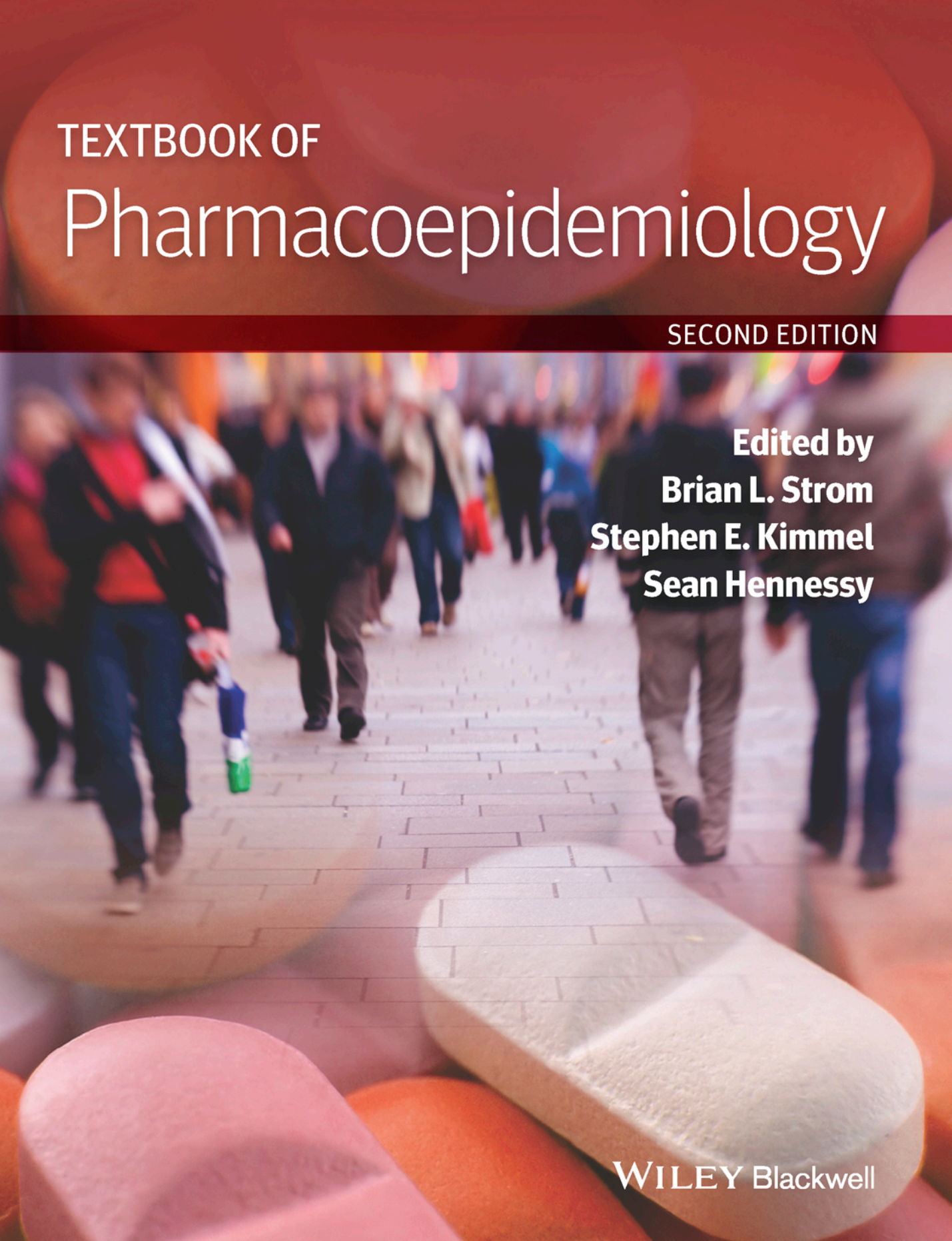
TEXTBOOK OF
Pharmacoepidemiology

SECOND EDITION



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WILEY Blackwell

Textbook of Pharmacoepidemiology

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Preface

It was a remarkable 23 years ago that the first edition of Strom's *Pharmacoepidemiology* was published. The preface to that book stated that pharmacoepidemiology was a new field with a new generation of pharmacoepidemiologists arising to join the field's few pioneers. Over the ensuing 23 years, the field indeed has grown and no longer deserves to be called "new." Many of those "new generation" scientists (including two of the editors of this book) are now "middle-aged" pharmacoepidemiologists. Despite its relatively brief academic life, a short history of pharmacoepidemiology and review of its current state will set the stage for the purpose of this textbook.

Pharmacoepidemiology originally arose from the union of the fields of clinical pharmacology and epidemiology. Pharmacoepidemiology studies the use of and the effects of medical products in large numbers of people and applies the methods of epidemiology to the content area of clinical pharmacology. This field represents the science underlying postmarketing medical product surveillance, studies of the effects of medical products (i.e., drugs, biologicals, devices) performed after a product has been approved for use. In recent years, pharmacoepidemiology has expanded to include many other types of studies, as well.

The field of pharmacoepidemiology has grown enormously since the first publication of Strom. The International Society of Pharmacoepidemiology, an early idea when the first edition of this book was written, has grown into a major international scientific force, with over 1460 members from 54 countries, an extremely successful annual meeting attracting more than 1200 attendees, a large number of very active committees and scientific interest groups, and its own journal. In addition, a number of established journals have targeted pharmacoepidemiology manuscripts as desirable. As new scientific developments occur within mainstream epidemiology, they are rapidly adopted, applied, and advanced within our field as well. We have also become institutionalized as a subfield within the field of clinical pharmacology, with the Drug Safety Scientific Section of the American Society for Clinical Pharmacology and Therapeutics, and with pharmacoepidemiology a required part of the clinical pharmacology board examination.

Most of the major international pharmaceutical companies have founded dedicated units to organize and lead their efforts in pharmacoepidemiology, pharmacoeconomics, and quality-of-life studies. The continuing parade of drug safety crises emphasizes the need for the field, and some foresighted manufacturers have begun to perform "prophylactic" pharmacoepidemiology studies, to have data in hand and available when questions arise, rather than waiting to begin to collect data after a crisis has developed. Pharmacoepidemiologic data are now routinely used for regulatory decisions, and many governmental agencies have been developing and expanding their own pharmacoepidemiology programs. Risk evaluation and mitigation strategies are now required by regulatory bodies with the marketing of new drugs, as a means of improving drugs' benefit/risk balance, and manufacturers are identifying ways to respond. Requirements that a drug be proven to be cost-effective have been added to many national, local, and insurance health care systems, either to justify reimbursement or even to justify drug availability. A number of schools of medicine, pharmacy, and public health have established research programs in pharmacoepidemiology, and a few of them have also established pharmacoepidemiology training programs in response to a desperate need for more pharmacoepidemiology personnel. Pharmacoepidemiologic research funding is now more plentiful, and even limited support for training is available.

In the United States, drug utilization review programs are required, by law, of each of the 50 state

Medicaid programs, and have been implemented as well in many managed care organizations. Now, years later, the utility of drug utilization review programs is being questioned. In addition, the Joint Commission on Accreditation of Health Care Organizations now requires that every hospital in the country have an adverse drug reaction monitoring program and a drug use evaluation program, turning every hospital into a mini-pharmacoepidemiology laboratory. Stimulated in part by the interests of the World Health Organization and the Rockefeller Foundation, there is even substantial interest in pharmacoepidemiology in the developing world. Yet, throughout the world, the increased concern by the public about privacy has made pharmacoepidemiologic research much more difficult to conduct.

In recent years, major new changes have been made in drug regulation and organization, largely in response to a series of accusations about myocardial infarction caused by analgesics, which was detected in long-term prevention trials rather than in normal use of the drugs. For example, FDA has been given new regulatory authority after drug marketing, and has also begun developing the Sentinel Initiative, a program to conduct medical product safety surveillance in a population to exceed 100 million. Further, the development, since January 1, 2006, of Medicare Part D, a US federal program to subsidize prescription drugs for Medicare recipients, introduces to pharmacoepidemiology a new database with a stable population of about 25 million in what may be the largest healthcare system in the world. A new movement has arisen in the US of "comparative effectiveness research," which in many ways learns from much longer experience in Europe, as well as decades of experience in pharmacoepidemiology. These developments portend major changes for our field.

In summary, there has been tremendous growth in the field of pharmacoepidemiology and a fair amount of maturation. With the growth and maturation of the field, Strom's *Pharmacoepidemiology* has grown and matured right along. *Pharmacoepidemiology* thus represents a comprehensive source of information about the field. As a reflection of the growth of the field, the 4th Edition of Strom was over twice as long as the first! We worked hard to avoid such growth in the 5th Edition, by aggressive pruning to go along with our additions.

So, why, one may ask, do we need a *Textbook of Pharmacoepidemiology*? The need arose precisely because of the growth of the field. With that, and the corresponding growth in the parent book, Strom's *Pharmacoepidemiology* has really become more of a reference book than a book usable as a textbook. Yet, there is increasing need for people to be trained in the field, and an increasing number of training programs. With the maturity of the field comes therefore the necessity for both comprehensive approaches (such as Strom's *Pharmacoepidemiology*) and more focused approaches. Therefore, *Textbook of Pharmacoepidemiology* was intended as a modified and shortened version of its parent, designed to meet the need of students. We believe that students can benefit from an approach that focuses on the core of the discipline, along with learning aids.

Textbook of Pharmacoepidemiology attempts to fill this need, providing a focused educational resource for students. It is our hope that this book will serve as a useful textbook for students at all levels: upper-level undergraduates, graduate students, post-doctoral fellows, and others who are learning the field. In order to achieve our goals, we have substantially shortened Strom's *Pharmacoepidemiology*, with a focus on what is needed by students, eliminating some chapters and shortening others. We also have provided case examples for most chapters and key points for all chapters. Each chapter is followed by a list of further reading.

So why update it? In looking at the 5th Edition of Strom, most chapters in the new edition were thoroughly revised. Ten new chapters were added, along with many new authors. The first edition of the textbook was simply getting out of date.

Specifically, we have tried to emphasize the methods of pharmacoepidemiology and the strengths and limitations of the field, while minimizing some of the technical specifications that are important for a reference book but not for students. Therefore, the first five chapters of Part I, "Introduction to Pharmacoepidemiology," lay out the cores of the discipline, and remain essentially

unchanged from Strom's *Pharmacoepidemiology*, with the exception of the inclusion of key points and lists of further reading. We have also included a chapter on different perspectives of the field (from academia, industry, regulatory agencies, and the legal system), as a shortened form of several chapters from the reference book. Part II focuses on "Sources of Pharmacoepidemiology Data" and includes important chapters about spontaneous pharmacovigilance reporting systems, and other approaches to pharmacoepidemiology studies. A substantially shortened chapter on Examples of Automated Databases is included, focused on the strengths and limitations of these data sources rather than providing extensive details about the content of each database. Part III summarizes "Special Issues in Pharmacoepidemiology Methodology" that we feel are important to more advanced pharmacoepidemiology students. Although no student is likely to become an expert in all of these methods, they form a core set of knowledge that we believe all pharmacoepidemiologists should have. In addition, one never knows what one will do later in one's own career, nor when one may be called upon to help others with the use of these methods. Part IV concludes the textbook with a collection of "Special Applications" of the field, and speculation about its future, always an important consideration for new investigators in charting a career path.

Pharmacoepidemiology may be maturing, but many exciting opportunities and challenges lie ahead as the field continues to grow and respond to unforeseeable future events. It is our hope that this book can serve as a useful introduction and resource for students of pharmacoepidemiology, both those enrolled in formal classes and those learning in "the real world," who will respond to the challenges that they encounter. Of course, we are always students of our own discipline, and the process of developing this textbook has been educational for us. We hope that this book will also be stimulating and educational for you.

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Rita Schinnar's contributions to this book were instrumental in helping to shorten several of the chapters that were merged together from *Pharmacoepidemiology, 5th edition*, and providing excellent editorial assistance with all the other chapters, as well as contributing a chapter. She also coordinated the entire process of contacting the authors and pulling the book together. Finally, we would like to thank all of the authors for the work that they did in helping to revise their book chapters for this textbook and provide case examples, key points, and suggested readings.

BLS would like to thank Steve Kimmel and Sean Hennessy for joining him as co-editors in this edition. Steve did the bulk of the work on the first edition of this textbook, and Steve and Sean joined BLS as co-editors for the 5th edition of *Pharmacoepidemiology*. These are two very special and talented men. It has been BLS's pleasure to help to train them, now too many years ago, help them cultivate their own careers, and see them blossom into star senior pharmacoepidemiologists in their own right, now extremely effective and successful. It is wonderful to be able to share with them this book, which has been an important part of BLS's life and career.

BLS would also like to thank his parents for the support and education that were critical to his being able to be successful in his career. BLS would also like to thank Paul D. Stolley, M.D., M.P.H. and the late Kenneth L. Melmon, M.D., for their direction, guidance, and inspiration in the formative years of his career. He would also like to thank his trainees, from whom he learns at least as much as he teaches. Last, but certainly not least, BLS would like to thank his family—Lani, Shayna, and Jordi—for accepting the time demands of the book, for tolerating his endless hours working at home (on its earlier editions, for the kids), and for their ever present love and support.

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PART I

Introduction to Pharmacoepidemiology

CHAPTER 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

Introduction

In recent decades, modern medicine has been blessed with a pharmaceutical armamentarium that is much more powerful than what it had before. Although this has given health care providers the ability to provide better medical care for their patients, it has also resulted 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 (ADRs), and 1.5 million US hospitalizations each year result from ADRs; yet, 20–70% of ADRs may be preventable. 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 many issues other than adverse reactions, as well.

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 reviewed, 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, and effects, of drugs and other medical devices in large numbers of people. The term pharmacoepidemiology obviously contains two components: "pharmaco" and "epidemiology." In order to better appreciate 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 4). Pharmacoepidemiology

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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 specific patient at hand. This individualization of therapy requires the determination of a risk/benefit ratio specific to the patient at hand. 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 his 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. 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 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*. 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 the drug unusually slowly, leading to drug levels that are too high (see also Chapter 4). Third, they may have normal drug levels, but for some reason are overly sensitive to them (see Chapter 14).

In contrast, Type B reactions tend to be uncommon, not related to dose, unpredictable, 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; see Chapter 14) 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 7), 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 13), as can attempts to compare the effects of drugs in the same class. This has led academic investigators, industry, 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 new field: pharmacoepidemiology.

Pharmacoepidemiology versus epidemiology

Epidemiology is the study of the distribution and determinants of diseases in populations. Since pharmacoepidemiology is the study of the use of and effects of drugs and other medical devices 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, i.e., 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 performing the clinical trials of drugs that are conducted before marketing, the major application of these methods 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 subsequent chapters, pharmacoepidemiology is considered of importance in the whole life cycle of a drug, from the time when it is first discovered or synthesized through 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 methodological issues have arisen. These are the primary foci of this book.

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 assure 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. 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. In 1952, the first textbook of adverse drug reactions was published. In the same year, the AMA Council on Pharmacy and Chemistry established the first official registry of adverse drug effects, to collect cases of drug-induced blood dyscrasias. 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. This approach was later transported to the University of Florida-Shands Teaching Hospital, as well.

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. Epidemiologic studies established its cause to be *in utero* exposure to thalidomide. In the United Kingdom, this resulted in the establishment in 1968 of the Committee on Safety of Medicines. Later, the World Health Organization established a bureau to collect and collate information from this and other similar national drug monitoring organizations (see Chapter 7).

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 man. The data from these studies were required to be submitted to 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 below. 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, 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 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, the so-called drug lag. However, the drugs that are marketed 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 neurological reaction until 1970. 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. The mid-1970s saw the UK discovery of the oculomucocutaneous syndrome caused by practolol, five years after drug marketing. In 1980, the drug ticrynafen was noted to cause deaths from liver disease. In 1982, benoxaprofen was noted to do the same. Subsequently the use of zomepirac, another nonsteroidal anti-inflammatory drug, was noted to be associated with an increased risk of anaphylactoid reactions. Serious blood dyscrasias were linked to phenylbutazone. Small intestinal perforations were noted to be caused by a particular slow release formulation of indomethacin. 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 (see "Studies of drug induced birth defects" in Chapter 22). Acute flank pain and reversible acute renal failure were noted to be caused by suprofen. Isotretinoin was almost removed from the US market because of the birth defects it causes. The Eosinophilia-Myalgia syndrome was linked to a particular brand of L-tryptophan. Triazolam, thought by the Netherlands in 1979 to be subject to a disproportionate number of central nervous system side effects, was discovered by the rest of the world to be problematic in the early 1990s. 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. 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. 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. An epidemic of deaths from asthma in New Zealand was traced to fenoterol, and later data suggested that similar, although smaller, risks might be present with other beta-agonist inhalers. The possibility was raised of cancer from depot-medroxyprogesterone, resulting in initial refusal to allow its marketing for this purpose in the US, multiple studies, and ultimate approval. Arrhythmias were linked to the use of the antihistamines terfenadine and astemizole. Hypertension, seizures, and strokes were noted from postpartum use of bromocriptine. Multiple different adverse reactions were linked to temafloxacin. Other examples include liver toxicity from amoxicillin-clavulanic acid; liver toxicity from bromfenac; cancer, myocardial infarction, and gastrointestinal bleeding from calcium channel blockers; arrhythmias with cisapride interactions; primary pulmonary hypertension and cardiac valvular disease from dexfenfluramine and fenfluramine; gastrointestinal bleeding, postoperative bleeding, deaths, and many other adverse reactions associated with ketorolac; multiple drug interactions with mibefradil; thrombosis from newer oral contraceptives; myocardial infarction from sildenafil; seizures with tramadol; anaphylactic reactions from vitamin K; liver toxicity from troglitazone; and intussusception from rotavirus vaccine.

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

Major adverse drug reactions continue to plague new drugs, and in fact are 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, pamoline-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 and Lyme were also withdrawn because of safety concerns (see "Special methodological issues in pharmacoepidemiology studies of vaccine safety" in Chapter 22). 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.

Since 1993, trying to deal with drug safety problems, FDA morphed its extant spontaneous

reporting system into the MedWatch program of collecting spontaneous reports of adverse reactions (see Chapter 7), 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.

According to a study by the US Government Accountability Office, 51% of approved drugs have serious adverse effects not detected before approval. Further, there is recognition that the initial dose recommended for a newly marketed drug is often incorrect, and needs monitoring and modification after marketing.

In some of the examples above, 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 executed in all of the different countries in which each drug was marketed. Most of these adverse discoveries have led to litigation, as well, and a few have even led to criminal charges against the pharmaceutical manufacturer and/or some of its employees (see Chapter 6).

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." To provide additional resources to 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. This legislation was reauthorized by Congress several times: PDUFA II–the Food and Drug Modernization Act of 1997; PDUFA III–the Public Health Security and Bioterrorism Preparedness and Response Act of 2002; PDUFA IV, the Food and Drug Administration Amendments (FDAAA-PL 110-85) of 2007; and PDUFA V, the Food and Drug Administration Safety and Innovation Act of 2012. The goals for PDUFA have been 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, III, and 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 FDA in the 1990s.

However, whereas 1400 FDA employees in 1998 worked with the drug approval process, only 52 monitored safety; FDA spent only $2.4 million in extramural safety research. This state of affairs has coincided with the growing numbers of drug crises cited above. With successive reauthorizations of PDUFA, this changed markedly. 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.

However, there now was growing concern, in Congress and the US public, that perhaps FDA was approving drugs too *fast*. There were also calls for the development of an independent drug safety board, with wider mission than FDA's regulatory mission, to complement the latter. Such a board could investigate drug safety crises, looking for ways to prevent them, and deal with issues such as improper physician prescribing of drugs, the need for training, and the development of new approaches to the field of pharmacoepidemiology.

Recurrent concerns about 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, followed in 2007 by the Institute of Medicine's independent assessment. Important weaknesses in the current system included failure of FDA's Office of New Drugs and Office of Drug Safety to communicate with each other on safety issues, failure of FDA to track ongoing postmarketing studies, ambiguous role of FDA's Office of Drug Safety in scientific

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

Indeed, with the passage of PDUFA IV, FDA authority was substantially increased, with the ability to require postmarketing studies and levy heavy fines if these requirements were not met. Further, its resources were substantially increased, with specific mandates 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) (see also "Comparative effectiveness research" in Chapter 22). In another use of the new PDUFA funds, the FDA plans to develop and implement agency-wide and special-purpose postmarket 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 22), 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.

Intellectual development of pharmacoepidemiology emerging from drug crises

Several developments of the 1960s can be thought to have marked the beginning of the field of pharmacoepidemiology. The Kefauver-Harris Amendments that were introduced in 1962 required formal safety studies for new drug applications. The DESI program that was undertaken by the FDA as part of the Kefauver-Harris Amendments required formal efficacy studies for old drugs that were approved earlier. These requirements created demand for new expertise and new methods. In addition, the mid-1960s saw the publication of a series of drug utilization studies. These studies 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 "Evaluating and improving physician prescribing" in Chapter 22).

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. 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. The Computerized Online Medicaid Analysis and Surveillance System (COMPASS®) was first developed in 1977, using Medicaid billing data to perform pharmacoepidemiologic studies (see Chapter 9). The Drug Surveillance Research Unit, now called the Drug Safety Research Trust, was developed in the United Kingdom in 1980, with its innovative system of Prescription Event Monitoring. Each of these represented major contributions to the field of pharmacoepidemiology. These and newer approaches are reviewed in Part II of this book.

In the examples of drug crises mentioned above, these were serious but uncommon drug effects, and these experiences have led to an accelerated search for new methods to study drug effects in large numbers of patients. This led to a shift from adverse effect studies to adverse event studies, with 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, 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, which were updated in 2007. Since the late 1990s, pharmacoepidemiologic research has also been increasingly burdened by concerns about patient confidentiality (see also Chapter 15).

There is also increasing recognition that most of the risk from most drugs to most patients occurs from known reactions to old drugs. Attempting 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 has been funding up to 14 Centers for Education and Research and Therapeutics (see "Comparative effectiveness research" in Chapter 22), although this has since been reduced to six centers.

The research and education activities sponsored by AHRQ through the CERTs program since the late 1990s take place in academic centers. These CERTs centers 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 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 health care 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 health care items and services. In response, AHRQ created in 2005 the DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network to support in academic settings the conduct of studies on effectiveness, safety, and usefulness of drugs and other treatments and services.

Another major new initiative of 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, there were new initiatives underway, ranging from FDA requirements for risk management plans, to a FDA Drug Safety and Risk Management Advisory Committee, and issuing risk minimization and management guidances in 2005 (see Chapters 6 and 22).

Another initiative 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: (a) "even apparently single events or errors are due most often to the convergence of multiple contributing factors," (b) "preventing errors and improving safety for patients requires a systems approach in order to modify the conditions that contribute to errors," and (c) "the problem is not bad people; the problem is that the system needs to be made safer." In this framework, the concern is not about substandard or negligent care, but rather, is 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 ADEs, prolonging hospital stays by 2 days, and increase costs by $2000–2600 per patient. Over 7000 US deaths were attributed to medication errors in 1993. Although these estimates have been disputed, the overall importance of reducing these errors has not been questioned. In recognition of this problem, AHRQ launched a