CHAPTER 9

Pharmacoepidemiology

ANDY STERGACHIS, THOMAS K. HAZLET, AND DENISE BOUDREAU

KEY CONCEPTS

1. Risks and benefits are commonly identified only after a drug is used widely by the general population.
2. Observational study designs are essential for the study of risks and benefits associated with marketed drugs.
3. Not all associations represent a cause-and-effect relationship.
4. Regulatory agencies are under pressure to identify and respond to postapproval drug safety issues.

1 The practice of pharmacotherapy presents numerous challenges to clinicians as they apply knowledge of the benefits and risks of pharmaceuticals to individual and population-based patient care. A great deal of our understanding about the efficacy and short-term safety of drugs arises from well-controlled studies conducted during the drug development and approval process. However, many additional risks and, increasingly, additional benefits are only identified after the drug is used widely by the general population. Our gaps in knowledge of risks and benefits at the time a drug is marketed is a result of numerous characteristics of preapproval studies, including limited sample size, relatively short study followup, restricted characteristics of persons studied, and differences in research settings from real-life conditions once a drug is marketed. Benefits and risks learned following a drug's approval may range from relatively minor to clinically important effects that seriously alter an individual drug's risk-to-benefit profile. The association between certain appetite-suppressant drugs and primary pulmonary hypertension and valvular heart disease, and between some cyclooxygenase-2 inhibitors and cardiovascular events, are two examples where serious adverse effects were discovered only after these drugs had come into widespread use.[1–4] These examples highlight the inherent limitations of the drug development process, the limitations of the regulatory framework for contemporary medical products (drugs, biologics, and medical devices), and the need to study populations receiving medications obtained through usual clinical practice. The liver toxicity seen with troglitazone and more recently, rosiglitazone, is another example of the valuable contribution of close monitoring to drug safety. The first thiazolidinedione introduced for treatment of type 2 diabetes mellitus in 1997, troglitazone was withdrawn from the market based on reports of serious hepatocellular injury. In mid-2007, heart attacks and related deaths were observed in pooled clinical trials data for some patients receiving rosiglitazone, another thiazolidinedione subsequently approved for diabetes.[5] Medical products must also be monitored closely following their introduction into the marketplace, and this information has value when applied to clinical practice. This chapter describes the role of pharmacoepidemiology in drug development and therapeutics and characterizes the primary methods and contemporary issues in this field.

As illustrated in Fig. 9–1, pharmaceuticals and other medical products are developed and used within a complex system involving contributions from numerous stakeholders, including manufacturers who develop and test products, the U.S. Food and Drug Administration (FDA) through its premarketing review and approval process and postmarketing surveillance programs, healthcare providers, and patients.

Whether or not a drug in fact achieves its desired effect in the real world, in contrast to randomized controlled trials (RCTs), is referred to as its *effectiveness,* not efficacy. Studies of drug effectiveness generally are conducted using observational study designs, although RCTs also play a role in determining a drug's effectiveness.[6] It is recognized widely that results from an RCT offer the best evidence that a drug will perform under ideal conditions, and it is likely that the "well-controlled" design of RCTs will continue to be required for new drug applications to the FDA. As described in regulations governing new drug applications, reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs.[7]

However, the rigorous circumstances surrounding the design and implementation of an RCT do not necessarily extrapolate to the individual patient. Fletcher et al.[8] drew a distinction between *efficacy*—Does the treatment work?—and *effectiveness*—Does the treatment's benefits outweigh its liabilities for those to whom it is offered in clinical practice? Figure 9–2 illustrates the tension between the conflicting goals of validity in efficacy trials and generalizability in effectiveness trials. For example, in an efficacy trial, subjects are selected using narrowly defined eligibility criteria and are monitored closely to ensure that they use or are exposed to the intervention in the manner defined in the trial's protocol and are cooperative with medical advice. In clinical practice, patients are not selected, and the manner in which the patient uses the intervention may vary widely from the intended use for which it was approved. Clinical outcomes among RCT subjects often are better than in nontrial patients.[9] Trials to evaluate therapeutic effectiveness in clinical practice are difficult or expensive for researchers. If results from an effectiveness study are inconclusive, such results could be a result of a lack of the intervention's efficacy, patient behavior (such as lack of patient adherence), or both.

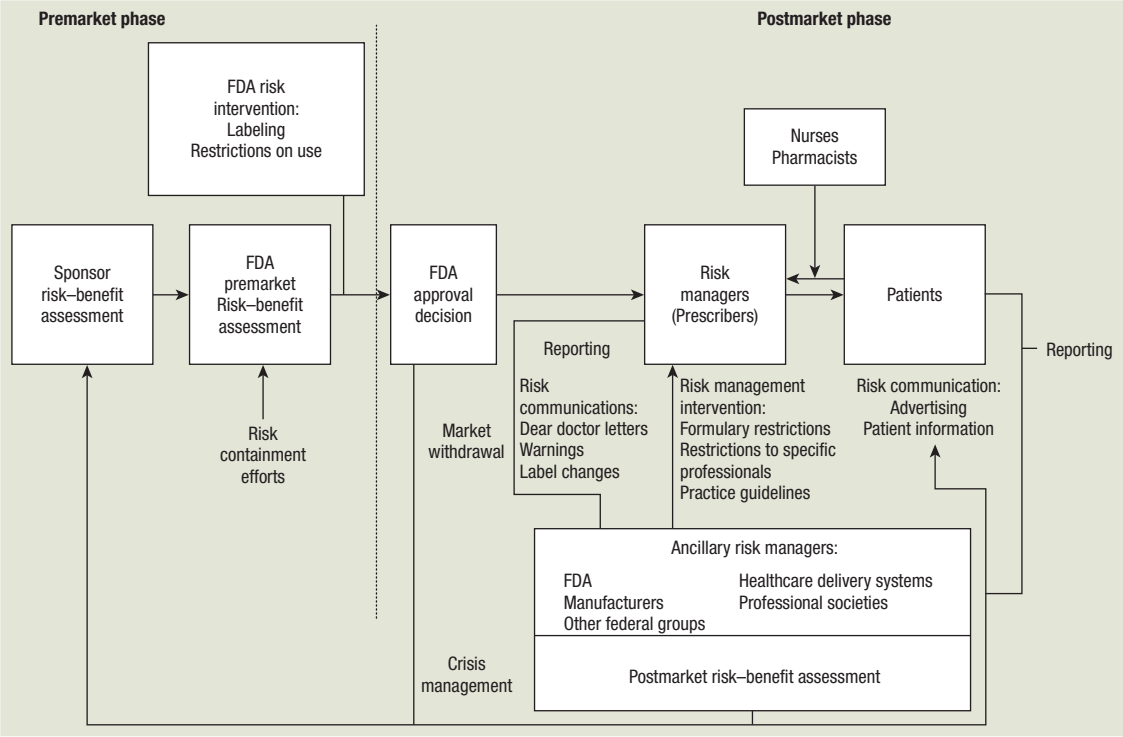

FIGURE 9-1. System for managing the risks of prescription drugs. *(From U.S. Food and Drug Administration. Managing the Risks from Medical Product Use: Creating a Risk Management Framework. http://www.fda.gov/oc/tfrm/executivesummary.html.)*

Pharmacoepidemiology is a discipline that provides valuable information about clinical and economic outcomes of drugs, devices, and biologics, particularly after their approval for clinical use. *Pharmacoepidemiology* is defined as the study of the use of and effects of drugs in large numbers of people.[10] The field as applied to the period after a drug enters the market is referred to as *postmarketing drug surveillance* (PMS). *Pharmacovigilance* is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems, and generally refers to the continual monitoring for unwanted effects and other safety-related aspects of marketed drugs.

Epidemiologic study designs are essential for evaluating drug safety and effectiveness in situations where it is either infeasible or unethical to assign patients randomly to active treatment or placebo. Although the randomized, controlled, blinded trial is the standard against which other designs are measured, it is often unsuitable for safety questions within the domain of pharmacoepidemiology. RCTs are sometimes used to provide evidence of safety of marketed drugs, although their high cost and other factors impede their use during the postapproval stage, primarily for market-driven reasons, for example, label extensions studies. Clinical trials conducted prior to drug approval cannot uncover every important health effect of a pharmaceutical agent. For example, the adverse health effects of drugs on the human fetus can be estimated only through observational but not experimental methods. The teratogenic effects of thalidomide in humans and, more recently, isotretinoin were identified through observational methods. Epidemiologic studies have challenged the suggested association between vaccine exposure (either whole-cell pertussis or the commonly used mercury-based preservative thimerosal) and autism.[11] As a discipline, pharmacoepidemiology traditionally has concerned itself with the study of adverse drug effects. However, epidemiologic studies of the patterns of drug prescribing and use are also essential to assess a drug's usefulness.[12]

Epidemiologic study designs, such as case-control and cohort studies, are used to identify beneficial effects of drugs in populations. For example, to determine the relationship between patterns of use of inhaled corticosteroids and the risk of fatal or near-fatal asthma, Suissa et al. conducted an epidemiologic study of 30,569 residents of Saskatchewan, Canada, who were dispensed three or more asthma drugs in any 1 year from September 1975 through December 1991.[13] The authors found the death rate to be 21% lower among inhaled corticosteroid users for each additional canister used in the preceding year and an increased death rate in patients who had discontinued inhaled corticosteroid use. These findings support practice guidelines and quality performance measurements that recommend the use of inhaled anti-inflammatory agents in patients with moderate to severe asthma.

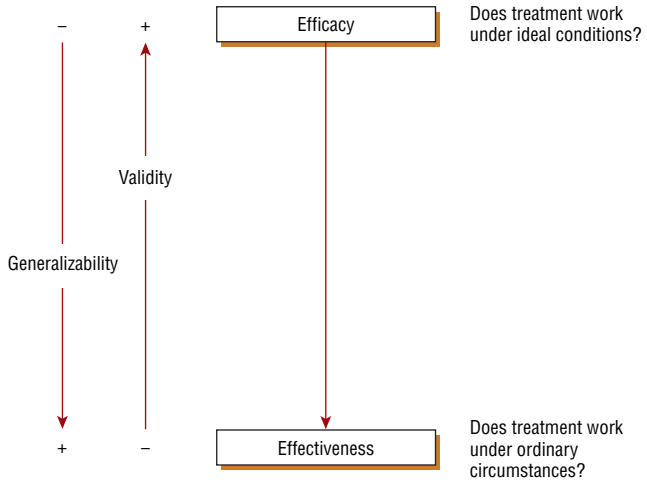

FIGURE 9-2. Schematic showing the tension between conflicting goals of validity in efficacy trials and generalizability in effectiveness trials.

LIMITS OF KNOWLEDGE AT THE TIME OF NEW DRUG APPROVAL

The new drug application process and the role of pharmacoepidemiology in the United States have evolved since the Food, Drug, and

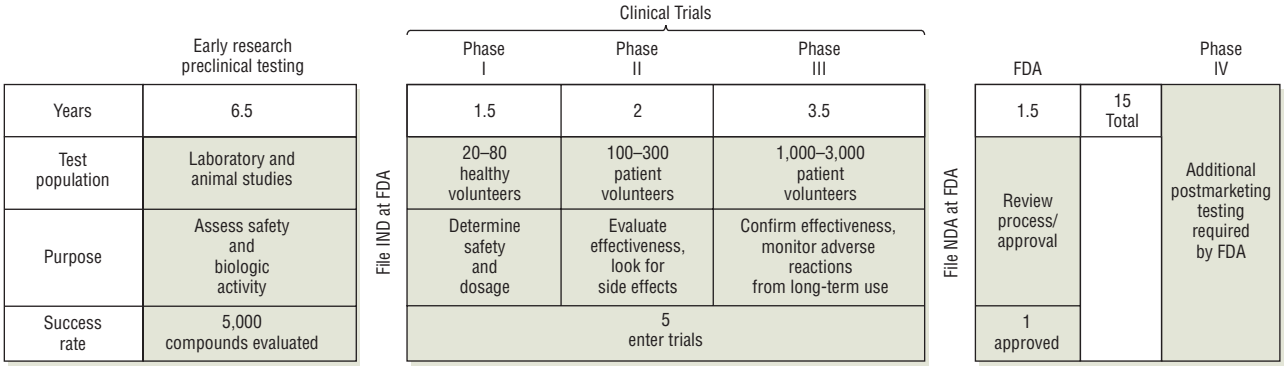

FIGURE 9-3. The drug development and approval process in the United States. (IND, investigational new drug; NDA, new drug application.)

Cosmetic Act of 1938 was enacted into law. The Food, Drug, and Cosmetic Act was adopted following the deaths of more than 100 patients as a consequence of renal failure from sulfanilamide prepared in a diethylene glycol vehicle.[14] For the first time in U.S. history, the Act required a drug to be proven safe under conditions of use intended by the manufacturer before marketing. The Act also required manufacturers to conduct preclinical toxicity testing and gather and submit clinical data about drug safety to the FDA prior to drug marketing under a new drug application. It also required new drugs to be labeled with adequate instructions and appropriate warnings for safe use. However, the Food, Drug, and Cosmetic Act required no proof of drug efficacy.

The Food, Drug, and Cosmetic Act was amended in 1962 following the epidemic of thalidomide-associated birth defects in Europe.[15] The Kefauver-Harris Amendments of 1962 strengthened the requirements for proof of drug safety and added a new requirement for demonstration of drug efficacy before marketing. Requiring "substantial evidence that the drug will have the effect it purports or is represented to have" resulted in the establishment of the RCT as the "gold standard" for proof of efficacy. The 1962 amendments also required manufacturers to report adverse drug events detected in the postmarketing setting to the FDA. Investigational new drug applications were required to be submitted to the FDA before clinical testing could begin. In 1985, requirements for manufacturers' adverse drug event (ADE) reporting were clarified, and specific regulations and guidelines were published to define the manufacturers' obligations in reviewing and reporting ADEs.

The Kefauver-Harris Amendments also identified explicit phases of preclinical animal testing followed by three phases of clinical testing (Fig. 9–3). In addition, postapproval surveillance or phase IV of drug development is now increasingly common. Today we are witnessing even more regulatory changes to the drug approval process as it pertains to pharmacoepidemiology. The Food and Drug Administration Modernization Act of 1997 resulted in new provisions stating that substantial evidence of drug effectiveness may consist of data from one adequate and well-controlled clinical investigation plus confirmatory evidence. This indicates that two or more well-controlled trials (the previous standard) are not always necessary and that the FDA should relate the number and type of trials to the specific product under development.

Phase III controlled clinical trials required by the FDA as part of the process of drug approval and labeling are the primary source of information about new drugs. Although these studies help to ensure that a drug is efficacious and does not cause unacceptable harm, premarketing studies fail to provide much of the information needed to make therapeutic decisions.[16] Table 9–1 describes the major limitations of premarketing controlled clinical trials, which lend support to the need for further evaluation of drugs after their approval for marketing by the FDA. Briefly, clinical trials performed during drug development cannot be depended on to detect rare adverse drug events and delayed adverse events. In addition, they cannot be used directly to address the performance of drugs in the populations that will use the drug in ways not studied in clinical trials because clinical trials restrict the complexity of the patients tested. Thus often not included in drug testing are many persons who are likely to receive new medicines eventually—the chronically ill, women of childbearing age, and pregnant women. Moreover, clinical trials are performed for patients with specified conditions. To improve the representativeness of populations included in clinical trials, the FDA has issued guidelines in support of inclusion of geriatric patients in phase II and phase III studies. Also, the FDA has issued guidelines and incentives to encourage manufacturers to provide efficacy, safety, pharmacokinetic, and pharmacodynamic information in support of the use of drugs and biologic products in pediatric and geriatric populations.

Despite the rigorous process for drug approval and regulation, several important medications have been removed from the market because of serious ADEs over the past 30 years. Examples of serious but uncommon effects include acute flank syndrome associated with suprofen,[17] the gastrointestinal effects associated with nonsteroidal antiinflammatory drugs in the elderly,[18] troglitazone and the risk of hepatotoxicity,[19] rhabdomyolysis in patients treated with certain lipid lowering drugs, and the adverse effects of cisapride (available only in the United States through a limited-use protocol from the manufacturer) when doses were too high or drug interactions resulted in QT-segment prolongation.[21]

Partially in response to concerns about ADEs, a number of epidemiology programs were developed beginning in the 1970s. An initial emphasis of early programs, such as the Boston Collaborative Drug Surveillance Program, was the estimation of drug use and adverse events among hospitalized patients.[22] The Drug Epidemiology Unit, now the Slone Epidemiology Unit, also was formed in the early 1970s to perform hospital-based case-control studies.[23] In the United Kingdom, the Drug Surveillance Research Unit established the Prescription Event Monitoring Program in 1980.[24] Subsequent resources for pharmacoepidemiol-

TABLE 9-1 Limitations of Premarketing Clinical Trials

Short duration	Premarketing studies are limited in time. Effects that develop following chronic use or those that have a long latency period cannot be detected.
Small sample size	Few drugs are studied in more than 4,000 subjects before FDA approval. Effects that occur with a frequency of less than 1/1,000 are difficult to detect.
Narrowly defined population	Premarketing studies generally do not include special populations such as children, women of childbearing age, or the elderly.
Narrow set of indications	Manufacturers pursue specific indications for use during premarketing studies.
Limited comparison groups	The comparison group is often limited to placebo.

ogy evolved from the use of Medicaid data, followed by the use of databases from health maintenance organizations (HMOs) and other population-based data sources. Since the time of the 1980 report of the Joint Commission on Prescription Drug Use, there has been considerable interest in the use of HMO records for postmarketing drug surveillance.[25] Advantages to conducting PMS in an HMO setting include the availability of an identifiable population base for the estimation of rates, large populations with stable membership that receive complete coverage of medical services and receive almost all their care within the system, and access to traditional and electronic medical records and computerized databases.[26] One evolution of the use of data from HMOs is the formation of the HMO Research Network, a group of 15 HMOs that facilitate health services and epidemiologic research in a managed-care setting.[27] One of the noteworthy developments in the field of pharmacoepidemiology has been the use of automated, linked databases that permit efficient and rapid studies of drug effects, although the Health Insurance Portability and Accountability Act of 1996 and the parallel evolution of individual state laws have complicated and impeded access to some epidemiology data.[28]

CLINICAL CONTROVERSY

The FDA's proposed risk-assessment guidelines identify a sponsor's responsibilities to anticipate adverse events with medical products using survey methods and other techniques during product development. Generally, a sponsor determines its product's intended use and intended population(s) during product development. Decisions as to which interactions to either explore or specifically test in clinical trials could be based on these determinations and/or surveys and epidemiologic analyses. Missing from the guidelines is an acknowledgment that many medical products are used "off label" (e.g., recent experience with gabapentin and thalidomide, whose dominant use has been off-label). What is the sponsor's obligation to assess the risk of anticipated off-label usage during drug development?

Source: Guidance for Industry Premarketing Risk Assessment, May 2004, U.S. Food and Drug Administration. 2004, http://www.fda.gov/cber/guidelines.htm.

ROLE OF THE FDA AND PHARMACOEPIDEMIOLOGY

Drug development should be viewed as a process that continues even after a drug is approved for marketing. As noted in the preceding section, it is not possible to detect all potential risks and benefits during premarketing studies. The FDA's PMS program provides important information on the clinical experience of medical products. The FDA's involvement in PMS includes monitoring approved drug use, monitoring the serious ADEs associated with the use of approved drugs, and the initiation of selected epidemiologic studies to estimate the risk or test specific hypotheses.[29] One of the primary uses of findings from PMS of drugs is modification of a drug's product labeling or package insert. A black box warning is the warning that appears at the top of a prescription drug's package insert notifying practitioners of significant risks, including life-threatening adverse effects. The FDA can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning required by the FDA. Other methods used to communicate the results of PMS efforts involve requiring the manufacturer to mail out a "Dear Doctor" letter, various listings on the FDA website (*www.fda.gov*), e-mail distributions of safety warnings to FDA listserve subscribers, presentation of findings at professional meetings, and publication of findings in peer-reviewed journals. There is considerable debate on the best ways to communicate the findings from studies of the adverse effects of medications as the body of evidence grows on the limitations of the FDA's risk-management efforts. The FDA recently appointed a new advisory committee to specifically address risk communication.[30]

A variety of activities and tools are used by the FDA's Center for Drug Evaluation and Research's Division of Pharmacovigilance and Epidemiology to monitor the ongoing safety of marketed drugs (Fig. 9–4). As a condition of approval for marketing, drug manufacturers are required to notify the FDA of all adverse events of which they are aware. It is important for clinicians to report ADEs either to the manufacturer, the MedWatch system at the FDA, or through an FDA MedWatch partner, the United States Pharmacopeia Medication Errors Reporting Program.[31] These programs depend on healthcare professionals to report serious ADEs observed in the course of their practices as part of their professional responsibility and on the lay public to volunteer information about possible ADEs. However, MedWatch is limited by underreporting and an inability to distinguish between drug-induced and naturally occurring serious events. It has been estimated that only approximately 1% of all ADEs and approximately 10% of all serious adverse drug reactions are reported to MedWatch.[32,33] The MedWatch form can be used to report ADEs or problems related to any medical product, with the exception of those occurring with vaccines. Reports concerning vaccines should be sent to the Vaccine Adverse Event Reporting System, a joint program of the FDA and the Centers for Disease Control and Prevention. Table 9–2 describes the FDA's MedWatch program.

The FDA provides limited funding for investigators to use large, automated databases to study the adverse effects of drugs marketed in the United States and its territories. Through contracts, the FDA has encouraged the use of large databases in pharmacoepidemiology. These arrangements are used to gain access to databases to help obtain answers to questions that the FDA has regarding particular drugs. The objectives of these programs include the rapid and efficient conduct of pharmacoepidemiologic research designed to test hypotheses, particularly those arising from the MedWatch program. Current programs receiving funding for PMS from the FDA include the HMO Research Network CERT, Ingenix Inc., the Kaiser Foundation Research Institute, and Vanderbilt University. Altogether, these sites include 23.5 million persons that cover a variety of types of persons, including managed care settings and persons on Medicaid. The FDA also maintains agreements for pharmacoepidemiology with the Veterans Administration, the Agency for Healthcare Research and Quality's Centers for Education and Research on Therapeutics (CERT), and has access to the United Kingdom's General Practice Research Database. Historically the FDA has lacked regulatory authority to require phase IV studies for previously approved drugs. The Prescription Drug User Fee Act Amendments of 2002 permitted fee revenues to be used for postapproval risk management activities for newly approved drugs for the first time.[34] Legislation proposed with the 2007 renewal of Prescription Drug User Fee Act will extend postmarketing surveillance activities to previously approved new drugs as well as generics, and removes the Prescription Drug User Fee Act III 3-year limitation of surveillance activities.[35]

The Food and Drug Administration Modernization Act does, however, require any sponsor of a drug that agreed to conduct a postmarketing study to report annually to the FDA on the progress of its postmarketing study commitments. The FDA uses postmarketing study commitments to gather additional information about a product's safety, efficacy, or optimal use.

The FDA has identified efficient risk management as the primary way to make the most effective use of agency resources and address these challenges. Efficient risk management requires using the best scientific data, developing quality standards, and using efficient systems and practices that provide clear and consistent decisions and communications for the American public and regulated industry. The FDA has long led the way in the science of risk management, and this

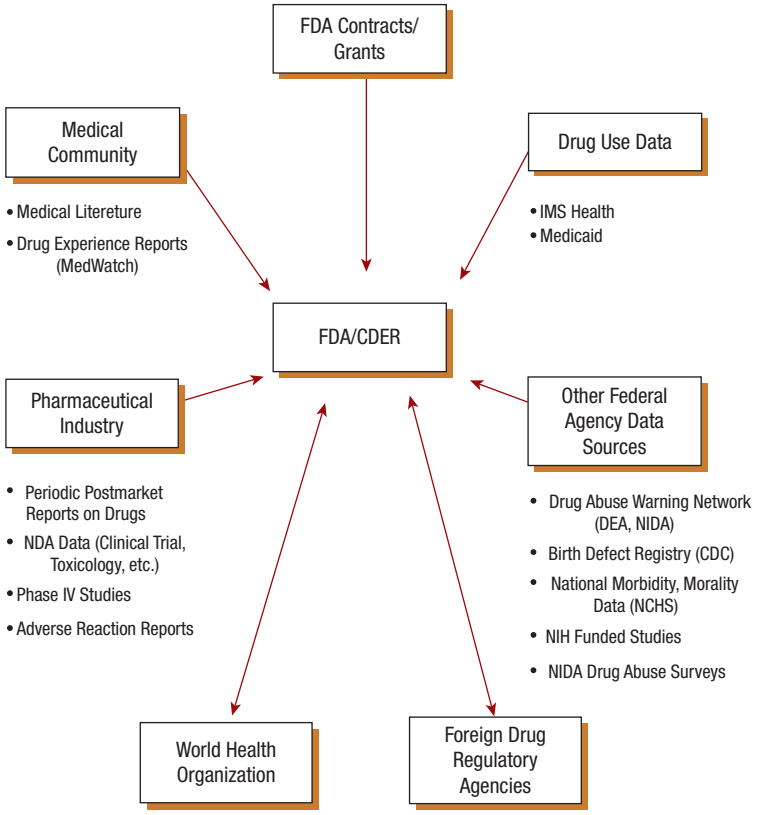

FIGURE 9-4. Sources of information used by the FDA for postmarketing surveillance and risk assessment. (CDC, Centers for Disease Control and Prevention; CDER, Center for Drug Evaluation and Research; DEA, Drug Enforcement Agency; NCHS, National Center for Health Statistics; NDA, new drug application; NIDA, National Institute on Drug Abuse; NIH, National Institutes of Health.) *(From http://www.fda.gov/cder/handbook/pmsinfo.htm.)*

ability is more important than ever given the expanding complexity of the agency's challenges and the need to reduce the health risks facing the public at the lowest possible cost to society.[36] The FDA issued a Guideline for Industry on Quality Risk Management that resulted from the International Conference on Harmonization.[37]

To assist in translating information about the risks and benefits of drugs into action, the federal Agency for Healthcare Research and Quality funds studies focused on patient outcomes associated with pharmaceutical therapy. The CERT is a research program administered by Agency for Healthcare Research and Quality, in consultation with the Food and Drug Administration. The mission of the CERT is to conduct research and provide education that will advance the optimal use of drugs, medical devices, and biologic products.[38] There are currently eleven CERT centers in the United States, including the Health Maintenance Organization Research Network CERT.

TABLE 9-2 Characteristics of the FDA's MedWatch Program

Report experiences with
- Medications (drugs or biologics)
- Medical devices (including in vitro diagnostics)
- Special nutritional products (dietary supplements, medical foods, infant formulas)
- Other products regulated by the FDA

Report *serious* adverse events. An event is serious when the patient outcome is
- Death
- Life-threatening (real risk of dying)
- Hospitalization (initial or prolonged)
- Disability (significant, persistent, or permanent)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if
- You're not certain that the product caused the event
- You don't have all the details

Report product problems—quality, performance, or safety concerns—such as
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures

Important numbers
- 1-899-FDA-0178 to fax report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone, for more information, or to obtain software for reporting by modem
- 1-800-822-7967 for a VAERS form for vaccines
- FDA MedWatch website: *http://www.fda.gov/medwatch/Download* reporting forms (PDF format) MedWatch information

CURRENT CONTROVERSY

In response to growing public concern about health risks posed by approved drugs, the FDA requested the Institute of Medicine to convene a committee to conduct an independent assessment of the current system for evaluating and ensuring drug safety postmarketing and make recommendations to improve risk assessment, surveillance, and the safe use of drugs. The Institute of Medicine report, released in 2006, found that there is a perception of crisis that has compromised the credibility of the FDA and of the pharmaceutical industry (Institute of Medicine. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Washington, DC: National Academies Press, 2007). The Institute of Medicine Committee on Assessment of the U.S. Drug Safety System found that the drug safety system is constrained by a lack of funding; an organizational culture in the Center for Drug Evaluation and Research that is not optimally functional; and unclear and insufficient regulatory authority particularly with respect to enforcement. Noting that resources to monitor medications' risk-to-benefit profiles taper off after approval, the Committee offered recommendations to ensure that consideration of safety extends from before product approval through the entire time the product is marketed and used, including recommendations pertaining to:

- Labeling requirements and advertising limits for new medications
- Clarifying authority and additional enforcement tools for the agency

- Clarifying the FDA's role in gathering and communicating additional information on marketed products' risks and benefits
- Facilitating public access to drug safety information by mandatory registration of clinical trial results
- Increasing the role of FDA's drug safety staff
- Boosting the FDA's funding and staffing

ADVERSE DRUG EVENTS

The field of pharmacoepidemiology concerns itself primarily with the study of adverse drug reactions (ADRs). According to the World Health Organization, an *adverse drug reaction* is any noxious, unintended, and undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, and it implies a causal relationship between use of the drug and the noxious event.[39] ADEs, in contrast, describe an injury resulting from administration of a drug, but use of this term implies that the relationship may be coincidental or that the event is not caused solely by the drug itself but rather may relate to the circumstances surrounding use of the drug.

Virtually any drug can have adverse effects. Between 3% and 11% of hospital admissions have been attributed to adverse effects.[40] The likelihood that a patient will experience an ADE during hospitalization ranges from 1% to 44%, depending on the type of hospital, the definition of an ADE, and the study methodology.[41] The economic impact of ADEs is substantial and potentially avoidable.[42,43] The incidence of serious and fatal ADRs in hospital patients was reported to be as high as 6.7% and 0.32%, respectively.[44] ADEs among older persons in the ambulatory clinical setting were studied among all Medicare enrollees cared for by a multispecialty group practice during a 1-year study period. The researchers reported an overall rate of ADEs of 50.1 per 1,000 person-years, with a rate of 13.8 preventable ADEs per 1,000 person-years.[45]

Although most ADEs can be anticipated, others are unpredictable, especially rare idiosyncratic reactions. ADRs are separated into type A and B reactions. Type A reactions are expected exaggerations of a drug's known pharmacologic effects. Consequently, they usually are dose-dependent, predictable, and preventable. Type A reactions are responsible for most of the ADEs encountered. Examples include hypotension with antihypertensive agents and anticholinergic effects with tricyclic antidepressants. Type A reactions tend to occur in individuals who have one of three characteristics[46]: First, the individual may have received more of a drug than is customarily required. Second, the individual may have received a conventional dose of the drug, but the individual may metabolize or excrete the drug unusually slowly, leading to drug levels that are too high, possibly owing to concomitant disease or drug interactions. Third, the individual may have normal drug levels but for some reason is overly sensitive to them. Most type A reactions are identified prior to drug marketing and are listed in a product's labeling.

Type B reactions are idiosyncratic and tend to be unrelated to the known pharmacologic action of a drug. They usually are unrelated to dose, are unpredictable and uncommon, and potentially are more serious than type A reactions. They may be caused by what are known as *hypersensitivity reactions* or *immunologic reactions*. Type B reactions may be the consequence of some other idiosyncratic reaction to the drug, such as an inherited susceptibility. These reactions may concentrate in certain body systems, including the liver, blood, skin, kidney, and nervous system.[47] Type B reactions represent a major focus of pharmacoepidemiologic studies of ADRs. Carcinogenic and teratogenic ADEs are considered type B reactions.

Because ADRs represent an important public health concern, institutions complying with the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) are required to perform numerous steps pertaining to the surveillance and management of ADRs. They must define significant ADRs, initiate intensive assessments for ADRs meeting the institution's definition, and be able to provide evidence during accreditation surveys of sufficiently detailed followup on the causes of ADRs.[48] The JCAHO recently instituted an additional requirement for reporting of sentinel events, which are those involving the occurrence of risk of death or serious physical or psychological injury. In situations where the sentinel event indicates an ongoing possibility of threat to life or safety, the JCAHO may conduct an unscheduled survey and require that the institution undertake extensive systems and process reviews and implement improvements to prevent recurrence of the sentinel event.

Risks from drugs and other medical products generally fall into four categories (Fig. 9–5). Most injuries and deaths associated with the use of medical products result from their known adverse effects. Some adverse effects are unavoidable, but others can be prevented or minimized by careful product choice and use. It is estimated that more than half the adverse effects from pharmaceuticals are avoidable.[49] Other sources of preventable adverse events are medication or device errors.

METHODOLOGIES FOR PHARMACOEPIDEMIOLOGIC STUDIES

2 A large number of study designs and methods are used to generate data on the uses and risks of new and older drugs. The types of study designs used in pharmacoepidemiology can be classified as experimental and observational. Experimental studies employ control in the assignment of individuals to exposure groups, usually through random assignment of individuals to the exposure under investigation, and then followup of individuals to detect the effects of exposure. For example, a recent clinical trial demonstrated that hormone-replacement therapy does not prevent coronary heart disease in women. This randomized, controlled primary prevention trial, the Women's Health Initiative, studied 16,608 postmenopausal women ages 50 to 79 years with an intact uterus at baseline recruited by 40 U.S. clinical centers during the period 1993 to 1998. Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year followup among healthy postmenopausal U.S. women.[50]

Observational epidemiologic study designs, such as case-control, cohort, and cross-sectional studies, are used extensively. Large automated databases, meta-analyses, RCTs, and hybrid designs, such as nested case-control studies, also play an important role in

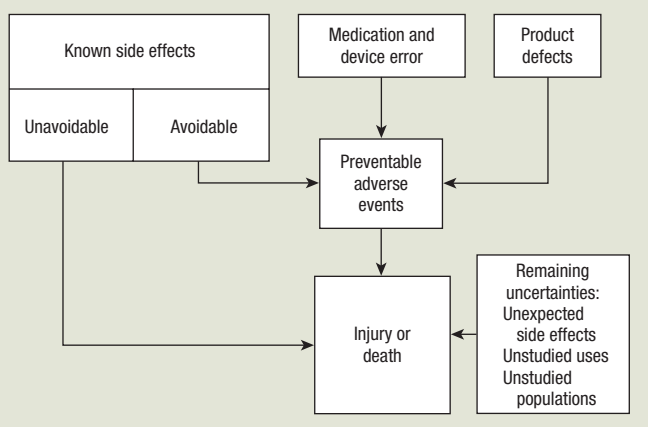

FIGURE 9-5. Sources of risk from medical products. *(From U.S. Food and Drug Administration. Managing the Risks from Medical Product Use: Creating a Risk Management Framework. http://www.fda.gov/oc/tfrm/executivesummary.html.)*

pharmacoepidemiology. Epidemiologic studies typically do not use randomization to determine who will receive a particular drug exposure. Rather, associations between exposure(s) and disease(s) under study are determined through the use of observational study designs and statistical analyses. Observational methods are used in most situations because ethics and cost limit the use of experimentation. For example, one would not experimentally subject individuals to certain drugs to determine if they develop cancer. Although observational studies are generally quicker and less costly than experimental studies, they have important disadvantages. One limitation of observational study designs in pharmacoepidemiology is confounding by indication. Confounding by indication occurs when subjects treated with the medication of interest differ from the nontreated group on a characteristic(s) also associated with the outcome. For example, a health user effect is one explanation for why observational studies have reported a decreased risk of cardiovascular disease events among women using hormone therapy compared to nonusers,[51] a hypothesis that was refuted in the Women's Health Initiative randomized controlled trial of hormone therapy use.[50] Although there are design and analytic techniques to cope with confounding, the possibility of distorted effects by confounding should be carefully considered in any observational study.

A number of methods are used to study health events associated with drug exposures. The usual approach to studying ADEs begins with the collection of spontaneous reports of drug-related morbidity or mortality. There is growing interest in using computerized databases containing medical care information for pharmacoepidemiologic studies.[52] These databases usually consist of patient-level data from two or more separate files (e.g., billing files for pharmacy and medical services reimbursement) that were developed originally for clinical or administrative applications.[53] Through record linkage, person-based longitudinal files can be created on an ad hoc basis. Multipurpose databases used for pharmacoepidemiologic studies include data from managed care organizations, the Medicaid program, the Medicare program, and geographically defined populations. In general, these databases include information on patient demographics, outpatient drugs, hospital discharge diagnoses, and ambulatory care encounters. The advantages and disadvantages of linked databases for pharmacoepidemiologic studies are the subject of numerous publications.[54,55]

CASE REPORTS AND CASE SERIES

Case reports, also referred to as spontaneous case reports or passive surveillance, describe a single patient who was exposed to a drug and experienced a particular, usually adverse, event. Such reports might be communicated by healthcare professionals or consumers to companies, regulatory agencies, or the World Health Organization, or reported in the medical literature. The FDA receives approximately 400,000 reports of suspected adverse events annually. Well-documented case reports can be viewed as a safety signal, alerting to the possibility of a rare adverse event not previously detected in premarketing studies. Spontaneous reports can also provide information on at-risk groups, risk factors, and clinical characteristics of known serious adverse drug reactions. The reporting of adverse events is influenced by several factors, including the elapsed time since its introduction into the marketplace, regulatory activity, and media attention.

Case series are collections of patients, all of whom have a single exposure, whose clinical outcomes are then evaluated and described. They are useful for quantifying the incidence of an adverse reaction, particularly for a newly approved drug. Furthermore, case series can be useful for being certain that the incidence rate of any particular adverse effects of concern does not occur in a population that is larger than that studied prior to drug's marketing. It is uncommon for a case report or a series of case reports to be used to make a statement about causation. If the event is rare and the exposure combination is very specific, the cause of the adverse health event may be inferred from a case-series study. In most situations, however, it is necessary to compare cases with a group of controls to identify risk factors. Thus the major disadvantage of a case-series study is the lack of a comparison group.

Active Surveillance

Active surveillance is the regular, periodic collection of case reports from healthcare providers or sentinel site facilities. Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous preorganized process. An example of active surveillance is the followup of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

A registry is a type of active surveillance whereby a list of patients presenting with the same characteristic(s) is followed. This characteristic can be a disease (disease registry) or a specific exposure (drug registry) or a type of exposure occurring during a specific life-event (pregnancy exposure registry). Registries can collect information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry, such as a cancer registry, might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

CASE-CONTROL STUDIES

A case-control study assembles a group of cases (people who have the disease of interest) and controls (people who do not). The exposure histories of the cases and the controls are determined to establish the extent of association between exposure(s) of interest and disease. Case-control studies compare patients with a specific disease with a control group composed of similar people but without the disease. Case-control studies attempt to identify risk factors for a disease by examining differences in antecedent exposure variables between cases and controls. For example, one can select cases of women of childbearing age with ovarian cysts and compare them with controls, looking for differences in prior use of oral contraceptives. Such a study was performed to determine if the then newly introduced triphasic oral contraceptives were associated with functional ovarian cysts.[56]

Case-control studies have been used extensively to assess the safety of pharmaceuticals. There are many examples of case-control studies that have identified important associations between drugs and adverse health events: vaginal cancer and diethylstilbestrol, Reye syndrome and aspirin, peptic ulcer disease and nonsteroidal antiinflammatory drugs, and venous thromboembolism and oral contraceptives. Data from case-control studies are used to calculate an odds ratio, which is the ratio of the odds of developing the disease for exposed patients to the odds of developing the disease for unexposed patients.

A classic example is a study of diethylstilbestrol given during pregnancy and the risk of vaginal adenocarcinoma among female offspring nearly a generation later.[57] The association between use of antibiotics and the risk of breast cancer was studied in a case-control study among women enrolled in a large, nonprofit health plan. Controls were selected from health plan records and frequency matched to cases on age and length of enrollment. Cases were identified from the Surveillance, Epidemiology, and End Results Cancer

Registry, whereas antibiotic use was ascertained from computerized pharmacy records.[58] An increased risk of breast cancer was reported for all antibiotic studies and a clear dose–response was observed.

A study of serious coronary heart disease risk in relation to the use of cyclooxygenase-2 selective inhibitors exemplifies a nested case-control design.[4] Serious coronary heart disease (myocardial infarction and sudden cardiac death) cases and controls, who were similar to cases in age, sex, and health plan region, were chosen from a large health plan. Information on medication use and relevant diagnoses were obtained from health plan data. Mortality status was determined from state death records. The investigators found an increased risk of serious coronary heart disease with rofecoxib use compared to celecoxib use. A nested case-control study is an efficient variation of a case-control and a cohort study, and commonly used when predictor variables are expensive to measure and can be assessed at the end of the study. In a nested case-control study, all cases (or a sample of all cases) and only a random sample of all controls are chosen for study from the same defined population.

An advantage of the case-control design for the study of drug-outcome relationships is its efficiency for the study of rare or delayed outcomes. Compared with other strategies, the case-control study is relatively inexpensive. One potential problem with case-control studies is their susceptibility to certain types of bias, including selection bias and information bias. *Selection bias* refers to systematic differences between those selected for study and those who are not, whereas *information bias* is systematic differences in the quality of information gathered for study and comparison groups.

COHORT STUDIES

A cohort study assembles a group of persons without the disease(s) of interest at the onset of the study, ascertains the exposure status of each person, and then follows the cohort over time to determine the development of disease in exposed and nonexposed persons. Cohort studies involve a comparison of the incidence of one or more outcome events among those who received a drug or some other exposure of interest compared with the incidence of the event(s) for a comparison group. For example, much information about the risk of fatal cardiovascular diseases among oral contraceptive users has come from the Royal College of General Practitioners Oral Contraception Study, in which 23,000 oral contraceptive users were compared with 23,000 nonusers chosen from the same British general practices.[59] Death certificate records were used to ascertain instances of fatal events during the followup period.

Cohort studies can be prospective, as the Royal College of General Practitioners study illustrates, or retrospective. Some prospective cohort studies follow a large population over decades. For example, the Nurses Health Study was begun in 1976 to investigate the potential long-term consequences of the use of oral contraceptives and was later expanded to include diet and nutrition and their relationship with the development of chronic diseases.[60] Prospective cohort studies are one of the most valid types of observational study designs because exposure is measured and recorded prior to the development of the health outcome(s) of interest. Using prospectively collected data from the Nurses Health Study, Chan et al. evaluated the association between long-term use of aspirin and nonsteroidal antiinflammatory drugs and risk of colorectal cancer.[61] The investigators confirmed previous results that long-term aspirin therapy (and non-aspirin nonsteroidal antiinflammatory drugs) are associated with a reduced risk of colorectal cancer compared to nonusers.

An alternative to the prospective cohort design is the retrospective cohort study. Retrospective cohort studies are useful when comparison cohorts of persons exposed and not exposed to drugs of interest can be identified at some time in the past from large preexisting databases and followed from that time to the present with regard to the incidence of a given outcome. Recently, Raebel et al. used a retrospective cohort design to describe the proportion of patients with poor serum drug concentration monitoring of drugs with narrow therapeutic ranges and factors associated with poor monitoring at 10 HMO Research Network sites.[62] Retrospective cohort studies are commonly used to evaluate the risks and benefits of marketed medications in large populations, especially with the availability of longitudinal electronic databases.

Prospective cohort studies can provide strong evidence of associations between drugs and diseases because the exposure is assessed before the outcome occurs. However, because many cohort studies require large numbers of people followed for long periods of time, they can be expensive and, in some instances, infeasible. Retrospective or historical cohort studies can overcome these limitations if high-quality data have been collected already.

EXPERIMENTAL AND QUASI-EXPERIMENTAL STUDY DESIGNS

Phase 4 clinical trials might be used to assess the risk or benefit in subpopulations that are inadequately studied in premarketing clinical trials, for example, the elderly and children, to better determine the benefit-to-risk profile of a drug. Another rationale for phase 4 trials is to evaluate the health risks and benefits of chronically used medications that were approved on the basis of short-term trials of surrogate end points, for example, blood pressure and lipid and hemoglobin A_{1c} levels, and for comparisons against other medications. One approach to the conduct of phase 4 trials is the use of large, simple trials.

One of the opportunities that has emerged with increased computerization in healthcare is the use of large, linked databases for exploring pharmaceutical outcomes. The ability to use transaction or claims data from an insurance company or state Medicaid agency and link these data to files containing diagnostic and other patient-specific information has allowed researchers to explore outcomes questions at relatively low expense. Because these studies do not rely on random assignment of subjects, they are described as *quasi-experimental.*[63] The typical design includes a treatment (exposed) group, a control (unexposed) group, and some type of posttest assessment for both. Although efforts may be made to match treatment and control groups for important patient characteristics, the groups are not equivalent in the sense of an RCT. A refinement to this design is one where an analysis of underlying trends—factors that could influence study outcomes and progress independent of the study—is made using time-series methods. These studies often are used to evaluate the consequences of a change of policy, such as a prescription limit, or addition or removal of a drug from the marketplace. For instance, Soumerai et al.[64] studied the effect of a prescription cap on the use of psychotropic drugs and emergency mental health services using claims data. They used pharmacy claims data collected over a 42-month period, including the 11 months that the prescription cap was in effect, and found that drug use decreased while costs to the state Medicaid program increased during the period of the cap.

A quasi-experimental design was used to study British Columbia's reference pricing policy for five therapeutic classes of drugs to determine if a worsening of health outcomes could be detected after implementation of the reference pricing policy. The authors reported that there was no worsening of health outcomes associated with implementing the reference pricing policy.[65]

INTERPRETATION OF PHARMACOEPIDEMIOLOGIC STUDIES

3 Not all associations represent a cause-and-effect relationship. Because most epidemiologic studies of drug effects do not employ

TABLE 9-3 Criteria for the Causal Nature of an Association

1. **The association makes biologic sense.** In other words, the proposed association is consistent with our knowledge of the mechanism of disease. You can use data from other human or animal studies, or data from in vitro studies.
2. **The suspected cause precedes the disease.** Even though this is self-evident, it can be overlooked when interpreting findings from certain observational studies.
3. **The association is strong.** Associations with a relative risk of less than 2.0 are considered to be weak; risks of 2.0 to 4.0 are considered moderate; and those greater than 4.0 are strong. You also need to consider the 95% confidence interval.
4. **The association is found consistently when studied using different methods or populations.** An important characteristic of science is that a finding is reproducible.
5. **There is a dose–response relationship.** For example, there is a higher risk among persons with greater exposure to a risk factor.

random allocation, it is important to determine if a legitimate cause-and-effect relationship exists. A central methodologic concern in observational studies is *confounding*—that is, the possibility that the apparent effect of an exposure or intervention is wholly or partly a result of other factors associated with it that have their own impact on the outcome of interest. Criteria have been proposed to help determine if an association is causal. The fewer criteria that are met, the less likely it is that an association is causal. Table 9–3 is adapted from the work of Hill and Stolly.[66,67] Practitioners should ask the series of questions listed in the table when interpreting findings from studies and considering whether a reported association is likely to be causal.

CONCLUSIONS

Pharmacoepidemiologic studies conducted during the postapproval period provide important information to assist in optimizing therapeutic responses to drugs. The aging U.S. population, the introduction of new drugs, and reimbursement policies make pharmacoepidemiology an essential part of clinical practice. Studies can provide valuable information about the relationship between therapeutic agents and adverse and beneficial health outcomes. Information from pharmacoepidemiologic studies also contributes to population-based care and drug regulatory and reimbursement decisions. At the level of individual patient care, a combination of medical and epidemiologic knowledge leads to the choice to use a particular medication. Moreover, patient monitoring to optimize the therapeutic response to drugs also involves epidemiologic data and logic to balance likely benefits against potential risks. Epidemiologic information can provide vital information regarding safety, patterns of drug use, and effectiveness to assist in the provision of evidence-based healthcare. New data resources and methodologies are likely to expand the field of pharmacoepidemiology. There is an inherent tradeoff between the need for more information about a drug's risks and the need to make a drug available for use. Because of limitations in the drug development process, more information emerges about a drug after its approval through PMS. The challenge—articulated in the FDA's recent *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*—will be to improve on this tradeoff through enhanced assessment methods for safety and utility and to better integrate these measures with manufacturing technology.[68] The findings and recommendations from the Institute of Medicine Committee on Assessment of the U.S. Drug Safety System have framed contemporary discourse on improving how drug safety is assessed throughout a drug's lifecycle.[69] Finally, the Food and Drug Administration Amendment Act of 2007 was signed into law on September 28, 2007 providing additional resources for postapproval safety studies and additions to FDA authorities.[70]

ABBREVIATIONS

ADE: adverse drug event

ADR: adverse drug reaction

CERT: Centers for Education and Research on Therapeutics

FDA: Food and Drug Administration

HMO: health maintenance organization

JCAHO: Joint Commission on Accreditation of Healthcare Organizations

PMS: postmarketing drug surveillance

RCT: randomized, controlled trial

REFERENCES

1. Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996;335:609–616.
2. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337:581–588.
3. Psaty BM, Furberg CD. COX-2 inhibitors—Lessons in drug safety. N Engl J Med 2005;352:1133–1135.
4. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: Nested case-control study. Lancet 2005;365(9458):475–481.
5. Rosiglitazone Maleate (marketed as Avandia, Avandamet, and Avandaryl) Information. *http://www.fda.gov/cder/drug/infopage/rosiglitazone/default.htm*.
6. Strom BL, Melmon KL. The use of pharmacoepidemiology to study beneficial drug effects. In: Strom BL, ed. Pharmacoepidemiology. New York: Wiley, 2005, 611–628.
7. Adequate and well-controlled studies. 21 CFR Part 314.126.
8. Fletcher RH, Fletcher SW, Wagner EH. Clinical Epidemiology, The Essentials, 3rd ed. Baltimore: Williams & Wilkins, 1996.
9. Fayers PM. Generalisation from phase III clinical trials: Survival, quality of life, and health economics. Lancet 1997;350:1025–1027.
10. Strom BL, ed. Pharmacoepidemiology. New York, Wiley: 1994.
11. Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and "vaccine damage." Curr Opin Neurol 2007;20(2):181–187.
12. Collett JP, Boissel JP. Pharmacoepidemiology: Epidemiologic approach to the study of drugs. Post Market Surveill 1991;5:3–14.
13. Suissa S, Ernst P, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000;343:332–336.
14. Geiling EMK, Cannon PR. Pathogenic effects of elixir of sulfanilamide (diethylene glycol) poisoning. JAMA 1938;111:919–926.
15. Lenz W. Malformations caused by drugs in pregnancy. Am J Dis Child 1966;112:99–106.
16. Ray WA, Griffin MR, Avorn J. Evaluating drugs after their approval for clinical use. N Engl J Med 1993;329:2029–2032.
17. Rossi AC, Bosco L, Faich GA, et al. The importance of adverse reaction reporting by physicians: Suprofen and the flank pain syndrome. JAMA 1988;259:1203–1204.
18. Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991;114:257–263.
19. Ault A. Troglitazone may cause irreversible liver damage. Lancet 1997;350:1451.
20. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004;292:2585–2590.
21. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: Impact of Food and Drug Administration regulatory action. JAMA 2000;284:3036–3039.
22. Jick H, Miettinen OS, Shapiro S, et al. Comprehensive drug surveillance. JAMA 1970;213:1455–1460.
23. Rosenberg L, Coogan PF, Palmer JR. Case-control surveillance. In: Strom BL, ed. Pharmacoepidemiology. New York: Wiley, 2005,185–202.

24. Inman WHW. Prescription event monitoring. Acta Med Scand Suppl 1984;683:119–126.
25. Joint Commission on Prescription Drug Use, 96th Congress. Washington, DC: US Government Printing Office, 1980.
26. Saunders KW, Davis RL, Stergachis A. Group health cooperative. In: Strom BL, ed. Pharmacoepidemiology, 4th ed. New York: Wiley, 2005:223–239.
27. Platt R, Davis R, Finkelstein J, Go AS, et al. Multicenter epidemiologic and health services research on therapeutics in the HMO Research Network Center for Education and Research on Therapeutics. Pharmacoepidemiol Drug Saf 2001;10:373–377.
28. Gibbs JN. State regulation of pharmaceutical clinical trials. Food Drug Law J 2004;59(2):265–285.
29. Arlett P, Moseley J, Seligman PJ. A view from a regulatory agency. In: Strom BL, ed. Pharmacoepidemiology, 4th ed. New York: Wiley, 2005:103–130.
30. FDA announces new advisory committee. *http://www.fda.gov/bbs/topics/NEWS/2007/NEW01648.html*.
31. USP Medication Errors Reporting Program. *http://www.usp.org/hqi/patientSafety/mer/*.
32. Kessler DA. Introducing MEDWatch: A new approach to reporting medication and device adverse events and product problems. JAMA 1993;269:2765–2768.
33. Scott HD, Rosenbaum SE, Waters WJ, et al. Rhode Island physicians recognition and reporting of adverse drug reactions. R I Med J 1987;70:311–316.
34. PDUFA Goals. *http://www.fda.gov/oc/pdufa3/2003plan/default.htm#update.*
35. Kennedy EM. S.1082. Prescription Drug User Fee Amendments of 2007. *http://thomas.loc.gov/cgi-bin/bdquery/z?d110:SN01082:@@@D&summ2=m&*.
36. Guidance for Industry. Development and Use of Risk Minimization Plans. *http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0188-gdl0002.pdf.*
37. Guidance for Industry. Q9. Quality Risk Managment, 2006. *http://www.fda.gov/cder/guidance/7153fnl.pdf.*
38. Centers for Education and Research on Therapeutics. *http://www.certs.hhs.gov/index.html.*
39. World Health Organization. International Drug Monitoring: The Role of the Hospital. Technical Report Series No 425. Geneva: World Health Organization, 1966.
40. Beard K. Adverse reactions as a cause of hospital admission in the aged. Drugs Aging 1992;2:356–367.
41. Koch KE. Adverse drug reactions. In: Brown T, ed. Handbook of Institutional Pharmacy Practice, 3d ed. Bethesda, MD: American Society of Hospital Pharmacists, 1992:279–291.
42. Johnson JA, Bootman JL. Drug-related morbidity and mortality: A cost-of-illness model. Arch Intern Med 1995;155:1949–1956.
43. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: Updating the cost-of-illness model. J Am Pharm Assoc 2001;41:192–198.
44. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA 1998;279:1200–1205.
45. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107–1116.
46. Strom BL. What is pharmacoepidemiology? In: Strom BL, ed. Pharmacoepidemiology, 4th ed. New York: Wiley, 2005:3–17.
47. Park BK, Pirmohamed M, Kitteringham NNR. Idiosyncratic drug reactions: A mechanistic evaluation of risk factors. Br J Clin Pharmacol 1992;34:377–395.
48. Joint Commission on Accreditation of Healthcare Organizations. Comprehensive Accreditation Manual for Hospitals: The Official Handbook. Oakbrook Terrace, IL: JCAHO, 2006.
49. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. J Gen Intern Med 1993;8:289–294.
50. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized, controlled trial. JAMA 2002;288:321–333.
51. Prentice RL, Langer RD, Stefanick ML, et al. Combined analysis of Women's Health Initiative observational and clinical trial data on postmenopausal hormone treatment and cardiovascular disease. Am J Epidemiol 2006;163:589–599.
52. Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. Epidemiol Rev 1990;12:87–107.
53. Stergachis A. Evaluating the quality of linked automated data sets for use in pharmacoepidemiology. In: Hartzema AG, Porta MS, Tilson HH, eds. Pharmacoepidemiology: An Introduction, 2d ed. Cincinnati: Harvey Whitney Books, 1991, 368–388.
54. Shapiro S. The role of automated records linkage in the postmarketing surveillance of drug safety: A critique. Clin Pharmacol Ther 1989;46:371–386.
55. Faich GA, Stadel BV. The future of automated record linkage for postmarketing surveillance: A response to Shapiro. Clin Pharmacol Ther 1989;46:387–389.
56. Holt VL, Daling JR, Weiss NS, et al. Functional ovarian cyst risk associated with use of monophasic and triphasic oral contraceptives. Obstet Gynecol 1992;79:529–533.
57. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971;284:878–881.
58. Velicer CM, Heckbert SR, Lampe JW, et al. Antibiotic use in relation to the risk of breast cancer. JAMA 2004;291:827–835.
59. Royal College of General Practitioners. Oral Contraceptives and Health. London: Pitman, 1974.
60. The Nurses' Health Study. *http://www.channing.harvard.edu/nhs.*
61. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 2005;294(8):914–923.
62. Raebel MA, Carroll NM, Andrade SE, et al. Monitoring of drugs with a narrow therapeutic range in ambulatory care. Am J Manag Care 2006;12:268–274.
63. Cook TD, Campbell DT. Quasi-Experimentation: Design and Analysis Issues for Field Settings. Boston: Houghton-Mifflin, 1979.
64. Soumerai SB, McLaughlin TJ, Ross-Degnan D, et al. Effects of limiting Medicaid drug-reimbursement benefits on the use of psychotropic agents and acute mental health services by patients with schizophrenia. N Engl J Med 1994;441:650–655.
65. Hazlet TK, Blough DK. Health services utilization with reference drug pricing of histamine(2) receptor antagonists in British Columbia elderly. Med Care 2002;40:640–649.
66. Hill AB. The environment and disease: Association or causation? Proc R Soc Med 1965;58:295–300.
67. Stolly PD. How to interpret studies of adverse drug reactions. Clin Pharmacol Ther 1990;48:337–339.
68. Challenges and Opportunity on the Critical Path to New Medical Products, 2004. *http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html.*
69. Institute of Medicine. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: National Academies Press, 2007.
70. Food and Drug Administration Amendments of 2007. *http://www.fda.gov/oc/initiatives/HR3580.pdf.*