classified card index for entries for contraception, dental deaths, drug therapy, operations plus anaesthesia, drug idiosyncrasy, mischance, accident, misadventure and medical mishap. We did not include deaths due to anaesthetic technique in the search.

In the second series, a computer database, which held an index of cases since 1995 was used, in addition to the classified card index. We searched the database using the terms 'therapeutic/accident', 'therapeutic/misadventure', 'medical mishap' and 'medical misadventure'.

For this current series, we hand searched the Coroner's determination, i.e. the official recording of the facts and verdict, to identify any deaths that mentioned a drug in the case description, the cause of death or the Coroner's verdict. We excluded cases in which illegal drugs were used and where the patient had taken a deliberate overdose of a drug, as in previous periods. We also excluded cases where an open verdict was returned.

RESULTS

1986–91

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. Non-steroidal 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.

2001–05

Hand searching of all the determinations of the Coroner's inquests from November 2001 to June 2005 identified 43 cases of death due to adverse drug events of 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 drug events were related to NSAIDs.

The details of the eight 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 centre 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. Thirty-six hours 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 centre, 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 haemorrhage underwent carotid angiography. Staff failed to recognise that no contrast medium (a clear, colourless 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 melaena and was presumed to have had acute gastrointestinal bleeding. Intravenous vitamin K was given because his international normalised ratio (INR) was increased. (The INR is a

measure of blood clotting where 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 ischaemic attacks. There was no history of peptic ulcer. Her warfarin (1 mg daily) was continued, and 1 month after admission, she was started on 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 haemorrhage 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 computerised tomography (CT) scan showed an acute haemorrhage 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 effect of warfarin, which is no longer effectively metabolised, and reducing the production of vitamin K-dependent clotting factors, which are synthesised 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 sudden onset of

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 2 doses of a prescribed medication'.

Comment: This case illustrates the danger of omitting potentially life-saving treatment.

OVERALL SUMMARY OF THE THREE SERIES

Table 50.1 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 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 adverse drug events over the course of the three series are presented in Table 50.2. 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

Table 50.1. General summary of the three series.

	1992 to June 1986–91	2000	November 2001 to June 2005
Population	11 90 000 (in 1986)	12 10 000 (in 1991)	13 20 000 (in 2004)
Deaths			
<i>n</i>	86 235	1 05 900	41 648
Per year	14 373	12 459	11 359
Coroner's inquests			
<i>n</i>	3277	4502	3366
Per year	546	530	918
Drug-related deaths			
<i>n</i>	46	40	43
Per year	8	5	12
Which were because of error or error related	10	16	7

Table 50.2. Drugs associated with fatal adverse drug 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)
Azaproazone + 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)
Dihydrocodeine, pethidine and diamorphine		Methadone
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		Anaesthesia
Spironolactone		Sildenafil
Suxamethonium		Carbamazepine
Unknown		Methyldopa
		Imatinib
		Streptokinase
		Spironolactone

is a significant increase in the number of deaths that is associated with warfarin. Table 50.3 demonstrates the increase in warfarin-associated deaths identified in the Coroner's inquests since 1986. Over the course of a 10-year period (1986–95), 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 United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) and the Committee

on Human Medicines (CHM) through the Yellow Card scheme.

This 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 50.1). When the data from the Yellow Card scheme are plotted alongside the number of warfarin prescriptions, a strong positive correlation is observed between the

Table 50.3. Number of deaths associated with warfarin identified by the Birmingham and Solihull Coroner and reported to the MHRA and CHM through the Yellow Card scheme from 1986 to June 2005.

Time period	Number of deaths identified by Birmingham and Solihull Coroner's inquests	Number of 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

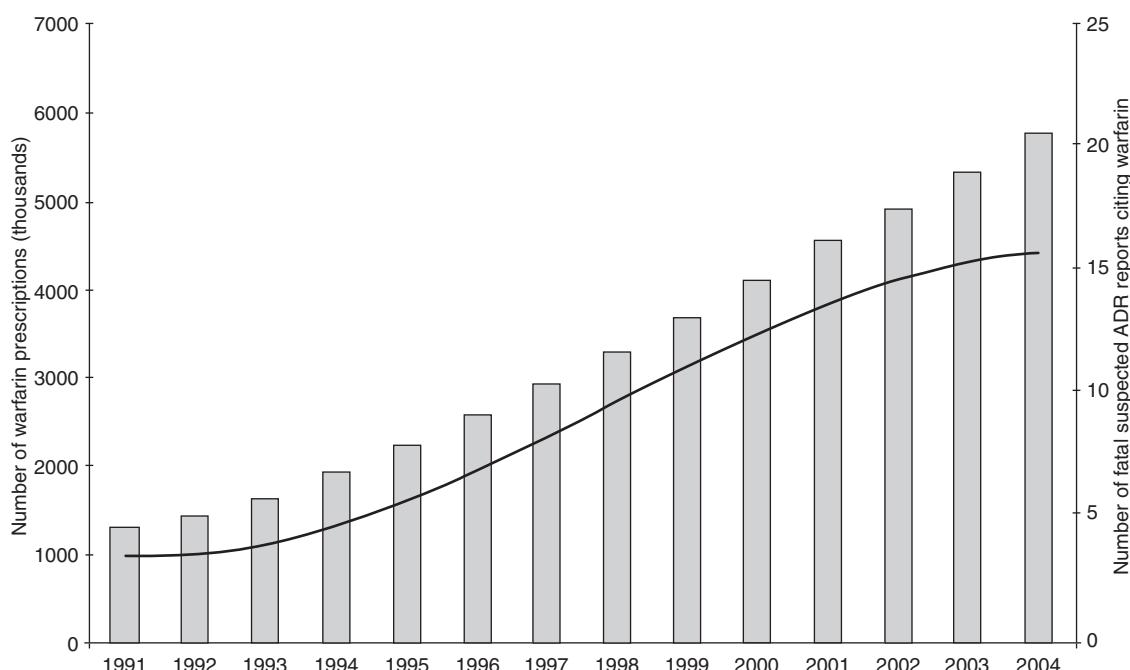


Figure 50.1. Trends in fatal suspected ADR reports to the MHRA and CHM citing warfarin (black line) and warfarin prescriptions (grey bars).

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 is, however, 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'. 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 difference 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.

THE LESSONS FROM DEATHS RELATED TO MEDICATION

Previous studies have highlighted slips as a major cause of medication errors (Koren, Barzilay and Greenwald, 1986). 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 emphasises 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 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 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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Pharmacogenetics and the Genetic Basis of ADRs

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INTRODUCTION

Health care providers and patients have long recognized that people often respond differently to the same medicine, both in terms of efficacy and ‘side effects’, or adverse drug reactions (ADRs). There are many factors that contribute to this inter-individual variability in response to medications, including the pathogenesis and severity of the disease being treated; concomitant medications and drug interactions; and the patient’s age, renal and liver function, concomitant illnesses, nutrition and lifestyle (smoking, alcohol use, weight and fitness) (Meyer, 2000). Genetic factors that affect the kinetics and dynamics of drugs play an even greater role in determining an individual’s risk of non-response or toxicity (Evans and Relling, 1999). Although it is difficult to define the relative contribution of genetic and environmental effects in an individual, it is clear that variation in genes coding for drug-metabolizing enzymes, drug transporters and drug receptors and targets accounts for a significant portion of the observed heterogeneity in drug response across populations.

The study of ADRs has been hampered by the use of ambiguous and inconsistent terminology and reporting. Edwards and Aronson (2000) proposed the following definition of an ADR: ‘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, alteration of the dosage regimen, or withdrawal of the product’. ADRs may result from health care provider, pharmacy or patient error or from a variety of genetic and environmental factors. Although definitions and figures vary, it is clear that ADRs are a significant cause of morbidity, mortality and health care expense. Lazarou, Pomeranz and Corey (1998) performed a meta-analysis of 39 prospective studies from US hospitals and found that 6.7% of inpatients have a serious ADR while hospitalized, resulting in 106 000 deaths per year. Johnson and Bootman (1995) used a cost of illness model to address the drug-related morbidity and mortality in the ambulatory care setting in the US from data collected in the early 1990s. Their estimate of the costs of adverse events

was \$76B/year. Ernst and Grizzle (2001) updated the estimates using data published since the 1995 study and updated values for May 2000 in dollars. Their estimates for the cost of drug-related morbidity and mortality exceeded \$177.4B in 2000. Pirmohammed *et al.* (2004) conducted a prospective analysis of all admissions to two general hospitals in the United Kingdom. They found that 6.5% of all hospital admissions were due to an adverse event and that the adverse event directly led to the hospitalization in 80% of the cases. They projected the annual cost of such admissions to the National Health Services to be \$847M. The overall fatality rate was 0.15% and the most common drugs implicated were aspirin, diuretics, warfarin and non-steroidal anti-inflammatory drugs. GI bleeding was the most common reaction.

The number, severity and cost of ADRs is now recognized as a significant public health issue and has triggered interest in discovering what causes them and if and how their occurrence can be predicted and prevented. In this chapter, we will focus on the current state of knowledge regarding the genetic basis of ADRs and the important role that pharmacogenetics will play in meeting the ultimate goal of providing safer, more effective medicines.

PHARMACOGENETICS

Pharmacogenetics is the study of genetic factors related to human variability in response to medicines. Its modern root lies in the work of Archibald Garrod, whose work on alcaptonuria in 1902 comprised the first proof of Mendel's laws of genetics in humans. Garrod hypothesized that adverse reactions after drug ingestion could result from genetically determined differences in bio-chemical processes and further suggested that enzymes play a role in the detoxification of foreign substances and that the lack of an enzyme in an individual might cause that mechanism to fail (Garrod, 1902).

Incidental clinical observations during the late 1940s and 1950s resulted in the discovery of several relatively common genetic variations related to ADRs. Hemolysis related to anti-malarial treatment was much more common among African-American soldiers during World War II, leading to the identification of inherited variants of glucose-6-phosphate

dehydrogenase (G-6-PD). Prolonged muscle relaxation and apnea after suxamethonium was found to be caused by an inherited deficiency of a plasma cholinesterase. Peripheral neuropathy was observed in a significant number of patients treated with the anti-tuberculosis drug isoniazid, leading to the identification of genetic differences in acetylation pathways.

The genetic variations related to these observations are called polymorphisms-inter-individual differences in DNA sequences at a specific chromosomal location that exist at a frequency of more than 1% in the general population. The two *alleles* (alternate forms of a gene) present at a given gene locus comprise the *genotype*, which now can be characterized at the DNA level. The progress of The Human Genome Project and advances in genomic technology enhance the likelihood that genetic markers that predict a percentage of adverse events, including lack of efficacy will be identified, validated and offered to the public in the next 5–10 years.

The influence of genotype on *phenotype* (observable features resulting from the action of one or more genes) – in this case, the influence of genes on drug kinetics or dynamics – now can be measured using advanced analytical methods for metabolite detection and clinical investigation tools such as receptor-density studies by positron emission tomography (Meyer, 2000).

The FDA approved the first commercially available kit to measure some P450 polymorphisms in 2004, thus moving the delivery of genetic tests that can affect drug response to be more readily available to clinical practice.

Pharmacogenetic mechanisms related to polymorphisms can result in clinically relevant sequelae in at least three ways:

- through genes associated with altered drug metabolism and transport: increased or decreased metabolism of a drug can affect the concentration of the drug and its active, inactive and toxic metabolites (e.g. metabolism of tricyclic anti-depressants),
- through genes associated with unexpected drug effects (e.g. haemolysis in G-6-PD deficiency) and
- through genes associated with genetic variation in drug targets, resulting in altered clinical response and frequency of ADRs (e.g. β_2 -adrenergic receptor variants and altered response to β_3 -agonists in asthmatic patients) (Meyer, 2000).

Inherited variations related to drug metabolism generally are monogenic (single gene) traits, and their clinical relevance in terms of pharmacokinetics and dynamics depends on their importance for the activation or inactivation of drug substrates (Evans and Relling, 1999). The most important effects include toxicity for medicines that have a narrow therapeutic window and are inactivated by a polymorphic enzyme (e.g. thioguanine, fluorouracil, mercaptopurine and azathioprine) and decreased efficacy of medicines that require activation by an enzyme that exhibits a polymorphism (e.g. codeine). These variant genes and the enzymes they code for also may be involved in some drug–drug interactions. Most of these monogenic traits have been identified on the basis of dramatic observed differences in response (efficacy and toxicity) among individuals. Although still not in common clinical use, functional enzyme analyses or genotyping to detect some of the common monogenic traits affecting drug metabolism are beginning to be used more frequently, especially in the field of cancer chemotherapy (Iyer and Ratain, 1998; Mancinelli, Cronin and Sadee, 2000).

The FDA has begun to include more pharmacogenetic data into the drug labels of medicines. According to Dr. Larry Lesko, 35% of all drugs have some pharmacogenetic data included in their drug label. In 2003–04, the labels of several medicines were modified to reflect the risks associated with certain genotypes. Azathioprine, 6-mercaptopurine, thioguanine and irinotecan have information about genotype effects on drug safety in their labels. Thioridazine has a black box warning related to P450 2D6 poor metabolizers. Strattera, a drug for attention deficit hyperactivity disorder also lists the drug–genotype interaction prominently in its drug label.

Although these monogenic traits affecting drug metabolism are important, the overall pharmacologic effects of drugs are more likely to be related to the interaction of several genes (*polygenic*), all encoding proteins that are involved in multiple pathways of metabolism, transport, disposition and action (Evans and Relling, 1999). These polygenic traits, which also may play a role in drug–drug interactions, are more challenging to uncover during clinical trials, especially when the mechanisms of drug metabolism and action are unknown. In contrast with the past, when clinical observations of individual differences in drug

response prompted biochemical and genetic research into the underlying causes, recent advances in molecular sequencing technology may reverse that process: laboratory identification of polymorphisms (especially those in gene regulatory or coding regions) may be the initiating observation, followed by biochemical and human studies to ascertain their phenotypic and clinical consequences (Evans and Relling, 1999).

Continued research in pharmacogenetics has the potential to result in the elucidation of the genetic basis of drug metabolism, disposition and response. In some cases, the results of research may provide clinicians with the ability to subclassify patients using pharmacogenetic-based diagnostic criteria. If research efforts are successful, then it will become possible, in many circumstances, to select medicines and determine appropriate dosing on the basis of an individual patient's inherited ability to metabolize and respond to specific drugs, thus reducing the enormous individual, societal and economic burdens currently related to treatment failures and ADRs.

The US National Institute of General Medical Sciences (NIGMS) and other components of the National Institutes of Health (NIH) are sponsoring a major research initiative, the Pharmacogenetics Research Network, to reach this goal. This network, established in 2000, initially comprised nine teams of investigators across the United States, with research projects including asthma treatments, tamoxifen and other cancer drugs, ethnic differences in response to anti-depressants, drug transporters, database design and ethical, legal and social ramifications of pharmacogenetic research (<http://www.nigms.nih.gov/PGRN.Network/Pharmacogeneticworkinggroup.htm>).

THE GENETIC BASIS OF ADRS

POLYMORPHISMS AFFECTING DRUG METABOLISM

Most drugs are degraded through a limited number of metabolic pathways, most of which involve microsomal hepatic enzymes. Ingelman-Sundberg *et al.* (1999) reported that about 40% of this human cytochrome (CYP) P450-dependent drug metabolism is carried out by polymorphic enzymes capable of altering these metabolic pathways. The CYP P450

monooxygenase system of enzymes detoxifies xenobiotics and activates procarcinogens and promutagens in the body through oxidative metabolic pathways. These enzymes play an important role in the elimination of endogenous substrates (such as cholesterol) and lipophilic compounds [such as central nervous system (CNS) drugs that cross the blood-brain barrier], which otherwise tend to accumulate to toxic concentrations. This very large and well-studied gene family consists of many isoforms – for example over 70 variant alleles of the CYP2D6

locus have been described (Ingelman-Sundberg *et al.*, 1999). The distribution of variant alleles for these enzymes differs among ethnic and racial subpopulations, with significant implications for clinical practice in various areas (Table 51.1). Alleles causing altered (enhanced or diminished) rates of drug metabolism have been described for many of the P450 enzymes, and the underlying molecular mechanisms have been identified for some. Table 51.2 summarizes some clinically significant polymorphisms affecting drug metabolism and the drugs and drug effects associated

Table 51.1. Population distribution of selected polymorphic drug-metabolizing enzymes.^a

Enzyme	Major polymorphisms	Functional consequences	Allele frequency (%)			
			Caucasian	Asian	Black African	Ethiopian and Saudi Arabian
CYP2A6	CYP2A6*2	Inactive enzyme	1–3	0		
	CYP2A6del	No enzyme	1	15		
CYP2C9	CYP2C9*2	↓ Affinity for P450 oxidoreductase	8–13	0		
	CYP2C9*3	Altered substrate specificity	6–9	2–3		
CYP2C19	CYP2C19*2	Inactive enzyme	13	23–32	13	14–15
	CYP2C19*3	Inactive enzyme	0	6–10	–	0–2
CYP2D6	CYP2D6*2xN	↑ Enzyme activity	1–5	0–2	2	10–16
	CYP2D6*4	Inactive enzyme	12–21	1	2	1–4
	CYP2D6*5	No enzyme	2–7	6	4	1–3
	CYP2D6*10	Unstable enzyme	1–2	51	6	3–9
	CYP2D6*17	↓ Substrate affinity	0	–	34	3–9
N-acetyl-transferase 2	NAT2	↓ Function	40–70	10–20	50–60	

^a Compiled from Ingelman-Sundberg *et al.* (1999), Meyer (2000) and references therein.

Table 51.2. Selected polymorphic enzymes associated with altered drug response.^a

Enzyme	Variant phenotypes	Selected drugs	Altered response
CYP2D6	Ultra-rapid metabolizers Poor metabolizers Extensive metabolizers	Anti-arrhythmics (some) Anti-depressants (some) Anti-psychotics (some) Opioids β -Adrenoreceptor antagonists (some) Debrisoquin Dextromethorphan Guanoxan Sparteine Phenformine Phenacetin	Poor: ↑ risk of toxicity Ultra-rapid: ↓ efficacy

Table 51.2. *Continued.*

Enzyme	Variant phenotypes	Selected drugs	Altered response
CYP2C19	Poor and extensive hydroxylators	Mephenytoin Hexobarbital Omeprazole Proguanil Diazepam Warfarin Tolbutamide Glipazide Phenytoin Non-steroidal anti-inflammatories Imipramine Losartan Nicotine	Poor: ↑ risk of toxicity Extensive: ↓ efficacy
CYP2C9	Poor metabolizers		↑ Response and risk of toxicity
CYP2A6	Poor nicotine metabolizers		Possibly ↓ risk of addiction
N-acetyltransferase 2	Slow and rapid acetylators	Isoniazid Sulfamethazine Procainamide Amonifide Dapsone Sufasalazine Paraminosalicylic acid Heterocyclic amines (food mutagens) 6-Mercaptopurine	Slow: ↓ clearance and ↑ risk of toxicity, including toxic neuritis, lupus erythematosus, bladder cancer Rapid: ↓ efficacy, ↑ risk of toxicity in some cases (amonifide); colorectal cancer
Thiopurine methyltransferase	Poor TPMT methylators	6-Thioguanine Azathiopurine 5-Fluorouracil	Bone marrow toxicity, liver damage
Dihydropyrimidine dehydrogenase	Slow inactivation		↑ Risk of toxicity
Plasma pseudocholinesterase	Slow ester hydrolysis	Succinylcholine	Prolonged apnea
Aldehyde dehydrogenase	Rapid and slow metabolizers	Ethanol	Slow: facial flushing
Catechol O-methyltransferase	Poor and rapid methylators	Levodopa Methyldopa	Poor: increased efficacy
Glucose-6-phosphate dehydrogenase	Poor metabolizers	Primaquine	Poor: increased efficacy Haemolysis
UGT-glucuronosyltransferase	Poor metabolizers	Irinotecan	Myelosuppression and diarrhoea

^a Compiled from Ingleman-Sundberg *et al.* (1999), Meyer (2000), Evans and Relling (1999), Sadee (2000), Mancinelli *et al.* (2000) and references therein.

with them; a comprehensive summary is available at <http://www.hapmap.org/cgi-perl/gbrowse/gbrowse>. Continuously updated descriptions of these alleles and accompanying references can be found at <http://www.imm.ki.se/CYPalleles/>.

CYP2D6, which encodes debrisoquin hydroxylase, was the first of these enzyme-coding genes to be cloned and characterized, and it remains among the most studied. It is involved in the metabolism of many commonly used drugs, including tricyclic anti-depressants, neuroleptics, anti-arrhythmics and other cardiovascular drugs and opioids. Variant alleles may differ from the wild-type (normal) gene by one or more point mutations, gene deletions, duplications, multiduplications or amplification. These may have no effect on enzyme activity or may code for an enzyme with reduced, absent or increased activity. The genetics and related biochemistry of these pathways are still being elucidated and are more complex than the following simplistic descriptions imply. *Extensive metabolizers*, representing 75%–85% of the general population, are homozygous or heterozygous for the wild-type, normal activity enzyme. *Intermediate* (10%–15% of the population) and *poor* (5%–10%) *metabolizers* carry two reduced or loss-of-activity alleles. These individuals are likely to exhibit increased drug plasma concentrations when given standard doses of drugs are metabolized by this enzyme; this functional overdose results in increased risk of dose-dependent ADRs associated with these drugs. These individuals also are likely to experience lack of efficacy with prodrugs that require activation by this enzyme; lack of morphine-related analgesic response to the prodrug codeine is one example. *Ultrarapid metabolizers* (1%–10%) carry duplicated or multiduplicated active genes; they will metabolize some drugs very rapidly, never achieving a therapeutic plasma drug concentration (and hence expected efficacy) at a standard dose. Alternately, an ultrarapid metabolizer-given codeine may experience an ADR usually associated with morphine because of the increased conversion of prodrug to active drug; this often is true of active metabolites, as well.

Two variant alleles of CYP2C9, which result in reduced affinity for P450 oxidoreductase or altered substrate specificity, are associated with increased risk of haemorrhage with standard doses of the anti-coagulant warfarin. The clearance of *S*-warfarin

in patients who are homozygous for one of the polymorphisms is reduced by 90% compared with patients who are homozygous for the wild-type allele (Ingleman-Sundberg *et al.* 1999). Similar reductions in drug clearance related to one of these polymorphisms have been documented with other CYP2C9 substrates such as ibuprofen and naproxen (non-steroidal anti-inflammatories), phenytoin (anti-epileptic), tolbutamide (hypoglycemic/anti-diabetic) and losartan (angiotensin II receptor antagonist) (Daly, 1995). The high frequency of these polymorphisms (up to 37% of one British population was heterozygous for one mutant CYP2C9 allele) and the severity of the potential ADR (haemorrhage with warfarin treatment) make this an important consideration in the selection and dose of warfarin and other affected drugs.

A second important polymorphism affecting the safety of warfarin was reported by Rieder *et al.* (2005). They reported that variants in the gene encoding Vitamin K epoxide reductase complex 1 (VKORC1) explained 25% of the variance in warfarin dose. The effect was three times that of CYP2C9.

Patients who are homozygous for the null allele of CYP2C19 (poor metabolizers) are extremely sensitive to the effects of omeprazole (anti-ulcer), diazepam (anti-anxiolytic), propranolol (β-blocker), amitriptyline (tricyclic anti-depressant) and other drugs (Touw, 1997). CYP2C19 also is involved in the oxidation of the anti-malarial prodrug proguanil to cycloguanil, although it is unknown whether the polymorphism relates to its anti-malarial effects. The frequency of this polymorphism (3%–6% in Caucasians and 8%–23% in Asians) defines it as clinically significant. Polymorphic alleles have been identified for several Phase II (conjugation) enzymes, and many of these are as important in drug metabolism as those associated with the Phase I (oxidation) enzymes discussed above. *N*-acetyltransferase 2, sulfotransferases, glucuronosyltransferases, catechol *O*-methyltransferase, dihydropyrimidine dehydrogenase (DPyDH) and thiopurine methyltransferase (TPMT) are among the Phase II enzymes known to have clinically significant effects on drug metabolism (Mancinelli, Cronin and Sadee, 2000); some of these are summarized in Table 51.2. Polymorphisms of genes coding for these enzymes are particularly relevant in cancer chemotherapy (severe toxicity for

homozygotes of null alleles of TPMT with thioguanine and azathioprine treatment and of DPYDH with 5-flourouracil treatment) and the treatment of Parkinson's disease with L-dopa (low methylators have an increased response to the drug).

POLYMORPHISMS AFFECTING DRUG TRANSPORT

Although cellular uptake of some drugs occurs through passive diffusion, membrane transporters also play a role in the absorption of medicines through the intestines, their excretion into bile and urine and their uptake into sites of action (such as brain, testes and cardiovascular tissue; tumour cells; synaptic cleft and infectious microorganisms) (Evans and Relling, 1999). Increasing attention is being focused on the possible role of polymorphisms of genes encoding drug transporters, some of which are summarized in Table 51.3.

One example of a transporter with relevance to drug response is *p*-glycoprotein (Pgp), an ATP-dependent transmembrane efflux pump that serves to extrude numerous drugs and other substances out of cells. Pgp is coded for by the multidrug resistance locus, MDR-1. Hoffmeyer *et al.* (2000) reported that a specific polymorphism, present in homozygous form in 24% of their Caucasian sample population, correlated with expression levels and function of MDR-1. Homozygous individuals had significantly lower

MDR-1 expression and exhibited a 4-fold increase in plasma digoxin concentration after a single oral dose of the drug. Other substrates of Pgp include important drugs with narrow therapeutic indices, such as chemotherapeutic agents, cyclosporin A, verapamil, terfenadine, fexofenadine and most HIV-1 protease inhibitors (Meyer, 2000). In addition, over-expression of MDR-1 in cancer tumours has been associated with resistance to adriamycin, paclitaxel and other anti-neoplastic agents, and additional similar extrusion pumps are reported to contribute to drug resistance in various tumours (Sadée, 2000). Unfortunately, using Pgp to predict response has not been as successful as originally hoped.

Another potentially important gene family with a number of reported variants that may affect function is that of the biogenic amine transporters, which play a role in the regulation of neurotransmitter concentrations (including serotonin, dopamine and GABA) in synaptic transmission (Jonsson *et al.*, 1998). These transporters are the direct target receptors for many drugs such as anti-depressants and cocaine; polymorphisms of the serotonin transporter, in particular, have been associated with the modulation of complex behaviour (Heils, Teufel and Petri, 1996) and may play a role in treatment with specific serotonin transporter inhibitors.

Mutations in other transporter-like proteins such as the sulfonylurea receptor (SUR) that regulates ATP-sensitive K⁺ channels and insulin secretion and

Table 51.3. Selected polymorphisms of drug transporters, receptors, targets and disease genes associated with altered drug response.^a

Drug transporter, receptor or target	Variant phenotype	Drugs	Altered response
Multidrug resistance protein MDR-1	Overexpression in tumours	Adriamycin Paclitaxel Other anti-neoplastics Digoxin	Resistance to treatment
	Low tissue expression	Anti-neoplastics Verapamil Terfenadine Fexofenadine Protease inhibitors (most) Albuterol	Possibly ↑ plasma drug concentration, risk of toxicity
β2 adrenergic receptor	↑ Receptor downregulation		↓ Response, poor control of asthma

(continued)

Table 51.3. *Continued.*

Drug transporter, receptor or target	Variant phenotype	Drugs	Altered response
5-HT2A serotonergic receptor	Multiple	Ventolin Clozapine	Variable drug efficacy
Sulphonylurea receptor (SUR1)	Altered β -cell ATP-dependent potassium channel activity	Tolbutamide	\downarrow Insulin response
HER2 receptor	Overexpression in some breast and other cancers	Trastuzumab	Receptor overexpression associated with \uparrow drug efficacy
Thymidylate synthase and dihydrofolate reductase	Overexpression in some tumour cells	5-Fluorouracil methotrexate	Overexpression linked to development of resistance to drug anti-metabolites in tumour cells
Cardiac ion channels (HERG, KvLQT1 and hKCNE2)	Delayed cardiac repolarization	Quinidine Cisapride Terfenadine Disopyramide Meflaquine Clarithromycin Pravastatin	Long Q-T syndrome, arrhythmias, torsade de pointes Polymorphisms associated with atherosclerosis progression and response to pravastatin
Cholesteryl ester transport protein (CETP), lipoprotein lipase (LDL) and β -fibrinogen Apolipoprotein E4		Tacrine Simvastatin	Presence of allele predicts poor response to tacrine, reduced cardiovascular mortality with simvastatin

^a Compiled from Ingleman-Sundberg *et al.* (1999), Meyer (2000), Evans and Relling (1999), Sadee (2000) and Manicelli *et al.* (2000) and references therein.

nuclear factors such as hepatocyte nuclear factor-1 alpha and factor-1 beta are being studied both for their role in aetiology of disease and response to therapy. Pearson *et al.* (2004) reported on an elegant study to evaluate the metabolic picture and response to metformin in patients with type 2 diabetes and maturity onset of the young caused by mutations in either HNF-1 alpha and HNF-1 beta.

POLYMORPHISMS AFFECTING DRUG RECEPTORS AND TARGETS

Many drugs interact with specific targets such as receptors, enzymes and other proteins involved with

cell cycle control, signal transduction and other cellular events. Genes encoding these targets occur in polymorphic forms that may alter their pharmacologic response to specific medicines. For example, variants affecting β -adrenergic receptors are a major determinant of β -agonist bronchodilator (e.g. albuterol) response in asthmatic patients. A specific common polymorphism has been linked to increased β receptor down-regulation in response to treatment with albuterol, which may result in decreased drug efficacy and duration of action (Tan *et al.*, 1997; Liggett, 2000). However, other studies have failed to show the expected correlation between the variant and clinical response (Lipworth *et al.*, 1999).

Drysdale *et al.* (2000) suggested that specific *haplotypes* (the array of alleles on a given chromosome) may have greater predictive value regarding response to β -agonist bronchodilators than the presence of individual polymorphisms. They reported marked variation in the ethnic distribution of the most frequently observed haplotypes (>20-fold differences) and in the mean β -agonist responses by haplotype pair (>2-fold differences). These authors suggested that the interactions of multiple polymorphisms within a haplotype may affect biologic and therapeutic phenotypes and that haplotypes may be useful as pharmacologically relevant predictive markers.

Arranz *et al.* (2000) completed a comprehensive study of variants in multiple neurotransmitters and receptors in 200 schizophrenic patients. They reported that a set of six sequence variants involving the 5-hydroxytryptamine (serotonin) receptor, the histamine receptor (H₂) and the promoter region of the serotonin transporter gene successfully predicted response to treatment with clozapine (a neuroleptic) in 76% of patients, with a sensitivity of 95% for satisfactory response. Several of these individual polymorphisms had been previously studied in this context, but with inconsistent findings. If the results of this retrospective study are prospectively validated, then they will form the basis of a simple test to optimize the usefulness of this expensive drug in a heterogeneously responsive group of patients.

The risk of drug-induced long QT syndrome, a cause of sudden cardiac death in individuals without structural heart disease, has been linked to five gene variants, each encoding structural subunits of cardiac ion channels that affect sodium or potassium transport and are affected by anti-arrhythmics and other drugs (Priori *et al.*, 1999). Priori *et al.* (1999) reported that a significant number of individuals carry 'silent mutations' of these genes; the resulting alterations are insufficient to prolong the QT interval at rest, but affected individuals may be especially sensitive to any drug that affects potassium currents. The combination of these silent mutations with even modest blockade induced by a variety of drugs used for many purposes can result in prolongation in action potential that is sufficient to trigger the onset of a serious ventricular arrhythmia (torsade de pointes). Roden and his colleagues, however, found less than 10% of patients suffering from drug-induced long QT actually had any of the known mutations

associated with familial long QT syndrome (Yang *et al.*, 2002).

Polymorphisms affecting steroid hormone nuclear receptors may affect individual response to drugs and hormones. For example, glucocorticoid resistance in asthma patients has been associated with increased expression of the glucocorticoid receptor 3-isoform (Sousa *et al.*, 2000); activating mutations of the mineralocorticoid receptor have been linked to hypertension exacerbated by pregnancy (Geller *et al.*, 2000) and dominant negative mutations of peroxisome proliferator-activated receptor gamma (PPAR gamma) have been associated with severe insulin resistance, diabetes mellitus and hypertension. Huizenga *et al.* (1998) identified a polymorphism affecting the glucocorticoid receptor that was present in 6% of their elderly study population. These individuals appeared healthy but exhibited increased sensitivity (reflected in cortisol suppression and insulin response) to exogenously administered glucocorticoids. The authors postulated that this increased lifelong sensitivity to endogenous glucocorticoids might be reflected in the observed trends towards increased body mass index and decreased bone mineral density in affected individuals. This polymorphism also may be related to the development of early or serious ADRS with exogenous glucocorticoid treatment in carriers, but this has not yet been established.

Some investigators have reported a relationship between variants in the angiotensin converting enzyme (ACE) gene and individual sensitivity to ACE inhibitors such as enalapril, lisinopril and captopril, but the results reported by other teams fail to show an association, so this finding remains to be confirmed (Navis *et al.*, 1999).

The beta adrenergic receptor is the target for drugs used to treat asthma, hypertension, and heart failure. Two polymorphisms appear to have an effect on some drugs for the treatment of asthma as well as risk of heart failure.

Small *et al.* (2002) reported that African Americans were at significantly greater risk of developing heart failure if they carried a single copy of the $\alpha 2c$ deletion of the adrenergic receptor. In animal models, this deletion results in an ineffective form of the receptor and higher norepinephrine levels. When combined with the 'hyperfunctioning' 389 mutation, the risk was multiplied several fold. The $\alpha 2c$ deletion is more common in African Americans, and the authors

hypothesize that this may be the reason for higher rates of heart failure in African Americans. The numbers in the study were smaller for Caucasians and did not result in a statistically significant risk. Hajjar and MacRae (2002) in their editorial accompanying this paper warn that the data must be replicated to be considered.

POLYMORPHISMS RELEVANT TO CANCER CHEMOTHERAPY

The basis of many forms of cancer chemotherapy involves the administration of maximum tolerated dosages with the goal of inflicting the greatest damage to malignant cells while causing the least damage to normal tissue. Genetic variations of drug-inactivating enzymes in normal tissues may increase the risk of severe toxicity or even death. As mentioned above, TPMT-deficient (homozygous; ~0.3% of the population) individuals treated for acute lymphoblastic leukaemia with standard doses of mercaptopurine, thioguanine and azathioprine (immunosuppressant) may experience severe and potentially lethal bone marrow toxicity. A dose reduction of up to 15-fold may be needed to avoid haematotoxicity in these patients (Evans *et al.*, 1991). TPMT genotyping or phenotyping (by assessing red blood cell enzyme levels) before the institution of therapy with any of these agents has become accepted practice at some medical centres (Sadee, 2000).

Several similar examples have been documented (Iyer and Ratain, 1998): patients with variant DPYDH cannot inactivate 5-fluorouracil, resulting in myelosuppression and neurotoxicity, while overexpression of DPYDH in tumours is linked to resistance to that drug; N-acetyltransferase-2 rapid acetylators (30%–60% of Caucasians and 80%–90% of Asians) are at risk of greater bone marrow toxicity with amonafide treatment (topo-isomerase II inhibitor), and patients who have a genetic deficiency of glucuronidation because of a variant promoter of UGT-glucuronosyltransferase UGTIA1 are at increased risk of myelosuppression and diarrhoea when treated with the topoisomerase I inhibitor irinotecan. At least one example of an *activating* variant of a co-factor/enzyme has been reported: mutations of NAD(P)H (nicotinamide-adenine dinucleotide phosphate, reduced form) : quinone oxidoreductase (which

activates cytotoxic anti-tumour quinones such as mitomycin C) protect against cytotoxic metabolites but also may reduce anti-tumour efficacy (Gaedigk *et al.*, 1998).

Growth factor receptors may be overexpressed in some tumours, potentially affecting the efficacy of chemotherapy. One example of this involves the humanized monoclonal antibody trastuzumab (HerceptinTM), which was designed to target an oncogene (HER2/neu) that is overexpressed in some breast cancers and other cancers with poor prognoses. Trastuzumab, when given with paclitaxel and doxorubicin, enhances the cytotoxic effects of the anti-neoplastic agents in breast cancer tissues with high HER2/neu expression. Some researchers suggest that an optimal approach to cancer chemotherapy would involve genotyping both malignant and normal cells when feasible (Sadee, 2000).

Unfortunately, the Epidermal Growth Factor Receptor (EGFR) story is not as clearcut, but the use of pharmacogenomics and drug probes are helping scientists to understand the redundant pathways of growth. Early enthusiasm about the effectiveness of EGFR inhibitors (erlotinib and gefitinib) was followed by studies that showed no benefit when combined with cytotoxic drugs. However, Lynch and associates reported activating mutations in the EGF receptor that appeared to underlay responsiveness of non-small cell lung cancer to gefitinib (2004). A subgroup of patients had impressive response: women, patients who had never smoked, patients with adenocarcinoma, and Asians. A majority of the tumours in these patients were found to have a mutation in the EGFR gene which increased the sensitivity of the tumour to anilinoquinazoline inhibitors of EGFR. This is a rapidly moving and potentially fruitful area of both basic and clinical research.

Adoption of predictive tests associated with drug treatment has been extremely high in oncology. The percentage of physicians using a predictive test prior to treatment with Herceptin has exceeded early estimates and sales of Herceptin have exceeded expectations. Clearly the use of a predictive test was a benefit to doctors, patients, and the developers of Herceptin, Genentech.

THE CHANGING PARADIGM OF DRUG DEVELOPMENT AND DELIVERY

OTHER RELEVANT POLYMORPHISMS

Some sequence polymorphisms that are involved in disease pathogenesis also may be involved in determining drug response, directly or indirectly. One example is apolipoprotein E4 (Apo-E4), a risk factor for familial late-onset and sporadic Alzheimer's Disease (AD) that has been reported to predict poor response to the cholinesterase inhibitor tacrine (Farlow *et al.*, 1996). The presence of the E4 allele also may be a factor in the success of prophylactic oestrogen therapy for AD (Sadee, 2000). In addition, Apo-E4 is associated with increased risk of coronary artery disease (CAD). Gerdes *et al.* (2000) reported that presence of this allele is associated with almost 2-fold increased risk of death in myocardial infarct survivors and that this increased mortality rate can be abolished by treatment with simvastatin (HMG-CoA/3-hydroxy-3methylglutaryl coenzyme A reductase inhibitor). Increased understanding of the underlying multigenic causes of AD, CAD and other diseases and neurodegenerative disorders may lead to the development of strategies for disease treatment and even prophylaxis for those at high risk of developing a disease.

Another example of a disease-related polymorphism that is predictive of drug response involves cholesteryl ester transfer protein (CETP) and pravastatin (HMG-CoA reductase inhibitor used to treat hypercholesterolemia). Kuivenhoven *et al.* (1998) reported a significant relationship between variation of the CETP gene and the progression of coronary atherosclerosis, independent of lipolytic plasma enzyme activity and plasma HDL cholesterol concentration. If these results are replicated, then the presence of a homozygous polymorphism at this site could be used to predict whether treatment with pravastatin will be effective. Replication of the study has led to variable results, but Boekholdt *et al.* (2005), conducted a meta analysis of seven large population-based studies (total patients >3500) and two randomized placebo control trials. They found that Taq1B polymorphism was associated with HDL-C and subsequent CAD, but not with Pravastatin therapy.

CURRENT CHALLENGES IN THE CLINICAL APPLICATION OF PHARMACOGENETIC KNOWLEDGE

It is clear from this cursory review of the current state of knowledge regarding the genetic basis of ADRs that many clinically significant genetic polymorphisms affecting drug response in humans have been described already. The emphasis to date has been on identification of mutant alleles at a single gene locus (e.g. Phase I and II hepatic enzymes, TPMT and DPYDH), and this research has been fruitful. However, drug response depends on the drug's interaction with the many proteins involved in its absorption, distribution, excretion and target site, each of which is coded for by genes that may be associated with common variants that may affect response. For example, one individual may exhibit polymorphisms of genes coding for two drug-related proteins: one that affects the degree of drug inactivation and one that determines the sensitivity of the drug receptor. The polymorphism affecting the drug's metabolism would determine the plasma concentrations to which the individual is exposed, and the polymorphic receptor would determine the nature of the individual's response at a given drug concentration. These polygenic interactions are much more difficult to establish during the course of clinical drug trials than are the monogenic effects discussed above but may have an even more significant impact on drug response.

The effects of environmental factors may be modified by wild-type or polymorphic genes, as well, introducing more confounding variables. The majority of these gene variants are relatively uncommon in the general population, making it difficult to establish their role in drug response and demonstrate clinical relevance, especially for heterozygous individuals who are likely to exhibit more subtle effects than homozygotes.

Clinical research in disease genetics and pharmacogenetics has, at times, produced discordant and contradictory results, creating confusion and resulting in a lack of credibility in the minds of many health care providers. Inconsistent results may be due to several factors, including the lack of strict diagnostic criteria for study entry, the heterogeneous nature of the diseases being studied, the use of different end points and scales for assessing drug efficacy

and ADRS, the presence of unknown or unidentified environmental factors and the polygenic nature of many drug effects (Evans and Relling, 1999). It is crucial in clinical pharmacogenetic research that the study sample be of adequate size to demonstrate the necessary statistical power and that the results be rigorously confirmed in comparable populations by other researchers (Manasco, Rieser and Pericak-Vance, 2000). In addition, once a drug has been approved, ongoing, systematic centralized collection of meaningful, evaluable data regarding drug efficacy and ADRs does not occur routinely, and pharmacogenetic data are rarely collected at all. As a result, opportunities for increasing our knowledge of dramatic and subtle genetic effects on drug response both in large numbers of diverse patients and specific diagnostic subsets of patients are lost.

Doroshow, in his review of the gefitinib clinical trial and regulators at the FDA in their guidance documents on drug/device co-development highlight the need to prospectively collect biological samples linked to clinical data and consent during Phase III trials (www.fda.gov/genomics). Experience from the development of Herceptin, Iressa and now Tarceva highlight the need to have samples that accompany the clinical data to enable market-ready tests to be developed, reviewed and marketed at the time of drug release.

In 2004, Merck removed its COX2 inhibitor Vioxx from the marketplace after it was found to be associated with increased risk of cardiovascular side effects. Considerable backlash directed towards the FDA and the pharmaceutical industry resulted. The increased scrutiny provided the impetus for enhanced pharmacovigilance efforts. Furthermore, there was a recognition that the AERS voluntary reporting system was not adequate to fully evaluate post-marketing safety.

Several of the guidance documents highlighted the opportunity the pharmacogenomics can play in identifying populations at risk.

Much pharmacogenetic research to date has involved identifying and categorizing drug-related polymorphisms while relatively little has been done to determine clinical relevance in well-defined populations. Clinicians do not know which variants should be assessed, how and by whom that should be done, what drugs might be affected, what course

of action would be appropriate based on the information obtained and who will cover the cost of the test. Should the dose be altered? By how much? Should the drug be avoided entirely? What about related drugs and polymorphisms? Must each be tested separately? What effects do the variants have on drug–drug and drug–environment interactions? What issues exist around professional liability and the ethical, legal and social aspects of such testing? Carefully designed, well-controlled clinical studies in appropriate populations must be carried out to begin to answer these pressing questions, and the information then must be made available to clinicians and reflected in ethically grounded standards of clinical practice and compensation procedures.

In addition, standard pharmacotherapy references and treatment guidelines formulated by various health care organizations rarely contain relevant pharmacogenetic information even when it is known, making it difficult for clinicians to gain access to existing data. Consumers, health care providers, payers and regulatory agencies lack basic education with regard to pharmacogenetics and timely access to relevant new data as they emerge. Although the lay press occasionally spot-lights a tragedy that could have been averted through the application of existing pharmacogenetic knowledge (such as ‘overdose’ deaths of slow drug metabolizers; Stipp, 2000), the need for increased professional and public awareness and education in this arena is equal to the need for continuing research.

Until recently, genotyping an individual was a laborious, time-consuming and costly proposition that was undertaken only if there was a high index of suspicion of an identified genetic disorder. The Human Genome Project and the multitude of high technology spin-offs from it are changing this situation. Automated instrumentation, new bioinformatics systems and novel strategies derived from genomic research will enable researchers to evaluate and analyze the wealth of genetic information that will continue to emerge. High-throughput DNA sequencing, gene mapping and transcriptional analyses are becoming economically and scientifically feasible as a result of innovations such as DNA, cDNA ('edited' version of a gene, containing only the parts that will be expressed as proteins) and oligonucleotide microarrays and

microfluidic analytical devices (Mancinelli, Cronin and Sadee, 2000).

Because genetic information does not change, it is conceivable that a consumer could have their genetic sample or genetic information in a central location that is available to healthcare providers in any location and at any time. The need for point of care genetic tests will ultimately be eliminated.

In contrast, tests that measure expression of a gene vary over time and thus the need for dynamic measurement for gene expression or protein expression will be needed in some cases.

SINGLE NUCLEOTIDE POLYMORPHISMS, MEDICINE RESPONSE TESTS AND 'GENETIC TESTS'

Many of the previously mentioned polymorphisms directly alter the metabolism, transport, action or excretion of medicines through identified (or identifiable) structural or functional effects; there

is a causal relationship between the polymorphism and the phenotype. New genomic techniques such as those mentioned above are making it possible to detect *associations* (which may or may not be causal) between specific genetic markers and individual response to medicines. Single nucleotide polymorphisms (SNPs, pronounced 'snips'), single-base differences in DNA sequence, are the most common form of human polymorphisms. They occur with an average frequency of about 1 per 1300 base pairs, serving as easily identifiable virtual mileposts along the three billion base pair human genome (International Human Genome Sequencing Consortium, 2001) (See Figure 51.1).

The SNP Consortium (a not-for-profit organization of pharmaceutical and bioinformational companies, academic centres and a charitable trust) produced an ordered high-density SNP map of the human genome, which is publicly available at <http://snp.cshl.org>. This map is being used to find disease genes and to correlate genetic information with individual

SNP: Single nucleotide base change at a specific chromosomal location

...GG **T** AACTG...
...GG **C** AACTG...

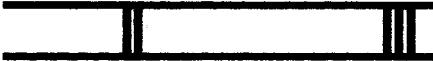
TERM	DEFINITION	USE
SNP Scan	Whole Genome SNP Scan 	Research
SNP Print	Only the SNPs that comprise a pattern associated with adverse drug reactions or drug efficacy 	Prediction of clinical response to a medicine

Figure 51.1. Single nucleotide polymorphisms (SNPs), SNP scans and SNP printssm.

responses to medicines. Although few of these SNPs are expected to be involved directly with disease or medicine response, they will be useful as analytical tools to track small segments of the genome. Individuals who carry a particular gene variant (allele) are likely to carry variants of several SNP markers that are close to or within that allele because of the phenomenon of linkage disequilibrium (LD; when alleles are in close physical proximity, they are likely to be inherited together).

The results of comprehensive analysis of genetic variability in genes related to the action of the medicine in question or the disease process as well as whole-genome SNP scanning obtained during Phase II clinical trials of a medicine can be used to identify specific SNP markers, patterns or haplotypes that correlate to patient responses (efficacy and ADRs). The medicine response-related data could form the basis for the selection of patients most likely to respond well in Phase III trials, possibly making these trials smaller, faster and more efficient if the goal of the study is to validate markers for efficacy. Studies designed to validate safety markers will require larger numbers of patients due to the rate of the adverse events.

The FDA has issued guidance related to co-development of a drug and predictive test. This guidance is focused on development of a predictive test if the markers are known at the time of Phase II trials. Unfortunately, this is not the usual case for drug development, but the emphasis on how samples are collected (with appropriate documented consent using processes that enable evaluation of chain of custody) and the need for a prospective approach to studying and replicating genetic findings will apply in other situations as well (www.fda.gov/genomics).

The FDA has also formed an interdisciplinary review group to review voluntary genomic data submissions (VGDS). The VGDS process enables sponsors to submit data to the agency and get feedback without being required to submit the data to the NDA. If genomic data are to be included as part of the label or as part of the decision making process, then the VGDS process does not apply.

Functional enzyme analysis of TPMT in red blood cells before treatment with specific cancer chemotherapy drugs is one example of an MRT in current use in the United States. Another is HercepTest[®],

which uses a polyclonal antibody to detect HER2 protein, reflecting HER2 expression in breast cancer cells; it is used to predict patient response to trastuzumab (Herceptin[®]), a humanized monoclonal antibody against the HER2 receptor. Researchers already have developed other tools for assessing HER2 expression, including a monoclonal antibody test for the HER2 protein, a test for circulating HER2 protein (in the extracellular domain) and a test using fluorescence *in situ* hybridization (FISH) directly to determine the number of copies of the HER2 gene (not its protein product). Because of the strong correlation between overexpression of HER2 protein and response to Herceptin[®], the US FDA required that a test kit to assess HER2 protein expression be commercially available before drug approval – an example of a regulatory agency mandating the availability of a predictive test linked to use of a specific drug.

Transcriptional analyses, in which the expression levels of DNA are measured, may provide another approach for predictive tests for medicine response (Kleyn and Vesell, 1998). RNA obtained from biopsied tissue and surgical specimens can be used for expression-based studies in some cancers, allowing detection of somatic changes associated with the development of some tumours and their response to chemotherapy. For example, the amplification of the oncogene *erb-B2* predicts a good response to treatment with a specific adjuvant therapy (cyclophosphamide-methotrexate-5-fluorouracil) for breast cancer (Muss *et al.*, 1994). Alternately, the expression of genes predicting drug response can be assayed at the protein level using antibody-based tests of serum or other tissues (Kleyn and Vesell, 2000).

Ongoing genetic and genomic research undoubtedly will result in the development of additional tools that can be incorporated into or used as the basis of medicine response tests. The rationale exists for conducting pharmacogenetic analyses to look for associations between drug responses (safety and efficacy) and genotype, and the technology exists for conducting these analyses. The missing piece is a pool of DNA samples with associated medical and medicine response data to facilitate the efficient conduct of pharmacogenetic research. Eventually, MRTs based on SNPs and other genetic polymorphisms will enable health care providers to identify patients at high risk of developing a given disease,

implement preventive therapy and lifestyle adjustments when appropriate and choose the medicines that are most likely to benefit the patient and least likely to result in serious ADRs (Mancinelli, Cronin and Sadee, 2000).

In the past, the term 'genetic testing' has been associated with the diagnosis of monogenic diseases such as cystic fibrosis and Huntingdon disease – conditions for which a causative, single, genetic mutation has been identified (Table 51.4). A newer area of genetic research and testing involves identification of genes related to the occurrence of common complex diseases such as asthma, heart disease and migraine. These diseases are likely to result from the interaction of multiple 'increased risk' or susceptibility genes with each other and possibly with environmental factors. These types of genetic research and testing (related to monogenic diseases and susceptibility genes) involve determining the likelihood of occurrence (prediction) or the presence (diagnosis) of disease in individuals. Although very useful and important, there are social and ethical risks related to the nature of the information revealed by these tests – what it means, who has access to it and how it can be used. There is general agreement on the need for genetic counselling to help patients and families understand and process the results of these disease- and risk-related genetic tests.

In contrast, the risks associated with tests to detect polymorphisms related to response to medicines, such as metabolic and drug receptor or target character-

istics and genomic profiles, are minimal: the data that are obtained are quite limited and specific to the drug(s) being considered. No information about disease, causal or susceptibility genes, is likely to be obtained. These tests, when validated, will be similar to routine laboratory tests such as blood typing, drug concentration monitoring and liver enzyme analyses. Although health care providers would discuss the results with patients, there would be no need for genetic counselling and ongoing psychosocial support related to interpretation of the results, with rare exceptions.

THE IMPACT OF PHARMACOGENETICS ON CLINICAL DRUG DEVELOPMENT

Historically, fewer than 10% of new chemical entities (NCEs) entering preclinical development are approved for clinical use, often because of unacceptable toxicity in animal studies or Phase I human trials or insufficient efficacy (Kleyn and Vesell, 1998). The cost of bringing a new drug to market is approximately \$500–800 million; the costs of ADRs and treatment failures, discussed earlier, are staggering. The application of pharmacogenetic research and knowledge could result in streamlining and improving the clinical development process in several ways:

- by initial toxicogenomic screening of compounds to detect selective metabolism, disposition or

Table 51.4. Comparison of different types of 'genetic testing'.

Application	Disease genetics	Pharmacogenetics/medicine response tests
What is being tested	Rare Mendelian (monogenic) diseases, 'causal' genes Complex common diseases (multifactorial), susceptibility genes	Genes related to drug metabolism or action SNP Prints SM related to drug safety or efficacy
Potential benefits	Prediction of occurrence, diagnosis of disease; insights into disease mechanisms and development of new medicines	Optimal individual response to medicine
Potential risks	Informational risk to patient and family, with related ethical, legal and social issues (employment, insurance etc.)	Low informational risk; data provided will relate only to individual response to specific medicines

- action related to known polymorphic enzymes, transporters or targets;
- by providing an ‘insurance policy’ for drug development outcomes. If the results of pivotal trials do not show efficacy in the whole population, subsetting the population on the basis of genetics may enable identification of a group with positive results that were diluted in the entire population and
- by enhancing the efficacy and safety profiles of medicines in targeted populations to enable better penetration in the marketplace.

Many pharmaceutical companies now routinely screen NCEs to see if they are metabolized selectively by known polymorphic enzymes, and development is discontinued or altered to include additional pharmacokinetic studies for many of those that are because of the potentially increased risk of serious ADRs or lack of efficacy in subpopulations of patients (Zuhlsdorf, 1998).

Initially, much of the benefits of genomics was expected to ‘rescue’ NCEs after the drug had been ‘killed’. In reality, the value that late in the drug’s lifetime has not been the case. In contrast, collecting and using genomic information during drug development and at the time of launch is money and time well spent.

However, understanding why certain drugs that have been removed from the marketplace due to serious adverse events can help in developing follow-on compounds. For example, terfenadine (Seldane) caused ADRs in patients who had a specific CYP2D6 gene polymorphism and also were taking erythromycin. They were unable to metabolize terfenadine in this situation, which caused toxic accumulation of the drug in the body. The FDA worked with the pharmaceutical manufacturer to distribute appropriate warnings about the possible risks of its use with concomitant medicines, but the company and FDA decided that the drug’s risk–benefit ratio did not justify its continued use. If a screening test to identify patients at risk for this problem had been available, it might have been possible to keep the drug on the market while protecting some of those most likely to experience toxicity from it (Bhandari *et al.*, 1999).

Perhaps, the most striking example was the removal of Vioxx, a COX2 inhibitor from the marketplace. Identification of the cardiovascular risk took many years to identify with many millions of patients exposed. It is clear that new methods to study tens to hundreds of thousands of patients over multiple years will be needed. These methods will likely rely on technology such as electronic data capture that can collect data quickly and efficiently from the patients as well as the physicians. A low cost, efficient, patient-administered DNA collection approach will also help to identify patients at risk without compromising the access to drugs.

Discussion of the potential impact of pharmacogenetics on clinical trial design is beyond the scope of this chapter, but it is clear that many pharmaceutical companies recognize its importance and are planning to initiate pharmacogenetic studies in the near future (Ball and Borman, 1997). Lichter and McNamara (1995) suggested one approach for incorporating pharmacogenetics into clinical trials:

- Perform preclinical identification of metabolic pathways and population screening for common DNA sequence variants of the relevant enzymes, transporters, receptors and target genes (and their homologues), as discussed above.
- Consider the ethnicity of study populations based on known differences in the frequency of specific polymorphisms.
- During Phase I trials, type subjects for the genes known to control the drug’s metabolic pathway(s) to allow possible correlation of ADRs with genotype and use this information as a basis for subject selection in Phase II and III studies.
- During Phase II trials, type any identified relevant polymorphisms in the entire study group. Also type the gene product and related targets in all subjects, allowing assessment of allele frequencies in the population and in responders versus non-responders. Use these data as a basis for subject selection in Phase III trials.
- If useful genetic markers of efficacy or ADRs are identified during Phase II, the Phase III group could be expanded to include a cohort prescreened to include likely responders and those at low risk of ADRs.

This approach is limited by its reliance on identified candidate genes (genes selected on the basis of existing knowledge or an informed guess) and molecular pharmacology to identify drug–receptor interaction, and down-stream signalling pathways, and unexpected associations (either causal or resulting from LD) may not be recognized.

Another approach that is being used already by some pharmaceutical companies has been thought to hold even greater promise as technological advances increase the accuracy, feasibility and cost-effectiveness of high-throughput whole-genome scanning. The benefit of whole genome scanning has not yet been realized.

Regardless of the genomic approach, collection of a single blood sample for DNA analysis from all consenting participants in selected Phase II and III clinical trials (after approval by the appropriate ethics review boards and provision of specific informed consent by subjects) enables pharmaceutical companies to have the key samples needed in case a safety or efficacy question arises. This sample may be used to identify the occurrence of known polymorphisms affecting drug response, to evaluate candidate genes suspected of being involved in the disease or drug response and to assess patterns of SNP or haplotype occurrence related to efficacy or ADRs, allowing the creation of a SNP PrintSM to screen potential subjects or patients (post-approval) for their likely response to the drug or determine heterogeneity of the disease in patients with similar phenotypes (Roses, 2000b).

Regulatory agencies might be concerned, appropriately, that the smaller numbers of patients in these streamlined clinical trials would be insufficient to detect rare ADRs (<1:1000) and that patients who did not receive or ‘pass’ the recommended MRT for the drug would nevertheless receive it and be at increased risk of harm. However, rare ADRs are not likely to be detected even in the relatively large clinical trials that are conducted now; it certainly is not feasible to enroll the approximately 65 000 patients that would be required to be 95% confident of detecting three or more cases of an ADR with an incidence of 1:10 000 (Lewis, 1981). The major, albeit rare, ADRs associated with dextroamphetamine, zomepirac, benoxaprofen, troglitazone and terfenadine were not detected until after they reached the market. Extensive pre-

approval safety testing in even larger populations is a possible solution, although, as noted above, it will be impractical to identify very rare ADRs in clinical trial study populations, and the increased cost and delayed time to market is likely to create significant financial barriers from the perspective of the pharmaceutical companies (and ultimately consumers and payers to whom the cost will be passed along) (Roses, 2000a).

One solution to this problem would be an extensive, regulated post-approval surveillance system that incorporates the collection of pharmacogenetic data. Roses (2000b) proposes that hundreds of thousands of patients receiving a medicine would have filter paper blood spots taken (perhaps from the original blood sample used for the MRT) and stored in a central location. As rare and/or serious ADRs are reported and characterized, DNA from affected patients could be compared with that of control patients, allowing ongoing refinement of the MRT. There is increasing pressure to improve the inconsistent and largely unregulated current system of post-marketing surveillance, and many authors agree on the need to incorporate pharmacogenetic data in some form into a revised system (Edwards and Aronson, 2000; Nelson, 2000).

Another approach is one that would put increasing control of medical data in the hands of those most directly affected by it – consumers. In this scenario, an individual could choose to have a one-time blood sample taken for DNA analysis and stored at a tightly secured central repository. As research into disease-related genes, genetic risk factors and genetic associations with medicine responses progressed, the consumer or a designated representative (such as a health care provider) could request that the sample be analyzed using relevant MRTs (including SNP PrintsSM) and other markers. This ‘bank’ could serve as a central repository for the samples themselves and as a central database of information including well-established knowledge, current research and even opportunities for clinical trial subjects with specific conditions or genotypes. It could trigger genetic ‘alerts’ to consumers who chose to provide a medical and family history as new research results potentially relevant to them became available. A host of ethical, legal and social issues would need to be addressed as part of this venture, but it presents one option for an

efficient, centralized and consumer-controlled bank of health-related genetic expertise and information.

CONCLUSION

The results of pharmacogenetic research will impact the discovery, development and safe, effective use of medicines in several ways:

- Many diseases will be diagnosed based on genotype (underlying mechanism of disease) rather than phenotype (presenting signs and symptoms) alone, enabling health care providers to determine the optimal therapeutic approach.
- Health care providers will increasingly use genomic data and other predictive tests as a basis for selecting the medicine and dose most likely to be efficacious and least likely to cause ADRs in individual patients.
- Identification of disease susceptibility genes will allow implementation of preventive measures or early treatment of specific diseases.
- New medicines will be designed to avoid or exploit specific polymorphisms of genes involved in disease susceptibility or drug metabolism, transport or action.

Many challenges remain to be overcome. The human genome is complex and dynamic, and although we have made great progress in unraveling its mysteries, it still holds many secrets. Diseases and responses to medicines are likely to involve many genes, each of which plays a specific role and interacts with other genes and the environment in complex, interdependent ways. Technological challenges involving statistics, bioinformatics tools, high-throughput sample processing, accuracy and cost still exist, although progress is being made in resolving them. In addition to these scientific and technological issues, we as a society have to deal with the many complicated ethical, legal and social questions that arise as a result of our increased understanding of our genetic heritage and our growing ability to affect it and alter its effect on us.

History has taught us that scientific knowledge and technological advances will continue; our human challenge is to apply what we learn skillfully and for

the betterment of all humanity. Although the clinical relevance of progress in pharmacogenetics is just beginning to become clear, it holds great promise for improving health and quality of life for millions of people throughout the world.

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Keynote Clinical Lessons from Pharmacovigilance

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INTRODUCTION

The history of predicting the future in medical sciences is fraught with difficulty. Almost invariably, major new developments lie just round the corner and are unforeseen by those working in the field. That said, we have always regarded the best guides to the future to be the lessons gained from mistakes made in the past.

Unfortunately, the public perception of drug safety is not one of the triumphs of science over disease. Rather it is one of vague unease and concern often aggravated by exaggerated and markedly adverse media publicity. Adverse drug effects are again being trumpeted as a major cause of admissions to hospital. This is being emphasised with no regard to separating out those adverse reactions that are predictable (due to pharmacological effects and thus reflect inappropriate prescribing or inadequate adherence to clinical advice by patients), from those that are idiosyncratic and thus unpredicted (due to intrinsic problems with medicines whether documented or as yet undiscovered). Nor is due attention directed towards the underlying disorders for

which the medicines were prescribed and which themselves may have major consequences if left untreated. For example, more and more patients are subjected to heroic chemotherapy with the objective of prolonging existence in advanced neoplasia. The therapy may be effective in one or more accepted sense, but may also be associated with undesired, possibly severe side effects, these being entirely predictable and accepted as a risk by the prescriber (and hopefully the patient) at the time of initiating therapy. At the outset, the potential benefits may appear to be worth the risks. For many patients this turns out not to be so.

Similarly, the increasingly widespread use of prophylactic anticoagulation in patients with unstable rhythms with the objective of preventing life-threatening embolic phenomena is associated with a predictable burden of haemorrhagic complications, some of which are undoubtedly life-threatening. Were the media to address the reasons for the drug exposure as well as the consequences thereof, perhaps a more balanced approach to the subject could be undertaken. Unfortunately this is likely to be asking too much in our litigation-conscious society.

Occasional sudden death from torsade de pointes in young individual recipients of antihistamine therapy has been another pressing cause for concern over the years. Despite this, there are little in the way of systematic efforts directed towards quantitating the frequency of such deaths. Identifying such patients and reviewing their treatment in the days and weeks preceding death could add valuable knowledge to our portfolio of information on this topic.

Another area of major current concern is the great parental anxiety about the potential hazards of the combined measles, mumps and rubella (MMR) vaccine. Clearly this is a problematic area. Vaccination is used to *prevent* illness, and the perception of risk in the 'treatment' of healthy individuals is different from the perception of risk in those suffering from disease. Some of those vaccinated may experience minor (local) side effects, while non-vaccinated children do not suffer any problems at the time when their peers are vaccinated. The reported associations between MMR vaccines, inflammatory bowel disease and autism have caused greatly increased concern about all vaccines in parents who have rarely seen the effects of mumps, measles, whooping cough or indeed most other contagious diseases in the raw. The overwhelming balance of evidence available at present indicates that this problem arises from a causal interpretation being placed erroneously onto an apparently random association. Such wrongful interpretations can cause enormous distress. They also cannot easily be rejected or proven wrong by the very nature of the information available to pharmacovigilators – one cannot prove that a drug or intervention is safe, only that there is a risk. One key feature of most of these recent pharmacovigilance problems is the substantial rarity with which they occur. This is because events occur as a consequence of the intrinsic properties of the medicine itself, rather than the way in which it is used. We shall return to this topic in the concluding section of this chapter.

Finally, recurrent headline-grabbing, but false, claims by the media of collusion between the pharmaceutical industry, drug regulators and advisory committees serve greatly to heighten public concern in an area where the echoes of the thalidomide disaster are still audible (House of Commons Health Committee: *The Influence of the Pharmaceutical Industry*. The Stationery Office, London: 2005).

If one then adds to the above concerns the epidemic of drug abuse that is hitting mainly the youth in western countries at the present time, the scene is set for a major lack of understanding of the true benefits and risks of modern therapeutic medicines. Patients at present seem to have high expectations for the efficacy of new medicines, together with expectations of low, or zero, risk. This balance is now unrealistic, and at the very least would contribute to major delays in licensing new products. The public perception of a 'pill for every ill' has been, if anything, stronger over the last 10 years. There is a strong feeling that drugs should be safe. After all, they are tested for years by increasingly sophisticated mechanisms. The fact that at the time of marketing only a few thousand individuals with the disease of interest may have been exposed to the drugs at the dose for which they are licensed is not generally understood by the public. Moreover, individual members of the public have increasing desires to participate in decisions concerning their health. People increasingly insist on full information about the risks of the diseases from which they suffer, the benefits of therapy to be obtained and the risks of such therapies. Whilst this is generally understandable and desirable, it often places physicians in difficult situations, particularly when patients choose not to fully inform their physicians about all their problems or about alternative therapies that they might be using. Should anything untoward happen, there is an inevitable tendency to blame the prescriber. Thus in the minds of many patients, the European Convention on Human Rights gives them complete justification for seeking information and making judgments on their own, independently of their physicians. However, should things go wrong, there is no such thing as an equivalent European Convention on Human Responsibility. So, any errors or misfortunes that might arise are not seen as, even partly, the responsibility of the patient, but rather attributed in their entirety to the medicines or the prescriber!

These topics raise an important problem in pharmacovigilance that has only recently begun to be recognised and dealt with. This is the question of acceptance of risk by the public. The former Chief Medical Officer of England (and before that of Scotland), Sir Kenneth Calman, has emphasised the need to have a public debate about this issue as it is clear that a substantial body of the general public

(and possibly even some members of the professions) have at best a very hazy understanding of the concepts and magnitude of risks and benefits as far as they apply to disease and its medical treatment. Clearly pharmacoepidemiologists should be to the fore in supporting the necessary endeavours to initiate and sustain any such efforts aimed at improving this sad state of affairs.

PHARMACOVIGILANCE

Pharmacovigilance is all about the safety of drugs in their conditions of normal routine use. It does involve collection and analysis of information about drugs as they are used in a community. No longer is the major focus that of the randomised controlled clinical trial where a well-defined subset of the population is exposed under carefully controlled circumstances to a medicine of interest and followed for a defined duration thereafter. We now enter the area of observational studies with all the problems in interpretation that such studies entail. It is important to realise that the interpretation of observational data can be much more complex than the interpretation of randomised controlled clinical trials. Such studies are, by their very nature, full of incomplete information and are likely to need careful recognition of confounding, either at the design or analysis stage. Indeed, some such studies cannot be interpreted because of insurmountable problems with bias or other distortions. The various types of studies involved have been covered in earlier chapters in this book. They fall broadly into three categories:

1. The anecdotal study in which reports of suspected problems are solicited and analysed to see if they can give hints about possible drug-related problems, exemplified by the *spontaneous reporting schemes*.
2. More detailed observational studies, but still without appropriate comparator groups who are not exposed to the medicine of interest, for example *ad hoc follow-up studies*.
3. Controlled studies, including *case-control and cohort studies*.

As long ago as 1987, giving the keynote address on pharmacoepidemiology and public health policy

at the International Society for Pharmacoepidemiology meeting in Minneapolis, one of us (DHL) made several points about this subject which we think are worthwhile repeating here. These are as follows:

1. It is the duty of pharmacoepidemiologists to ensure that spontaneous reports of suspected adverse reactions are used wisely in the full knowledge of their substantial limitations.
2. It is our duty as pharmacoepidemiologists to ensure that other sources of information are available which can be interpreted in a reasonably rapid time frame. Good data in 6 years is no substitute for usable data in 6 months or less.
3. Pharmacoepidemiology will not prosper if it develops as an intellectual subject which plots the history of why drugs fall from favour. It must be a live and contemporary subject, providing answers to current problems of drug use and drug safety in real time.

These aphorisms are as relevant today as they were when first spoken. They apply across the board to all types of studies. Thankfully we have made progress in the intervening years, albeit not as much as we would have liked.

SPONTANEOUS REPORTING SCHEMES

There is widespread agreement that spontaneous reporting schemes are here to stay. They are economical and embrace the entire population of patients and reporters. However, it is important to treat all such reports as hypotheses. Some events will almost certainly be causally linked with the suspect drug, whereas others will turn out not to be so. With secular trends in widening the reporter base to include nurses, pharmacists, other health professionals and now patients, the balance may vary somewhat from region to region and from one group of reporters to another. It is important that standardised procedures are adopted to review and analyse all such spontaneous reports. In so doing, there is a danger that the output from any review could be made available without the benefit of careful clinical and pharmacological expertise and input with serious consequences to all concerned. The rule here is to appreciate that the raw information from spontaneous reporting schemes

are anecdotes – no more and no less. They have to be treated as such. Sophisticated analyses of anecdotal data are justified if great care is taken with the subsequent interpretation, otherwise more harm could arise than good. Careful review of all reported suspect reactions to a particular medicine may point to a subpopulation at especial risk. Such reviews can rarely be automated, but require careful, time-consuming analysis by trained, experienced observers. Such people are in short supply; nevertheless, they are extremely valuable in the context of logical interpretation of spontaneous reporting schemes. Signal detection can now be enhanced by advances in information technology, including techniques for interrogation and analysis of databases of spontaneous reports.

The development of Augmented Spontaneous Reporting Schemes whereby potential reporters are contacted about details of outcomes after specific medicines have been prescribed in the hope that they will respond in greater numbers and with better quality information is to be encouraged. These schemes are best developed in New Zealand and by the Drug Safety Research Unit in Southampton (United Kingdom). The present authors believe that these schemes should be encouraged and developed further in the coming decade. They are not without their problems, however. This is especially so in the United Kingdom at present where there is a severe epidemic of concern within the public psyche about confidentiality of medical information. Whilst no one would disagree with the need to maintain confidentiality when dealing with information on illness, and all would support the need for great care in this area, nonetheless there are circumstances in which the need to link information from several different sources is necessary to ensure appropriate interpretation of the data. This is most marked in the case of cancer registry data, but is also a clear feature of many pharmacovigilance issues.

The problem becomes particularly acute when we observe the controversy about patient confidentiality in the United Kingdom at the present time. The regulatory authority for prescribers (the General Medical Council) has been rigid in its emphasis of the need for total patient confidentiality. Whilst at first sight this seems entirely reasonable and laudable, observational research could be seriously damaged by such an approach: in particular, studies such as cancer registries and drug safety monitoring studies are

uniquely vulnerable since both require coordination of disparate data sources (e.g. demographic data, drug prescription data, hospital records and general practice records) to form a relevant patient record. In the absence of adequate *anonymous* patient registration numbers to bring these records together, identifiable information may be required solely to coordinate such information. If this can only be undertaken by receiving individual patient consent, an unknown proportion of patients (possibly up to 30%) will for one reason or another be unable or unwilling to give such permission. Thus the value of the resulting data set is dramatically reduced as it no longer constitutes a random sample from the population. Warlow and colleagues have recently demonstrated this consent bias in observational research (Al-Shahi, Vousden and Warlow, BMJ 2005; 331: 942–5). In a follow-up study of patients with intracranial arterio-venous malformations, outcomes were clearly different between those who did and did not give consent. Moreover, in the case of prospective databases involving literally millions of patient-years of observations, the practicalities of obtaining patient approval to use identifiable information solely to permit record linkage with the objective of furthering public health objectives of potential benefit to all people in the land seem at first sight almost insurmountable as well as being prohibitively expensive. Are we then to cease this type of research? Surely the answer to this must be a resounding ‘No’! We must find other more practical ways of achieving the desired end of maintaining quality research into drug safety and into cancer surveillance whilst fulfilling the need for confidentiality for all patients. We would suggest that a reasonable position to adopt would be one in which it was a recognised duty on patients receiving treatment in the National Health Service to accept that their information would be used for routine monitoring purposes, including disease incidence and prevalence studies and studies into the safety of medicines. Such studies will require records to be linked across several areas, and identifiers may be needed for this purpose. At all times such confidential information would be kept to the minimum necessary and would be used solely for this purpose. Data can be protected by coding and restriction at various levels in the capture-and-research process. Any breach of this confidentiality would be dealt with severely by fines or suspension

of a licence to practise. As far as we know, there is no record of any confidential information being placed in the public domain from such data sets. Thus the obsessive concentration on confidentiality to the exclusion of all other facets of this issue is likely to do substantial harm to world-class research if the issue of *post hoc* anonymisation cannot be adequately and economically addressed.

In summary, anonymised records should be the usual type of information used by pharmacovigilance and pharmacoepidemiologists; however, there are times when, for the public good and because anonymised information is not readily available, identifiable data will be required for linkage purposes. With suitable safeguards in place and enforced, the public can be reassured that such records can and should become a part of participation in NHS treatment, including public health monitoring and research.

DISEASE REGISTRIES

For many years it has been known that a number of disorders are at particularly high risk of being drug-induced. Calls have been made to commence registries for such disorders, similar to the initiatives on aplastic anaemia following the chloramphenicol problem or the registry of vaginal adenocarcinoma in young women which proved so useful in identifying high dose stilboestrol in pregnancy as the culprit. These calls have yet to lead to action and this seems to be an opportunity missed. Such registries could prove to be valuable additions to the pharmacovigilance arena as well as providing additional information about the natural history of the selected key disorders in the twenty-first century.

FOLLOW-UP STUDIES

In the era before large automated data sets became available for pharmacoepidemiology research, a number of *ad hoc* studies were mounted to look at the safety aspects of specific drugs. These studies had undoubtedly problems, and were generally expensive to mount and to conduct. Nonetheless they

served to provide quantitation for several interesting risks, refute others, and they also helped to improve our understanding of methodology in this arena. They were, however, reported as being unhelpful to members of the UK Medicines Control Agency in their periodic safety assessments of licenced medicines (Waller *et al.*, 1992; 304: 1470–2). Perhaps regulators should generally remain aloof from issuing guidance on methodology until such time as the issues are clear-cut and generally accepted by experts within the field. We are now left with the main source of information in this area being the multipurpose databases.

MULTIPURPOSE DATABASES

Large data sets based on demographic information, disease occurrences and prescribing information are now available from several sources for use by trained and competent researchers. We now have extensive populations in diverse geographical settings for whom routine information about demography, drug exposure and disease experience are available in reasonably standardised formats. We have skilled analysts available to review such data sets for important causal associations between drugs and events. These information sets are extremely powerful tools and must be used with skill and great care lest the results reported turn out to be erroneous. In such circumstances great damage could be done both to public health and also to the data sets themselves. It is therefore crucially important that investigators ensure that validity of their observations by careful scrutiny of at least a sample (if not all) of the basic records. To rely solely on computer codes for disease identification without the ability to return to verify basic written records is likely to lead to significant potential for serious error. Failure to undertake proper validation could easily lead to inappropriate damage to the reputation of individual medicines, or even the parent data set itself.

Recently there have been some examples of conflicting conclusions emanating from different investigators reviewing the same topic from within the largest database in the United Kingdom, the General Practice Research Database. This may seem surprising at first sight. However, it must be clearly understood that the worldwide experience in this exciting area is

confined to relatively small groups of investigators, as there are formidable logistical problems to overcome in entering and conducting research on these data resources. For example, drug-, symptom- and disease-codes tend to change with time during the years of data accrual. This is not territory for the amateur or the unwary! One simply cannot go to these extremely complex information systems and expect to perform high-quality research overnight. The issues are usually technically challenging and epidemiologically extremely complex.

Classical epidemiology is well used to dealing with fixed properties of individual patients, such as sex, height, weight, parity, smoking habits and so on or one-off exposures to toxic substances, such as chemicals or infective agents. It is not so comfortable dealing with intermittent exposures at varying doses that are usually the case in drug epidemiology studies. There are some areas where the exposure status can be somewhat constant. Examples of these would be the use of oral contraceptives and hormone treatments (replacement therapies with oestrogens, insulin, thyroxine, etc.). Even here, however, patients regularly change individual preparations, and great care must be taken to ensure accuracy and fairness in data interpretation. In other areas intermittent exposures are the norm.

In embarking upon a drug safety study in a large database, the investigator must clearly specify the hypothesis to be tested. (Such databases are so complex as to be generally unsuitable for hypothesis generation except under very confined circumstances arising usually within an individual study.) Once one has defined the hypothesis, exposure and outcome status have to be assessed accurately. The nature of the study design has to be identified. Is it a follow-up study, a case-control study or will it be a nested case-control study within a large group of subjects exposed to an individual medicine or class of medicines?

Failure of clarity at this stage could doom the study from the onset. Investigators interested in a particular hypothesis can often be mesmerised by the apparent abundance of information available to them. They should keep in mind that it is crucial to restrict themselves to appropriate comparisons. Thus if one is looking at the effect of, say, hormone replacement therapy on osteoporosis, the relevant outcome measure available in such databases is generally

a fracture. However, not all fractures are relevant. Indeed, many are irrelevant to the hypothesis, as they will have an obvious and sufficient cause, such as a road traffic or other accident, an underlying neoplasm or pre-existing bone disease. Similarly, not all exposures to hormones are relevant. For example, it would seem unlikely (biologically implausible) that a single prescription for such treatment would be relevant to the outcome of interest. Trained epidemiologists are used to thinking of chance, bias and confounding as explanations for any associations they see in data. Although the items mentioned above are forms of bias, they tend to be obscure to all but those trained in the complexities of pharmacoepidemiology. Yet they are crucial issues to consider before one embarks on a seemingly large and promising study. Reflect that a negative outcome to a project could be because the study drug does not cause the outcome of interest. However, it could also arise from the fact that there is so much 'noise' in the system that an investigator cannot see the true link between drug and disease when it is in front of him because of inappropriate inclusions in the disease and drug exposure categories and inappropriate inclusions and exclusions in the comparator population. Finally, there is the problem of missing information found in all systems, yet requiring particularly careful handling in a multipurpose database. Such information rarely leads to a false-positive conclusion, but it could result in missing a key finding. The main safeguard here is familiarity with the data set itself.

Without due care and attention, the availability of more and more powerful information systems could lead to an epidemic of poorly undertaken studies that would reflect badly on the fledgling science of pharmacoepidemiology. This would be a matter of great regret, as the subject is of major importance for the future safety of patients, prescribers, dispensers and manufacturers alike. All have different perspectives, yet all share a common goal of getting the safest medicines to the appropriate patients at the right dose and at the right time. For a guide to some of the less obvious pitfalls in this type of research, see the paper by Jick and colleagues in the *Lancet* (1998; 352: 1767-70).

The development of pharmacovigilance is now at a critical stage. With powerful new tools at our disposal we have at last the opportunity to provide the public with some of the reassurances it requires from the

industry and the professions. Ironically, it has taken over 35 years since David Finney originally recommended this approach in a seminal article in the *Journal of Chronic Diseases* (1965; 18: 77–98). It is crucial that we continue to meet this challenge with enthusiasm and skill, seizing the opportunities that present in these powerful information systems and surmounting the local difficulties relating to anonymisation of data sets, scientific rigor and credibility. For once we in the United Kingdom are in possession of a world-beating facility for research in the form of the General Practice Research Database, due to the foresight of its founding practitioner, the commitment of large numbers of collaborating general practitioners, and the realisation among researchers and the Regulatory Authority in the United Kingdom that this is a resource beyond value.

OVER-THE-COUNTER AND ALTERNATIVE MEDICINES

Multipurpose databases generally concentrate information collection upon prescription medicines. Over-the-counter (OTC) and alternative medicines are excluded or dealt with in a non-standard manner. Whilst OTC medicines usually have been reviewed in detail when they were prescription medicines, the same cannot be said for alternative medicines such as herbal and homeopathic preparations. Many of these have been found to be associated with serious health hazards in the past, and some have also been found to interact with prescription medicines. We need some method other than relying solely on spontaneous reporting systems to be reassured that these preparations are indeed acceptably safe. The resulting system need not be as all embracing as the large databases; however, the work needs to be done, and done both rapidly and cost-efficiently in the near future. In the United Kingdom, the Herbal Medicines Advisory Committee has been established to advise the Licensing Authority directly on this issue.

NEW PRESCRIBERS

The large databases are perhaps best developed in the United Kingdom because of its unique feature of the general practitioner being the gateway through which patients progress to specialist care. As the system

changes and others such as nurses and pharmacists begin to initiate primary prescriptions in measurable numbers, these systems could become less effective. There will have to be careful thought directed towards the best ways in which the relevant information can be captured economically to ensure the continuing maintenance and viability of the databases. This can most readily be achieved by channeling records of all prescriptions through a patient's practitioner, thereby ensuring not only continuity of records but also safety in therapy. With advances in transferable electronic patient records and the use of a unique patient identifier, these tasks become easier, in theory at least.

EVIDENCE-BASED MEDICINE

'Evidence-based medicine' is the new buzz term used to describe that which virtually all prescribers have been striving for throughout their professional lives. With better evidence from large clinical trials, there is increasing information to suggest that additions of several more medicines to the base package of treatment can result in better outcomes. What is not known is the effect of adopting this approach in real life. Will patients comply with all the additional medicines or will they attempt to reduce and rationalise the number of pills they have to take? If the latter, will they take the most important ones or will they take a random selection such that they end up worse off than before? So far, the large databases have been used primarily to study the effects of medicines on patients. They have rarely been used to study prescribers' or patients' behaviour. For obvious reasons, this area is complex. It could also be perceived as being potentially threatening to the very practitioners who supply the data in the first place! Nevertheless, these problems could easily be surmounted by ensuring adequate anonymisation for prescribers, and indeed this has been a feature of some of the large databases throughout their existence. Practitioners have nothing to fear about such developments if they are conducted in an inquiring mode rather than in a potentially inquisitorial mode. Indeed, they could learn substantial amounts from them. Guidelines and other advice from central sources now have the potential for considerable influence on prescribing decisions. Multipurpose databases are well placed to allow study of the sequelae of this

trend. This includes not only drug utilisation studies linked to cost containment strategies, but also much needed outcome studies that might tell if such advice has any real clinical benefit for patients.

HOSPITAL DRUG MONITORING

Drug safety monitoring started with detailed studies of suspected adverse drug effects in hospitalised patients. Recently, most pharmacovigilance work of an observational nature has been confined to community practice, because the number of drugs used and the number of underlying conditions experienced by patients are generally fewer there than in hospitals. This leads to easier interpretation of data but does leave a gap in our knowledge of the safety of drugs whose use is confined to the hospital setting, such as anaesthetics and third-line antibiotics. There will need to be some efforts directed from time to time towards correcting these omissions, probably by *ad hoc* studies in hospitals such as have been undertaken by the Boston Collaborative Drug Surveillance Program in the 1970s and 1980s, the Medicines Evaluation and Monitoring Group in Dundee and more recently by Pirmohamed and colleagues (BMJ 2004; 329: 15–19).

Such studies would be greatly facilitated by more widespread use of computerised prescribing systems in hospitals. The research potential of this type of system would be further enhanced if such systems were linked directly with patients' general practice records. This is entirely practicable if the will, finance and issues of patient confidentiality can be resolved. Such efforts, if associated with real-time feedback, could also be used to monitor standards of prescribing in target areas of concern.

GENOME RESEARCH AND PHARMACOVIGILANCE

The large pharmacovigilance databases have been, and will continue to be, remarkably useful in focusing on safety issues of individual drugs or families of drugs. Nonetheless, in the foreseeable future this will not be sufficient on its own to justify their expansion and increasingly widespread use. Some have been in

existence for over 10 years and hence have capability of detecting drug-induced neoplasias, which could remain undetected in those exposed to long-term therapies using other techniques. The only significant area in which this seems to have occurred to date, apart from very rare tumours in users of regular hormone therapies, is with the long-term immunosuppressed patients. This is good news insofar as it goes. The power of the databases to recognise tumour formation in long-term recipients of individual medicines or classes of medicines would be greatly enhanced were they to include a sizeable sub-population for whom genetic footprints were known. Such an advance is now coming within our grasp. Whilst a number of groups are looking at setting up new surveillance systems to include genetic profiles in the information they capture, the real prizes are likely to be won by grafting this additional information on to existing large data sets in which long-term studies have already been undertaken. The pay-off from this research is likely to be not only a greater understanding of the links between the genome and adverse drug events, but also a better understanding of tumour genesis in the population at large. Were these issues to be clarified, it is theoretically possible that a proportion of susceptible individuals could be advised to avoid certain drugs before they have ever been exposed to them. One suspects this will take several decades to achieve, but it could have the overall benefit of reducing individual risks of adverse events and prolonging the useful life of those drugs that have problems in a specific small sub-set of the population of recipients, but are otherwise acceptably safe and of good reputation. Clearly, such a development could only go ahead with the full approval of participating individuals. Nonetheless, it will also require societal debates if it is to experience seamless progress to its desired end. Genome research not only has significance for the population, but it also has important relevance to individual participants. The legal implications of acquiring knowledge about one's genetic information cannot be ignored. It is not merely a matter for the individual, but also a matter for the entire family involved. The consequences for individuals seeking life insurance, a mortgage, paying maintenance together with numerous other life-decisions with long-term consequences are potentially enormous and must be considered carefully before we embark on such monitoring projects.

RESPONSES TO RISKS

One frustrating problem over the years has been the relatively restricted nature of interventions available to Drug Regulatory Authorities in the event that a licensed medicine turns out to have unsuspected toxicity. These are suspension, revocation or modification to the summary of product characteristics. In these situations the perceived need to take action in relation to the risk from the product is often greater than the apparent risk itself warrants. There is an understandable tendency to emphasise risk and forget about benefit. An example of this would be the manner in which the recent controversy about the risks of the third-generation oral contraceptive pills and thromboembolic disease. As well as being of great intrinsic interest, this example emphasises that not all risks relate to new or nearly new drugs. Pharmacovigilance needs to remain alert to the potential problems of drugs at all stages in their development and use. Another example of a relatively old drug running into problems in the past was nomifensine, an effective antidepressant in which evidence came to light about the risks of acute haemolysis under unusual circumstances of use. Given the relatively long-established position of the medicine itself, the company involved found it easier to withdraw it from sale than risk litigation by continuing use with adequate warnings. Was this the right decision? What happened to the long-term recipients who were receiving benefits from this drug? Did they transfer to an older antidepressant, or to a newer one (for which we had no comparable information), or discontinue treatment? What were the outcomes in relation to recurrence of depression, suicides and adverse effects to replacement therapies? Unfortunately, we do not know the answers to these questions. Clearly, the company involved in manufacturing nomifensine was not going to fund such a study.

A more recent example has been the change in drug use patterns that has followed the various safety restrictions and withdrawals in the antipsychotic drugs class. As thioridazine fell from favour due to a combination of demonstrated safety concerns and lack of efficacy in dementia sufferers, so patients were treated with newer (and more expensive) atypical antipsychotics. In due course, drugs from this class prescribed to sufficient numbers of patients showed statistically significant problems with excess cardiac

and cerebrovascular events. Now many of those are disallowed. The result? We are using even newer drugs that have not been used in adequate amounts to allow any sort of quantification of risk, or we are using old drugs with very significant tolerability and safety problems, for example chlorpromazine and haloperidol. Has public health been well served by this sequence? A study to assess the balance of risks and benefits over time would need to include not only life-threatening events, but also quality-of-life issues, functional ability and economic aspects too.

The COX-2 story has been covered elsewhere in this book. Regulatory authorities were catapulted into the limelight because of the company decision to withdraw rofecoxib from the marketplace, in turn precipitated by emerging results of an increased risk of myocardial infarction from a (unfinished) randomised placebo controlled trial. What were the main lessons for pharmacovigilance from this still-evolving sequence of events? A number of points are worth mentioning. First, drugs are usually licensed on surrogate endpoints, so we must keep an open mind about all-cause outcomes to ensure that the risk–benefit balance remains positive. In this case, despite the fact that core efficacy was no different from comparators, use of a drug was driven by the rationale that certain side effects might be avoided. This channelling of use was bound to affect the overall risk–benefit ratio. Secondly, we must be alert to the signals of science. A large outcome study with this drug had shown a very weak signal of cardiovascular events but no notice was taken, while pathophysiological plausibility had already been published and discussed. Thirdly, we are reminded that all methods of assessing post-marketing safety have their place. Numerous observational studies on COX-2 drugs had indicated a possible hazard, while it was the ‘gold standard’ RCT (albeit unfinished, with all the problems attendant on that aspect) that brought matters to a head. Finally, the perils of direct to consumer and ‘blockbuster’ marketing are plain to see. Excessive marketing zeal is likely to have exacerbated the channelling phenomenon and may also have stimulated exposure of those who would have been deemed at risk from, and would otherwise have remained unexposed to, other older drugs.

The issue of regulatory response to signals or demonstrated hazards is one of public health, and

thus requires public funding. With the continuing development of multipurpose databases and other data resources, we should be better at managing such events in future. The need for post-withdrawal surveillance studies in large databases is likely to persist so that some of these questions can be answered. Sensible collaboration among pharmaceutical companies, academic researchers and regulatory authorities is surely to be encouraged.

CONCLUSIONS

The future for pharmacovigilance and pharmacoepidemiology should be bright. That there is a need for this type of information is without doubt. The original

vision of Professor Finney that it should be possible to uncover most significant drug-induced disorders by systematic analysis of routine information collected as part of everyday clinical practice is on the verge of fulfillment. Funding is a chronic problem for workers in the field. The pharmaceutical industry cannot be expected to fund all this effort. So far it has contributed the lion's share of the initiative. Research Councils and others involved in the public conduct of affairs also need to contribute if the systems we have evolved to date are to realise their full potential. The signs are good with the Medicines and Healthcare products Regulatory Agency in the United Kingdom now contributing substantially to the development of the General Practice Research Database.

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Figure 32.1. Exanthematous morbilliform eruption consisting of erythematous macules and papules of the trunk.



Figure 32.3. Bullous eruption of the arm corresponding to a phototoxic eruption on a sun-exposed area.



Figure 32.2. Urticaria with oedematous papules and plaques, which generally last a few hours.



Figure 32.4. Cutaneous necrotizing vasculitis, consisting of purpuric papules, which predominate on the lower extremities.



Figure 32.5. Acute generalized exanthematous pustulosis.



Figure 32.6. DRESS syndrome presenting as exfoliative dermatitis.



Figure 32.7. Fixed drug eruption, characterized by round, sharply demarcated erythematous plaques.



Figure 32.8. Drug-induced pemphigus with erosion of mucous membrane.



Figure 32.9. Toxic epidermal necrolysis characterized by skin necrosis, with flaccid blisters and epidermal detachment on the trunk.