# Part I

# Introduction

# 1

# What Is Pharmacoepidemiology?

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> *A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals.*
>
> Sir William Osler, 1891

In recent decades, modern medicine has been blessed with a pharmaceutical armamentarium that is much more powerful than it had before. Although this has given healthcare providers the ability to provide better medical care for their patients, it has resulted too in the ability to do much greater harm. It has also generated an enormous number of product liability suits against pharmaceutical manufacturers, some appropriate and others inappropriate. In fact, the history of drug regulation parallels the history of major adverse drug reaction "disasters." Each change in pharmaceutical law was a political reaction to an epidemic of adverse drug reactions. A 1998 study estimated that 100 000 Americans die each year from adverse drug reactions, and 1.5 million US hospitalizations each year result from adverse drug reactions; yet, 20–70% of adverse drug reactions may be preventable [1]. The harm that drugs can cause has also led to the development of the field of pharmacoepidemiology, which is the focus of this book. More recently, the field has expanded its focus to include in addition many issues other than adverse reactions.

To clarify what is, and what is not, included within the discipline of pharmacoepidemiology, this chapter will begin by defining pharmacoepidemiology, differentiating it from other related fields. The history of drug regulation will then be briefly and selectively reviewed, focusing on the US experience as an example, demonstrating how it has led to the development of this new field. Next, the current regulatory process for the approval of new drugs will be outlined, in order to place the use of pharmacoepidemiology and postmarketing drug surveillance into proper perspective. Finally, the potential scientific and clinical contributions of pharmacoepidemiology will be discussed.

## Definition of Pharmacoepidemiology

*Pharmacoepidemiology* is the study of the use of and the effects of drugs in large numbers of people. The term pharmacoepidemiology obviously contains two components: "pharmaco" and "epidemiology." In order to better appreciate

*Pharmacoepidemiology*, Sixth Edition. Edited by Brian L. Strom, Stephen E. Kimmel and Sean Hennessy.
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and understand what is and what is not included in this new field, it is useful to compare its scope to that of other related fields. The scope of pharmacoepidemiology will first be compared to that of clinical pharmacology, and then to that of epidemiology.

## Pharmacoepidemiology versus Clinical Pharmacology

*Pharmacology* is the study of the effects of drugs. *Clinical pharmacology* is the study of the effects of drugs in humans (see also Chapter 2). Pharmacoepidemiology obviously can be considered, therefore, to fall within clinical pharmacology. In attempting to optimize the use of drugs, one central principle of clinical pharmacology is that therapy should be individualized, or tailored, to the needs of the particular patient at hand. This individualization of therapy requires the determination of a risk/benefit ratio specific to the patient. Doing so requires a prescriber to be aware of the potential beneficial and harmful effects of the drug in question and to know how elements of the patient's clinical status might modify the probability of a good therapeutic outcome. For example, consider a patient with a serious infection, serious liver impairment, and mild impairment of his or her renal function. In considering whether to use gentamicin to treat the infection, it is not sufficient to know that gentamicin has a small probability of causing renal disease. A good clinician should realize that a patient who has impaired liver function is at a greater risk of suffering from this adverse effect than one with normal liver function [2]. Pharmacoepidemiology can be useful in providing information about the beneficial and harmful effects of any drug, thus permitting a better assessment of the risk/benefit balance for the use of any particular drug in any particular patient.

Clinical pharmacology is traditionally divided into two basic areas: pharmacokinetics and pharmacodynamics. *Pharmacokinetics* is the study of the relationship between the dose administered of a drug and the serum or blood level achieved. It deals with drug absorption, distribution, metabolism, and excretion. *Pharmacodynamics* is the study of the relationship between drug level and drug effect. Together, these two fields allow one to predict the effect one might observe in a patient from administering a certain drug regimen. Pharmacoepidemiology encompasses elements of both of these fields, exploring the effects achieved by administering a drug regimen. It does not normally involve or require the measurement of drug levels. However, pharmacoepidemiology can be used to shed light on the pharmacokinetics of a drug when used in clinical practice, such as exploring whether aminophylline is more likely to cause nausea when administered to a patient who is simultaneously taking cimetidine. However, to date this is a relatively novel application of the field.

Specifically, the field of pharmacoepidemiology has primarily concerned itself with the study of adverse drug effects. Adverse reactions have traditionally been separated into those which are the result of an exaggerated but otherwise usual pharmacologic effect of the drug, sometimes called *type A reactions*, versus those which are aberrant effects, so called *type B reactions* [3]. Type A reactions tend to be common, dose-related, predictable, and less serious. They can usually be treated by simply reducing the dose of the drug. They tend to occur in individuals who have one of three characteristics. First, the individuals may have received more of a drug than is customarily required. Second, they may have received a conventional amount of the drug, but they may metabolize or excrete it unusually slowly, leading to drug levels that are too high (see also Chapter 2). Third, they may have normal drug levels, but for some reason are overly sensitive to the drug.

In contrast, type B reactions tend to be uncommon, not related to dose, unpredictable,

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and potentially more serious. They usually require cessation of the drug. They may be due to what are known as hypersensitivity reactions or immunologic reactions. Alternatively, type B reactions may be some other idiosyncratic reaction to the drug, either due to some inherited susceptibility (e.g., glucose-6-phosphate dehydrogenase deficiency) or due to some other mechanism. Regardless, type B reactions are the most difficult to predict or even detect, and represent the major focus of many pharmacoepidemiologic studies of adverse drug reactions.

One typical approach to studying adverse drug reactions has been the collection of spontaneous reports of drug-related morbidity or mortality (see Chapter 10), sometimes called pharmacovigilance (although other times that term is used to refer to all of pharmacoepidemiology). However, determining causation in case reports of adverse reactions can be problematic (see Chapter 29), as can attempts to compare the effects of drugs in the same class (see Chapter 26). Further, drug–drug interactions, predicted based on pharmacokinetic data (see Chapter 2), require massive sample sizes to confirm in people (see Chapter 40). This has led academic investigators, industry, the US Food and Drug Administration (FDA), and the legal community to turn to the field of epidemiology. Specifically, *studies of adverse effects* have been supplemented with *studies of adverse events*. In the former, investigators examine case reports of purported adverse drug reactions and attempt to make a subjective clinical judgment on an *individual* basis about whether the adverse outcome was actually caused by the antecedent drug exposure. In the latter, controlled studies are performed examining whether the adverse outcome under study occurs more often in an exposed *population* than in an unexposed population. This marriage of the fields of clinical pharmacology and epidemiology has resulted in the development of a further field: pharmacoepidemiology.

## Pharmacoepidemiology versus Epidemiology

Epidemiology is the study of the distribution and determinants of diseases in populations (see Chapter 3). Since pharmacoepidemiology is the study of the use of and effects of drugs in large numbers of people, it obviously falls within epidemiology as well. Epidemiology is also traditionally subdivided into two basic areas. The field began as the study of infectious diseases in large populations; that is, epidemics. It has since been expanded to encompass the study of chronic diseases. The field of pharmacoepidemiology uses the techniques of chronic disease epidemiology to study the use of and the effects of drugs. Although application of the methods of pharmacoepidemiology can be useful in undertaking the clinical trials of drugs that are performed before marketing [4], the major application of these principles is after drug marketing. This has primarily been in the context of postmarketing drug surveillance, although in recent years the interests of pharmacoepidemiologists have broadened considerably. Now, as will be made clearer in future chapters, pharmacoepidemiology is considered of importance in the whole life cycle of a drug, from the time it is first discovered or synthesized through to when it is no longer sold as a drug.

Thus, pharmacoepidemiology is a relatively new applied field, bridging between clinical pharmacology and epidemiology. From clinical pharmacology, pharmacoepidemiology borrows its focus of inquiry. From epidemiology, pharmacoepidemiology borrows its methods of inquiry. In other words, it applies the methods of epidemiology to the content area of clinical pharmacology. In the process, multiple special logistical approaches have been developed and multiple special methodologic issues have arisen. These are the primary foci of this book.

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## Historical Background

### Early Legislation

The history of drug regulation in the US is similar to that in most developed countries, and reflects the growing involvement of governments in attempting to insure that only safe and effective drug products were available and that appropriate manufacturing and marketing practices were used. The initial US law, the Pure Food and Drug Act, was passed in 1906, in response to excessive adulteration and misbranding of the food and drugs available at that time. There were no restrictions on sales or requirements for proof of the efficacy or safety of marketed drugs. Rather, the law simply gave the federal government the power to remove from the market any product that was adulterated or misbranded. The burden of proof was on the federal government.

In 1937, over 100 people died from renal failure as a result of the marketing by the Massengill Company of elixir of sulfanilimide dissolved in diethylene glycol [5]. In response, Congress passed the 1938 Food, Drug, and Cosmetic Act. Preclinical toxicity testing was required for the first time. In addition, manufacturers were required to gather clinical data about drug safety and to submit these data to FDA before drug marketing. The FDA had 60 days to object to marketing or else it would proceed. No proof of efficacy was required.

Little attention was paid to adverse drug reactions until the early 1950s, when it was discovered that chloramphenicol could cause aplastic anemia [6]. In 1952, the first textbook of adverse drug reactions was published [7]. In the same year, the American Medical Association (AMA) Council on Pharmacy and Chemistry established the first official registry of adverse drug effects, to collect cases of drug-induced blood dyscrasias [8]. In 1960, the FDA began to collect reports of adverse drug reactions and sponsored new hospital-based drug-monitoring programs. The Johns Hopkins Hospital and the Boston Collaborative Drug Surveillance Program developed the use of in-hospital monitors to perform cohort studies to explore the short-term effects of drugs used in hospitals [9,10]. This approach was later to be transported to the University of Florida–Shands Teaching Hospital as well [11].

In the winter of 1961, the world experienced the infamous "thalidomide disaster." Thalidomide was marketed as a mild hypnotic, and had no obvious advantage over other drugs in its class. Shortly after its marketing, a dramatic increase was seen in the frequency of a previously rare birth defect, phocomelia: the absence of limbs or parts of limbs, sometimes with the presence instead of flippers [12]. Epidemiologic studies established its cause to be *in utero* exposure to thalidomide. In the UK, this resulted in the establishment in 1968 of the Committee on Safety of Medicines. Later, the World Health Organization (WHO) established a bureau to collect and collate information from this and other similar national drug-monitoring organizations (see Chapter 10).

The US had never permitted the marketing of thalidomide and so was fortunately spared this epidemic. However, the "thalidomide disaster" was so dramatic that it resulted in regulatory change in the US as well. Specifically, in 1962 the Kefauver–Harris Amendments were passed. These amendments strengthened the requirements for proof of drug safety, requiring extensive preclinical pharmacologic and toxicologic testing before a drug could be tested in humans. The data from these studies were required to be submitted to the FDA in an Investigational New Drug (IND) application before clinical studies could begin. Three explicit phases of clinical testing were defined, which are described in more detail later in this chapter. In addition, a new requirement was added to the clinical testing, for "substantial evidence that the drug will have the effect it purports or is represented to have." "Substantial evidence" was defined as "adequate and well-controlled investigations,

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including clinical investigations." Functionally, this has generally been interpreted as requiring randomized clinical trials to document drug efficacy before marketing. This new procedure also delayed drug marketing until the FDA explicitly gave approval. With some modifications, these are the requirements still in place in the US today. In addition, the amendments required the review of all drugs approved between 1938 and 1962, to determine if they too were efficacious. The resulting DESI (Drug Efficacy Study Implementation) process, conducted by the National Academy of Sciences' National Research Council with support from a contract from the FDA, was not completed until years later, and resulted in the removal from the US market of many ineffective drugs and drug combinations. The result of all these changes was a great prolongation of the approval process, with attendant increases in the cost of drug development, in what was termed the "drug lag" [13] (discussed later in the chapter). However, the drugs that do reach the market are presumably much safer and more effective.

## Drug Crises and Resulting Regulatory Actions

Despite the more stringent process for drug regulation, subsequent years have seen a series of major adverse drug reactions. Subacute myelo-optic-neuropathy (SMON) was found in Japan to be caused by clioquinol, a drug marketed in the early 1930s but not discovered to cause this severe neurologic reaction until 1970 [14]. In the 1970s, clear cell adenocarcinoma of the cervix and vagina and other genital malformations were found to be due to *in utero* exposure to diethylstilbestrol two decades earlier [15]. The mid-1970s saw the UK discovery of the oculomucocutaneous syndrome caused by practolol, five years after drug marketing [16]. In 1980, the drug ticrynafen was noted to cause deaths from liver disease [17]. In 1982, benoxaprofen was noted to do the same [18]. Subsequently the use of zomepirac, another nonsteroidal anti-inflammatory drug, was noted to be associated with an increased risk of anaphylactoid reactions [19]. Serious blood dyscrasias were linked to phenylbutazone [20]. Small intestinal perforations were noted to be caused by a particular slow-release formulation of indomethacin [21]. Bendectin®, a combination product indicated to treat nausea and vomiting in pregnancy, was removed from the market because of litigation claiming it was a teratogen, despite the absence of valid scientific evidence to justify this claim [22] (see Chapter 22). Acute flank pain and reversible acute renal failure were noted to be caused by suprofen [23]. Isotretinoin was almost removed from the US market because of the birth defects it causes [24,25]. The Eosinophilia-Myalgia syndrome was linked to a particular brand of L-tryptophan [26]. Triazolam, thought by The Netherlands in 1979 to be subject to a disproportionate number of central nervous system side effects [27], was discovered by the rest of the world to be problematic in the early 1990s [28–30]. Silicone breast implants, inserted by the millions in the US for cosmetic purposes, were accused of causing cancer, rheumatologic disease, and many other problems, and restricted from use except for breast reconstruction after mastectomy [31]. Human insulin was marketed as one of the first of the new biotechnology drugs, but soon thereafter was accused of causing a disproportionate amount of hypoglycemia [32–36]. Fluoxetine was marketed as a major new, important and commercially successful psychiatric product, but then lost a large part of its market due to accusations about its association with suicidal ideation [37,38]. An epidemic of deaths from asthma in New Zealand was traced to fenoterol [39–41], and later data suggested that similar, although smaller, risks might be present with other beta-agonist inhalers [42]. The possibility was raised of cancer from depot-medroxyprogesterone, resulting in initial refusal to allow its marketing for this purpose in the US

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[43], multiple studies [44,45], and ultimate approval. Arrhythmias were linked to the use of the antihistamines terfenadine and astemizole [46,47]. Hypertension, seizures, and strokes were noted from postpartum use of bromocriptine [48,49]. Multiple different adverse reactions were linked to temafloxacin [50]. Other examples include liver toxicity from amoxicillin-clavulanic acid [51]; liver toxicity from bromfenac [52,53]; cancer, myocardial infarction, and gastrointestinal bleeding from calcium channel blockers [54–61]; arrhythmias with cisapride interactions [62–65]; primary pulmonary hypertension and cardiac valvular disease from dexfenfluramine and fenfluramine [66–68]; gastrointestinal bleeding, postoperative bleeding, deaths, and many other adverse reactions associated with ketorolac [69–72]; multiple drug interactions with mibefradil [73]; thrombosis from newer oral contraceptives [74–77]; myocardial infarction from sildenafil [78]; seizures from tramadol [79,80]; anaphylactic reactions from vitamin K [81]; liver toxicity from troglitazone [82–85]; and intussusception from rotavirus vaccine [86].

Later drug crises have occurred due to allegations of ischemic colitis from alosetron [87]; rhabdomyolysis from cerivastatin [88]; bronchospasm from rapacuronium [89]; torsades de pointes from ziprasidone [90]; hemorrhagic stroke from phenylpropanolamine [91]; arthralgia, myalgia, and neurologic conditions from Lyme vaccine [92]; multiple joint and other symptoms from anthrax vaccine [93]; myocarditis and myocardial infarction from smallpox vaccine [94]; and heart attack and stroke from rofecoxib [95].

Major adverse drug reactions continue to plague new drugs, and in fact have been as common if not more common in the last several decades. In total, 36 different oral prescription drug products have been removed from the US market since 1980 alone (alosetron, 2000; aprotinin, 2007; astemizole, 1999; benoxaprofen, 1982; bromfenac, 1998; cerivastatin, 2001; cisapride, 2000; dexfenfluramine, 1997; efalizumab, 2009; encainide, 1991; etretinate, 1998; fenfluramine, 1998; flosequinan, 1993; grepafloxin, 1999; levomethadyl, 2003; lumiracoxib, 2007; mibefradil, 1998; natalizumab, 2005; nomifensine, 1986; palladone, 2005; pemoline, 2005; pergolide, 2010; phenylpropanolamine, 2000; propoxyphene, 2010; rapacuronium, 2001; rimonabant, 2010; rofecoxib, 2004; sibutramine, 2010; suprofen, 1987; tegaserod, 2007; terfenadine, 1998; temafloxacin, 1992; ticrynafen, 1980; troglitazone, 2000; valdecoxib, 2007; zomepirac, 1983). The licensed vaccines against rotavirus [86] and Lyme [92] were also withdrawn because of safety concerns (see Chapter 20). Further, between 1990 and 2004, at least 15 noncardiac drugs, including astemizole, cisapride, droperidol, grepafloxacin, halofantrine, pimozide, propoxyphene, rofecoxib, sertindole, sibutramine, terfenadine, terodiline, thioridazine, vevacetylmethadol, and ziprasidone, were subject to significant regulatory actions because of cardiac concerns [96].

Since 1993, trying to deal with drug safety problems, the FDA morphed its extant spontaneous reporting system into the MedWatch program of collecting spontaneous reports of adverse reactions (see Chapters 8 and 10), as part of that issuing monthly notifications of label changes. Compared to the 20–25 safety-related label changes that were being made every month by mid-1999, between 19 and 57 safety-related label changes (boxed warnings, warnings, contraindications, precautions, adverse events) were made every month in 2009 [97]. From January of 2010 to July of 2016, there were 3324 safety-related label changes, with a range per month of 19–87 (median 41). Among all safety-related label changes (January 2010 to July 2016), 8%, 13%, 56%, and 65% were boxed warnings, contraindications, warnings, and precautions, respectively [97].

According to a study from a number of years ago by the US Government Accountability Office, 51% of approved drugs have serious

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adverse effects not detected before approval [98]. Further, there is recognition that the initial dose recommended for a newly marketed drug is often incorrect, and needs monitoring and modification after marketing [99–101].

In some of the examples given, the drug was never convincingly linked to the adverse reaction, yet many of these accusations led to the removal of the drug involved from the market. Interestingly, however, this withdrawal was not necessarily performed in all of the different countries in which each drug was marketed. Most of these discoveries have led to litigation as well, and a few have even resulted in criminal charges against the pharmaceutical manufacturer and/or some of its employees (see Chapter 9).

## Legislative Actions Resulting from Drug Crises

Through the 1980s, there was concern that an underfunded FDA was approving drugs too slowly, and that the US suffered, compared to Europe, from a "drug lag" [102]. To provide additional resources to the FDA to help expedite the drug review and approval process, Congress passed in 1992 the Prescription Drug User Fee Act (PDUFA), allowing the FDA to charge manufacturers a fee for reviewing new drug applications [103,104]. This legislation was reauthorized by Congress three more times: PDUFA II, also called the Food and Drug Modernization Act of 1997; PDUFA III, also called the Public Health Security and Bioterrorism Preparedness and Response Act of 2002; and PDUFA IV, also called the Food and Drug Administration Amendments (FDAAA-PL 110-85) of 2007. The goals for PDUFA I–IV were to enable the FDA to complete review of over 90% of priority drug applications in 6 months, and complete review of over 90% of standard drug applications in 12 months (under PDUFA I) or 10 months (under PDUFA II–IV). In addition to reauthorizing the collection of user fees from the pharmaceutical industry, PDUFA II allowed the FDA to accept a single well-controlled clinical study under certain conditions, to reduce drug development time. The result was a system where more than 550 new drugs were approved by the FDA in the 1990s [105].

However, whereas 1400 FDA employees in 1998 worked with the drug approval process, only 52 monitored safety; FDA spent a mere $2.4 million on extramural safety research. This state of affairs coincided with the growing numbers of drug crises already cited. With successive reauthorizations of PDUFA, this markedly changed. PDUFA III for the first time allowed the FDA to use a small portion of the user fees for postmarketing drug safety monitoring, to address safety concerns.

Nevertheless, there now was growing concern, in Congress and among the US public, that perhaps the FDA was approving drugs too *fast* [106,107]. There were also calls for the development of an independent drug safety board, analogous to the National Transportation Safety Board [108,109], with a mission much wider than the FDA's regulatory mission, to complement the latter. For example, such a board could investigate drug safety crises such as those discussed, looking for ways to prevent them, and could deal with issues such as improper physician use of drugs, the need for training, and the development of new approaches to the field of pharmacoepidemiology.

Recurrent concerns about the FDA's management of postmarketing drug safety issues led to a systematic review of the entire drug risk assessment process. In 2006, the US General Accountability Office issued its report of a review of the organizational structure and effectiveness of FDA's postmarketing drug safety decision-making [100], followed in 2007 by the Institute of Medicine's independent assessment [110]. Important weaknesses were noted in the current system, including failure of the FDA's Office of New Drugs and Office of Drug Safety to communicate with each other on safety issues, failure of the FDA to track ongoing postmarketing studies, the ambiguous role of the

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FDA's Office of Drug Safety in scientific advisory committees, limited authority by the FDA to require the pharmaceutical industry to perform studies to obtain needed data, concerns about culture problems at the FDA where recommendations by members of its drug safety staff were not followed, and concerns about conflicts of interest involving advisory committee members. This Institute of Medicine report was influential in shaping PDUFA IV.

Indeed, with the passage of those amendments, the FDA's authority was substantially increased, with the ability, for example, to require postmarketing studies and levy heavy fines if these requirements were not met. Further, its resources were substantially increased, with a specific charge to (i) fund epidemiology best practices and data acquisition ($7 million in fiscal 2008, increasing to $9.5 million in fiscal 2012); (ii) fund new drug trade name review ($5.3 million in fiscal 2008, rising to $6.5 million in fiscal 2012); and (iii) fund risk management and communication ($4 million in fiscal 2008, rising to $5 million in fiscal 2012) [111] (see also Chapter 24). In addition, in another use of the new PDUFA funds, the FDA plans to develop and implement agency-wide and special-purpose postmarket information technology (IT) systems, including the MedWatch Plus Portal, the FDA Adverse Event Reporting System, the Sentinel System (a virtual national medical product safety system; see Chapter 25), and the Phonetic and Orthographic Computer Analysis System to find similarities in spelling or sound between proposed proprietary drug names that might increase the risk of confusion and medication errors [111].

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), the fifth authorization of PDUFA, expanded the FDA's authority with the ability to safeguard and advance public health by: (i) "giving the authority to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products"; (ii) "promoting innovation to speed patient access to safe and effective products"; (iii) "increasing stakeholder involvement in FDA processes"; and (iv) "enhancing the safety of the drug supply chain" [112]. Also enacted in 2012, the Generic Drug User Fee Amendments (GDUFA) permitted the FDA to assess industry user fees with the intention of increasing the predictability and timeliness of generic drug application reviews [113]. The Biosimilar User Fee Act (BsUFA), also enacted in 2012, authorized the FDA to collect fees directly from biosimilar drug product applicants to expedite the review of biosimilar applications [114]. The FDA Reauthorization Act of 2017 (FDARA) reauthorized PDUFA, GDUFA, and BsUFA through fiscal year 2022.

Among other aims, the 21st Century Cures Act (enacted in December 2016) was intended to expedite the process by which new drugs and devices are approved by easing the requirements put on drug companies looking for FDA approval on new products or new indications on existing drugs. It calls for the use of "data summaries" to support the approval of certain drugs for new indications, rather than full clinical trial data. It also allows drug companies to promote off-label uses to insurance companies, enabling them to expand their markets. Of particular relevance to pharmacoepidemiology, it permits the use of "real world evidence" rather than just clinical trial results [115]. Depending on how these new rules are interpreted, this could massively change drug development in the US, and in particular the role of pharmacoepidemiology in that drug development.

## Intellectual Development of Pharmacoepidemiology Emerging from Drug Crises

Several developments in the 1960s can be thought to have marked the beginning of the field of pharmacoepidemiology. The Kefauver–Harris Amendments that were introduced in

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1962 required formal safety studies for new drug applications. The DESI program that was undertaken by the FDA as part of those amendments required formal efficacy studies for old drugs that were approved earlier. These requirements created a demand for new expertise and new methods. In addition, the mid-1960s saw the publication of a series of drug utilization studies [116–120]. These provided the first descriptive information on how physicians use drugs, and began a series of investigations of the frequency and determinants of poor prescribing (see also Chapters 18 and 19).

In part in response to concerns about adverse drug effects, the early 1970s saw the development of the Drug Epidemiology Unit, now the Slone Epidemiology Center, which extended the hospital-based approach of the Boston Collaborative Drug Surveillance Program by collecting lifetime drug exposure histories from hospitalized patients and using these to perform hospital-based case–control studies [121] (see Chapter 16). The year 1976 saw the formation of the Joint Commission on Prescription Drug Use, an interdisciplinary committee of experts charged with reviewing the state of the art of pharmacoepidemiology at that time, as well as providing recommendations for the future [122]. The Computerized Online Medicaid Analysis and Surveillance System (COMPASS®) was first developed in 1977, using Medicaid billing data to perform pharmacoepidemiologic studies [123] (see Chapter 12). The Drug Surveillance Research Unit, now called the Drug Safety Research Trust, was developed in the UK in 1980, with its innovative system of prescription event monitoring [124] (see Chapter 15). Each of these represented major contributions to the field of pharmacoepidemiology, and together with newer approaches are reviewed in Part III of this book.

In the examples of drug crises mentioned earlier, there were serious but uncommon drug effects, and these experiences led to an accelerated search for new methods to study drug effects in large numbers of patients. This resulted in a shift from adverse effect studies to adverse event studies, with a concomitant increasing use of new data resources and new methods to study adverse reactions. The American Society for Clinical Pharmacology and Therapeutics issued, in 1990, a position paper on the use of purported postmarketing drug surveillance studies for promotional purposes [125], and the International Society for Pharmacoepidemiology (ISPE) issued, in 1996, Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States [126], which were updated in 2007 [127] and 2015. Since the late 1990s, pharmacoepidemiologic research has also been increasingly burdened by concerns about patient confidentiality [128–132] (see also Chapter 31).

There is also increasing recognition that most of the risk from most drugs to most patients occurs from known reactions to old drugs. As an attempt to address concerns about underuse, overuse, and adverse events of medical products and medical errors that may cause serious impairment to patient health, a new program of Centers for Education and Research on Therapeutics (CERTs) was authorized under the FDA Modernization Act of 1997 (as part of the same legislation that reauthorized PDUFA II). Starting in 1999 and incrementally adding more centers in 2002, 2006, and 2007, the Agency for Healthcare Research and Quality (AHRQ) that was selected to administer this program had funded up to 14 CERTs [133], although the program ended in 2016 (see also Chapter 6).

The research and education activities sponsored by AHRQ through the CERTs program since the late 1990s take place in academic centers. The CERTs conduct research on therapeutics, exploring new uses of drugs, ways to improve the effective uses of drugs, and the risks associated with new uses or combinations of drugs. They also develop educational modules and materials for disseminating the research

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findings about medical products. With the development of direct-to-consumer advertising of drugs since the mid-1980s in the US, the CERTs' role in educating the public and healthcare professionals by providing evidence-based information has become especially important.

Another impetus for research on drugs resulted from one of the mandates (in Sec. 1013) of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 to provide beneficiaries with scientific information on the outcomes, comparative clinical effectiveness, and appropriateness of healthcare items and services [134]. In response, the AHRQ created in 2005 the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network to support in academic settings the conduct of studies on the effectiveness, safety, and usefulness of drugs and other treatments and services [135]. This too ended, in 2012.

Another major new initiative of close relevance to pharmacoepidemiology is risk management. There is increasing recognition that the risk/benefit balance of some drugs can only be considered acceptable with active management of their use, to maximize their efficacy and/or minimize their risk. In response, in the late 1990s, new initiatives ranged from FDA requirements for risk management plans to an FDA Drug Safety and Risk Management Advisory Committee, and the issuing of risk minimization and management guidance in 2005. More information is provided in Chapters 8 and 24.

Another initiative closely related to pharmacoepidemiology is the Patient Safety movement. In the Institute of Medicine's report, "To Err Is Human: Building a Safer Health System," the authors note that (i) "even apparently single events or errors are due most often to the convergence of multiple contributing factors"; (ii) "preventing errors and improving safety for patients requires a systems approach in order to modify the conditions that contribute to errors"; and (iii) "the problem is not bad people; the problem is that the system needs to be made safer" [136]. In this framework, the concern is not about substandard or negligent care, but rather about errors made by even the best trained, brightest, and most competent professional health caregivers and/or patients. From this perspective, the important research questions ask about the conditions under which people make errors, the types of errors being made, and the types of systems that can be put into place to prevent errors altogether when possible. Errors that are not prevented must be identified and corrected efficiently and quickly, before they inflict harm. Turning specifically to medications, from 2.4% to 6.5% of hospitalized patients suffer adverse drug effects, prolonging hospital stays by 2 days, and increasing costs by $2000–2600 per patient [137–140]. Over 7000 US deaths were attributed to medication errors in 1993 [141]. Although these estimates have been disputed [142–147], the overall importance of reducing these errors has not been questioned. In recognition of this problem, the AHRQ launched a major new grant program of over 100 projects at its peak with over $50 million/year of funding. While only a portion of this is dedicated to medication errors, they are clearly a focus of interest and relevance to many. More information is provided in Chapter 41.

The 1990s and especially the 2000s saw another shift in the field, away from its exclusive emphasis on drug utilization and adverse reactions, to the inclusion of other interests as well, such as the use of pharmacoepidemiology to study beneficial drug effects, the application of health economics to the study of drug effects, quality-of-life studies, meta-analysis, studies of biologics, data mining, studies of drugs of abuse, drug interactions, and so on. These new foci are discussed in more detail in Parts IV and V of this book.

Moreover, with the publication of the results from the Women's Health Initiative indicating that combination hormone replacement therapy

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causes an increased risk of myocardial infarction rather than a decreased risk [148,149], there has been increased concern about reliance solely on nonexperimental methods to study drug safety after marketing [150–153]. This led to increased use of massive randomized clinical trials as part of postmarketing surveillance (see Chapter 32). This is especially important because often the surrogate markers used for drug development cannot necessarily be relied upon to map completely to true clinical outcomes [154].

Finally, with the advent of the Obama administration in the US, there was enormous interest in comparative effectiveness research (CER). CER was defined in 2009 by the Federal Coordinating Council for Comparative Effectiveness Research as "the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances" [155]. By this definition, CER includes three key elements: (i) evidence synthesis, evidence generation, and evidence dissemination. Typically, CER is conducted through observational studies of either large administrative or medical record databases (see Part IIIb), or large naturalistic clinical trials (see Chapter 32). In many ways, the UK has been focusing on CER for years via its National Institute for Health and Clinical Excellence (NICE), an independent organization responsible for providing national guidance on promoting good health and preventing and treating ill health [156]. However, the Obama administration included $1.1 billion for CER in its federal stimulus package, and had plans for hundreds of millions of dollars of support per year thereafter. While CER does not overlap completely with pharmacoepidemiology, the scientific approaches are very close. Pharmacoepidemiologists evaluate the use and effects of medications. CER investigators compare, in the real world, the safety and benefits of one treatment to those of another. CER extends beyond pharmacoepidemiology in that it can include more than just drugs; pharmacoepidemiology extends beyond CER in that it includes studies comparing exposed to unexposed patients, not just alternative exposures. However, to date, most work done in CER has been in pharmacoepidemiology. See Chapter 26 for more discussion.

## The Current Drug Approval Process

### Drug Approval in the US

Until the early 1990s, there was a decline in the number of novel drugs approved per year [101,157], while the cost of bringing a drug to market has risen sharply [158]. The total cost of drug development to the pharmaceutical industry increased from $24 billion in 1999, to $32 billion in 2002 [159], and to $65.2 billion on research and development in 2008 [160]. The cost to discover and develop a drug that successfully reached the market rose from over $800 million in 2004 [161] to an estimated $1.3–1.7 billion currently [162]. In addition to the sizable costs of research and development, a substantial part of the total cost is determined also by the regulatory requirement to test new drugs during several premarketing and postmarketing phases, as will be reviewed next.

The current drug approval process in the US and most other developed countries includes preclinical animal testing followed by three phases of clinical testing. Phase I testing is usually conducted in just a few normal volunteers, and represents the initial trials of the drug in

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humans. Phase I trials are generally conducted by clinical pharmacologists, to determine the metabolism of the drug in humans, a safe dosage range in humans, and to exclude any extremely common toxic reactions that are unique to humans.

Phase II testing is also generally conducted by clinical pharmacologists, on a small number of patients who have the target disease. Phase II testing is usually the first time patients are exposed to the drug. Exceptions are drugs that are so toxic that it would not normally be considered ethical to expose healthy individuals to them, like cytotoxic drugs. For these, patients are used for Phase I testing as well. The goals of Phase II testing are to obtain more information on the pharmacokinetics of the drug and on any relatively common adverse reactions, and to obtain initial information on its possible efficacy. Specifically, Phase II is used to determine the daily dosage and regimen to be tested more rigorously in Phase III.

Phase III testing is performed by clinician-investigators in a much larger number of patients, in order to rigorously evaluate the drug's efficacy and provide more information on its toxicity. At least one of the Phase III studies needs to be a randomized clinical trial (see Chapter 3). To meet FDA standards, at least one of the randomized clinical trials usually needs to be conducted in the US. Generally between 500 and 3000 patients are exposed to a drug during Phase III, even if drug efficacy can be demonstrated with much smaller numbers, in order to be able to detect less common adverse reactions. For example, a study including 3000 patients would allow one to be 95% certain of detecting any adverse reactions that occur in at least 1 exposed patient out of 1000. At the other extreme, a total of 500 patients would allow one to be 95% certain of detecting any adverse reactions that occur in 6 or more patients out of every 1000 exposed. Adverse reactions that occur less commonly than these are less likely to be detected in these premarketing studies. The sample sizes needed to detect drug effects are discussed in more detail in Chapter 4. Nowadays, with the increased focus on drug safety, premarketing dossiers are sometimes being extended well beyond 3000 patients. However, as one can tell from the sample size calculations in Chapter 4 and Appendix A, by itself these larger numbers lead to little additional information being gained about adverse drug reactions, unless one were to increase to perhaps 30 000 patients, well beyond the scope of most premarketing studies.

Finally, Phase IV testing is the evaluation of the effects of drugs after general marketing. The bulk of this book is devoted to such efforts.

## Drug Approval in Other Countries

Outside the US, national systems for the regulation and approval of new drugs vary greatly, even among developed countries and especially between developed and developing countries. While in most developed countries at least the general process of drug development is very analogous to that in the US, its implementation varies widely. A WHO comparative analysis of drug regulation in 10 countries found that not all even have a written national drug policy document [163]. Regulation of medicines in some countries is centralized in a single agency that performs the gamut of functions, involving product registration, licensing, product review, approval for clinical trials, postmarketing surveillance, and inspection of manufacturing practice. Examples for this are Health Canada [164], the China Food and Drug Administration (CFDA) [165], the Medicines Agency in Denmark [166], the Medicines Agency in Norway [167], the Center for Drug Administration in Singapore [168], and the Medicines and Medical Devices Safety Authority in New Zealand [169]. In other countries, regulatory functions are distributed among different agencies. An example of the latter is The Netherlands, where the Ministry of Health,

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Welfare and Sports performs the functions of licensing; the Healthcare Inspectorate checks on general manufacturing practice; and the Medicines Evaluation Board performs the functions of product assessment and registration and adverse drug reaction monitoring [163]. As another example, in Singapore two independent agencies (the Center for Pharmaceutical Administration and the Center for Drug Evaluation) were previously responsible for medicinal regulation and evaluation, but are currently merged into a single agency (the Center for Drug Administration) [168].

Another dimension on which countries may vary is the degree of autonomy of regulatory decisions from political influence. Drug regulation in most countries is performed by a department within the executive branch (Australia, Cuba, Cyprus, Tunisia, and Venezuela are examples cited by the WHO report, and Denmark [166], India [170], and New Zealand [169] are other examples). In other countries, this function is performed by an independent commission or board. An example of the latter arrangement is The Netherlands, where members of the Medicines Evaluation Board are appointed directly by the Crown, thereby enabling actions that are independent of interference by other government authorities, such as the Ministry of Health [163]. All 10 countries examined by the WHO require registration of pharmaceutical products, but they differ on the documentation requirements for evidence of safety and efficacy [163]. Some countries carry out independent assessments while others, especially many developing countries, rely on WHO assessments or other sources [163]. With the exception of Cyprus, the remaining nine countries surveyed by the WHO were found to regulate the conduct of clinical trials, but with varying rates of participation of healthcare professionals in reporting adverse drug reactions [163]. Another source noted that countries also differ on the extent of emphasis on quantitative or qualitative analysis for assessing pre- and postmarketing data [171].

Further, within Europe, each country has its own regulatory agency, for instance the UK Medicines and Healthcare Products Regulatory Agency (MHRA), formed in 2003 as a merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). In addition, since January 1998, some drug registration and approval within the European Union (EU) has shifted away from the national licensing authorities of EU members to the centralized authority of the European Medicines Evaluation Agency (EMEA), which was established in 1993 [172]. To facilitate this centralized approval process, the EMEA pushed for harmonization of drug approvals. While the goals of harmonization are to create a single pharmaceutical market in Europe and to shorten approval times, concerns were voiced that harmonized safety standards would lower the stricter standards that were favored by some countries such as Sweden, and would compromise patient safety [173]. Now called the European Medicines Agency (EMA), this is a decentralized EU body responsible for the scientific evaluation and supervision of medicines. These functions are performed by the EMA's Committee for Medicinal Products for Human Use (CHMP). EMA authorization to market a drug is valid in all EU countries, but individual national medicines agencies are responsible for monitoring the safety of approved drugs and sharing this information with the EMA [174].

## Potential Contributions of Pharmacoepidemiology

The potential contributions of pharmacoepidemiology are now well recognized, even though the field is still relatively new. However, some contributions are already apparent (see Table 1.1). In fact, in the 1970s the FDA requested postmarketing research at the time of approval for about one third of drugs, compared to over 70% in the 1990s [175]. Since the passage

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**Table 1.1** Potential contributions of pharmacoepidemiology.

| |
|---|
| A) Information which supplements the information available from premarketing studies – better quantitation of the incidence of known adverse and beneficial effects |
| 1) Higher precision |
| 2) In patients not studied prior to marketing, e.g., the elderly, children, pregnant women |
| 3) As modified by other drugs and other illnesses |
| 4) Relative to other drugs used for the same indication |
| B) New types of information not available from premarketing studies |
| 1) Discovery of previously undetected adverse and beneficial effects |
| i) Uncommon effects |
| ii) Delayed effects |
| 2) Patterns of drug utilization |
| 3) The effects of drug overdoses |
| 4) The economic implications of drug use |
| C) General contributions of pharmacoepidemiology |
| 1) Reassurances about drug safety |
| 2) Fulfillment of ethical and legal obligations |

of PDUFA IV, the FDA has the right to require that such studies be completed. In this section of this chapter, we will first review the potential for pharmacoepidemiologic studies to supplement the information available prior to marketing, and then review the new types of information obtainable from postmarketing pharmacoepidemiologic studies, but not obtainable prior to drug marketing. Finally, we will review the general, and probably most important, potential contributions such studies can make. In each case, the relevant information available from premarketing studies will be briefly examined first, to clarify how postmarketing studies can supplement it.

## Supplementary Information

Premarketing studies of drug effects are necessarily limited in size. After marketing, nonexperimental epidemiologic studies can be performed, evaluating the effects of drugs administered as part of ongoing medical care. These allow the cost-effective accumulation of much larger numbers of patients than those studied prior to marketing, resulting in a more precise measurement of the incidence of adverse and beneficial drug effects (see Chapter 4). For example, at the time of drug marketing, prazosin was known to cause a dose-dependent first dose syncope [176,177], but the FDA requested that the manufacturer conduct a postmarketing surveillance study of the drug in the US to quantitate its incidence more precisely [122]. In recent years, there has even been an attempt, in selected special cases, to release critically important drugs more quickly by taking advantage of the work that can be performed after marketing. Probably the best-known early example was zidovudine [178,179]. More recently, this has been the case with a number of cancer drugs, including at least one where initial expectations of efficacy were not confirmed in definitive trials after marketing, and were then proven again later in a subgroup, leading to the product being removed from the market and then marketed again. As already noted, the increased sample size available after marketing also permits a more precise determination of the correct dose to be used [99,101,180,181]. The study of drug interactions, as previously discussed, is analogous (see also Chapter 40).

Premarketing studies also tend to be very artificial. Important subgroups of patients are not typically included in studies conducted before drug marketing, usually for ethical reasons. Examples include the elderly, children, and pregnant women. Studies of the effects of drugs in these populations generally must be conducted after drug marketing [182]. (See also Chapter 22.)

Additionally, for reasons of statistical efficiency, premarketing clinical trials generally seek subjects who are as homogenous as possible, in order to reduce unexplained variability in the outcome variables measured and increase

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the probability of detecting a difference between the study groups, if one truly exists. For these reasons, certain patients are often excluded, including those with other illnesses or those who are receiving other drugs. Postmarketing studies can explore how factors such as other illnesses and other drugs might modify the effects of the drugs, as well as looking at the effects of differences in drug regimen, adherence, and so on [183]. For example, after marketing, the ophthalmic preparation of timolol was noted to cause many serious episodes of heart block and asthma, resulting in more than 10 deaths. These effects were not detected prior to marketing, as patients with underlying cardiovascular or respiratory disease were excluded from the premarketing studies [184].

Finally, to obtain approval to market a drug, a manufacturer needs to evaluate its overall safety and efficacy, but does not need to evaluate its safety and efficacy relative to any other drugs available for the same indication. To the contrary, with the exception of illnesses that could not ethically be treated with placebos, such as serious infections and malignancies, it is generally considered preferable, or even mandatory, to have studies with placebo controls. There are a number of reasons for this preference. First, it is easier to show that a new drug is more effective than a placebo than to show that it is more effective than another effective drug. Second, one cannot actually prove that a new drug is as effective as a standard drug. A study showing that a new drug is no worse than another effective drug does not provide assurance that it is better than a placebo; one simply could have failed to detect that it was in fact worse than the standard drug. One could require a demonstration that a new drug is more effective than another effective drug, but this is a standard that does not and should not have to be met. Yet, optimal medical care requires information on the effects of a drug relative to the alternatives available for the same indication. This information must often await studies conducted after drug marketing. Indeed, as noted, this is a major component of the new focus on CER (see Chapter 26).

## New Types of Information Not Available from Premarketing Studies

As already mentioned, premarketing studies are necessarily limited in size (see also Chapter 4). The additional sample size available in postmarketing studies permits the study of drug effects that may be uncommon but important, such as drug-induced agranulocytosis [185].

Premarketing studies are also necessarily limited in time; they must come to an end, or the drug could never be marketed. In contrast, postmarketing studies permit the study of delayed drug effects, such as the unusual clear cell adenocarcinoma of the vagina and cervix, which occurred two decades later in women exposed *in utero* to diethylstilbestrol [15].

The patterns of physician prescribing and patient drug utilization often cannot be predicted prior to marketing, despite pharmaceutical manufacturers' best attempts to predict when planning for drug marketing. Studies of how a drug is actually being used, and determinants of changes in these usage patterns, can only be performed after drug marketing (see Chapters 18 and 19).

In most cases, premarketing studies are performed using selected patients who are closely observed. Rarely are there any significant overdoses in this population. Thus, the study of the effects of a drug when ingested in extremely high doses is rarely possible before drug marketing. Again, this must await postmarketing pharmacoepidemiologic studies [186].

Finally, it is only in the past decade or two that pharmacoepidemiologists have become more sensitive to the costs of medical care, and the techniques of health economics been applied to evaluate the cost implications of drug use [187]. It is clear that exploration of the costs of drug use requires consideration of more than just the

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costs of the drugs themselves. The costs of a drug's adverse effects may be substantially higher than the cost of the drug itself, if these adverse effects result in additional medical care and possibly even hospitalizations [188]. Conversely, a drug's beneficial effects could reduce the need for medical care, resulting in savings that could be much larger than the cost of the drug itself. As with studies of drug utilization, the economic implications of drug use can be predicted prior to marketing, but can only be rigorously studied after marketing (see Chapter 34).

### General Contributions of Pharmacoepidemiology

Lastly, it is important to review the general contributions that pharmacoepidemiology can make. As an academic or a clinician, one is most interested in the new information about drug effects and drug costs that can be gained from pharmacoepidemiology. Certainly, these are the findings that receive the greatest public and political attention. However, often no new information is obtained, particularly about new adverse drug effects. This is not a disappointing outcome, but in fact a very reassuring one, and this reassurance about drug safety is one of the most important contributions that pharmacoepidemiologic studies can make. Related to this is the reassurance that the sponsor of the study, whether manufacturer or regulator, is fulfilling its organizational duty ethically and responsibly by looking for any undiscovered problems that may exist. In an era of product liability litigation, this is an important assurance. One cannot change whether a drug causes an adverse reaction, and the fact that it does will hopefully eventually become evident. What can be changed is the perception about whether a manufacturer did everything possible to detect it and was not negligent in its behavior.

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