SECTION 1

MAGNITUDE/SIGNIFICANCE OF DRUG-INDUCED DISEASES

Impact on the Health Care System

CHAPTER 1

Drug Safety and Drug-Induced Disease: The Regulatory, Legal, and Practice Environments

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The regulatory, legal, and practice environments in health care surrounding drug safety have been the subject of much scrutiny in recent years. The highly publicized market withdrawal of almost a dozen widely used drug products for safety reasons between 2000 and 2006 has served as a focal point of concerns about the safety of the United States (U.S.) drug-approval and safety surveillance systems.[1] Since 1969, 75 drugs and combination drug products have been removed from the U.S. market for safety reasons. This represents less than 1% of all marketed drugs.[2] Other safety-related regulatory actions (e.g., labeling changes, such as the addition of precautions, contraindications, or black box warnings) are far more common and, although less publicized, have the potential for significant impact on patient safety if these therapies are not properly managed. Other adverse events of medication therapy, such as medication errors, have also heightened public awareness and concern about all aspects of drug safety. As medication experts, pharmacists play a critical role in ensuring drug safety through their activities in selecting and monitoring drug therapy, communicating risk versus benefit to patients to allow for informed decision making, and reporting suspected adverse drug events and drug-induced diseases.

The extent of adverse drug events, which includes but is not limited to drug-induced diseases, is staggering. Since its inception in 1969 through 2002, the Adverse Event Reporting System (AERS) of the Food and Drug Administration (FDA) received approximately 2.3 million reports of adverse events on more than 6,000 drug products.[2] In 2006, the FDA Center for Drug Evaluation and Research recorded 471,000 safety reports via AERS and issued 16 public health advisories (i.e., descriptions of safety concern with recommended actions).[3] The Center for Biologics Evaluation and Research received more than 19,000 reports via the Vaccine Adverse Event Reporting System as well as approximately 4,000 AERS reports. Meanwhile, it is commonly held that most adverse events are not reported to spontaneous reporting systems in the United States.

Drug-induced disease can result from unanticipated or anticipated drug effects. Disease also can occur from product impurities, as was the case with deaths attributed to the use of contaminated heparin in 2008.[4] Vigilance on the part of regulatory authorities, drug manufacturers, clinicians, and patients is necessary to minimize the potential for harm that is inherent in drug use.

DRUG SAFETY: THE REGULATORY ENVIRONMENT

The FDA and Regulatory Efforts to Ensure Drug Safety

Until recently, FDA efforts to provide drug safety had largely focused on premarket strategies. However, as the history of the agency demonstrates (Figure 1–1), much of the FDA's regulatory authority was created in response to harm, or concern for harm, associated with drugs already on the market.[5] The origins of the FDA can be traced back to the late 1860s, when its predecessor, the Bureau of Chemistry, was established as part of the Department of Agriculture. Over the years, there were repeated attempts to introduce legislation to

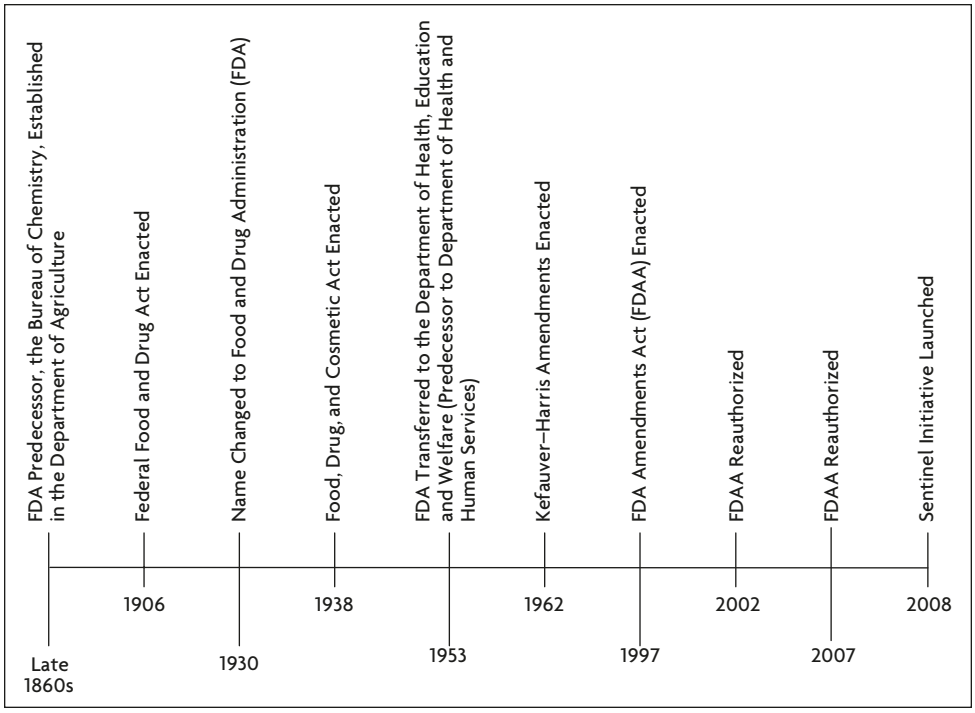

FIGURE 1–1 History of FDA Drug Safety Activities and Regulations.[5]

address concerns about adulterated drug products from overseas. However, it was not until 1906, when the Federal Food and Drugs Act was passed, that the focus of the agency shifted from a scientific to a regulatory body. While that legislation permitted regulation of drug-product labeling, the impetus for the law was not drug safety, but rather concerns for *food safety,* which were prompted by Upton Sinclair's *The Jungle*. The novel exposed unsanitary conditions in the meatpacking industry, which at the time, was considered the greater threat to public safety.

It wasn't until passage of the Food, Drug, and Cosmetic Act in 1938 that legislation began to focus on premarket drug safety. Once again, this authority was granted in response to a safety incident in which an antifreeze-like ingredient in the elixir sulfanilamide resulted in more than 100 deaths.[5] In 1962, the Kefauver–Harris Amendments to the 1938 Act introduced a requirement to demonstrate both efficacy and safety prior to drug approval. This was the first legislation that focused on adverse events caused by active ingredients and was spurred by reports of birth defects following the use of thalidomide abroad. Severe malformations, including a flipper-like appearance of limbs caused by very short or absent long bones resulted in withdrawal of the drug from worldwide markets. A U.S.-based drug manufacturer had applied for, but never received, approval to market the drug in the U.S.

Significant efforts to improve drug safety have been addressed within the FDA Amendments Acts (FDAAs) of 1992, 1997, 2002, and 2007. Most notably, the 2007 reauthorization of the act grants the FDA increased authority to request that manufacturers complete postmarketing safety studies and requires that manufacturers develop and submit risk evaluation and mitigation strategies (REMS) for all drug products for which they seek FDA approval.[6-8] While patient and prescriber education programs are potential components of REMS programs, more stringent programs, such as patient and provider registries or required laboratory monitoring and reporting may be included in a more comprehensive restrictive drug distribution system, or RDDS. FDAA 2007 also requires that the FDA establish a mechanism to increase and coordinate postmarketing surveillance efforts. The requirement was addressed by establishment of the Sentinel Initiative in 2008, which is discussed in greater detail in Chapter 4, "Postmarketing Surveillance for Drug-Induced Diseases."

The FDA's Safety-Related Regulatory Actions

The FDA considers and may request a number of regulatory actions when a serious or life-threatening safety concern is identified for a drug. Each action has the potential to decrease or

eliminate patient access to drug therapy. Therefore, the decision about the specific course of action to take must carefully balance the effectiveness of the drug, other therapeutic options for the condition being treated, the type of possible harm to patients, and the potential for its occurrence.

Regulatory options following drug approval include clinician and patient warnings, labeling changes, and product withdrawals. To increase transparency as well as consumer and clinician awareness, the Prescription Drug User Fee Act (a component of FDAA 2007 that authorizes the FDA to use fees collected from pharmaceutical manufacturers to conduct safety activities) requires the FDA to generate quarterly reports that include information on recently identified, potentially serious risks and new safety information generated from the AERS database.[8,9] Introduction of this program and enhanced reporting via the MedWatch program generate extensive amounts of safety information. While this is beneficial, it has also generated concern among clinicians because the most appropriate course of action when a safety concern arises is frequently unclear. Safety information is and always will be an evolving area, but the FDA and professional associations such as the American Society of Health-System Pharmacists are collaborating to determine how this information can be made available in ways that are most useful to clinicians and their patients.

Restricted drug distribution systems (RDDS) have been used to provide continued availability of drugs that are associated with significant safety concerns but provide a health benefit if used appropriately in specific patient populations. RDDS can include clinician or facility registration, patient registries that are used to track and evaluate response to therapies, and performance-linked access systems. The FDA can request that these programs be established for drugs that are already approved or as a condition for approval. For example, in 1999, the drug thalidomide, which had previously been removed from world markets, was approved in the U.S. for the treatment of lesions caused by Hansen's disease, or leprosy.[10] However, to prevent or reduce the risk of significant drug-induced disease, thalidomide is available only through physicians and pharmacists registered in the System for Thalidomide Education and Prescribing Safety (STEPS) program. The drug cannot be prescribed for women of childbearing age, unless the patient meets certain criteria (e.g., ability to comprehend and follow pregnancy precautions). The physician must also document proof of a negative pregnancy test 24 hours prior to initiation of therapy and on an ongoing basis while the drug is used. Oral and printed patient education materials are also a significant component of the STEPS program.

TABLE 1–1 FDA-Approved Drugs with RDDS[11]

Drugs

- Clofaziminea
- Gefitinib
- Dofetilide
- Bosentan
- Iloprost
- Ambrisentan
- Encainide[a]
- Clozapine
- Sodium oxybate
- Buprenorphine tablets
- α1-Proteinase inhibitor (Human)
- Alosetron
- Cisapride[a]
- Mifepristone
- Isotretinoin
- Alendronate (40 mg tablet only)
- Natalizumab
- Lenalidomide
- Thalidomide

FDA = Food and Drug Administration; RDDS = Restricted Drug Distribution Systems.

[a] Drug available only through FDA-established compassionate-use programs.

Thalidomide is 1 of almost two dozen drugs marketed in the U.S. that have an RDDS (Table 1–1).[11] This list is expected to grow based on the FDA's increased authority to require these programs under the Prescription Drug User Fee Act IV (PDUFA IV). While these programs provide for ongoing availability of drug therapies, they also present challenges to clinicians and patients.[13] RDDS are not currently standardized, and each drug manufacturer may establish its own management processes, including clinician registration requirements. The variability and complexity of these processes have the potential to delay or limit patient access to therapies, especially as patients move between health care settings. At the urging of professional organizations and others, the FDA is evaluating strategies to minimize unintended con-

sequences that these programs may have on the continuity of care and patient access to these high-risk drugs.

A recent trend toward shortened time frames for drug approval has been criticized as a significant contributor to drug safety problems, but this perception is misleading because it implies a direct cause-and-effect relationship between shortened average time to drug approval and drug withdrawals or other safety issues. Safety concerns can arise throughout a product's life cycle.[14] An example is aprotinin, an antithrombolytic agent that was used in cardiac surgery for 14 years before accumulating reports of increased morbidity and mortality led to its voluntary withdrawal from the U.S. market in late 2007.[15]

An FDA assessment of the timing of safety-related actions for 444 new molecular entities (NMEs) approved between 1991 and 2006 demonstrated that regulatory actions occur throughout a product's life cycle.[16] Among drugs approved by the FDA during that time frame, 78% had a least one safety-related action and 3% were withdrawn from U.S. market. A subanalysis of drugs approved from 1991 through 1995 (i.e., representing drugs that were marketed for a minimum of 13 years) found that 27% of NMEs underwent changes or additions to boxed warnings, warnings, or precautions sections of the FDA-approved labeling. No drugs in this subgroup were removed from the market. For drugs marketed less than 5 years (i.e., those approved from 2003 through 2006), 44% underwent safety-related labeling changes, and there were no market withdrawals. These data demonstrate that safety actions occur on an ongoing basis and that newer drugs are not necessarily more prone to safety issues. Rather, it is likely that new safety signals will be generated throughout the life cycle of a drug.

DRUG SAFETY IN THE LEGAL ENVIRONMENT

Drug safety has been the subject of countless court rulings, with most cases focusing on who is responsible for ensuring the safe use of drug products—pharmaceutical manufacturers, prescribers, other health care professionals, or a combination of these entities.

Pharmaceutical Manufacturers

State and federal courts have commonly found pharmaceutical manufacturers to be the primary entity responsible for drug safety. Historically, there has been significant litigation against pharmaceutical manufacturers alleging that they hid, misrepresented, or otherwise failed to meet the obligation to inform clinicians and patients about known or suspected risks associated with a drug's use. In *Feldman v. Lederle Laboratories* (1984), one of the more unusual cases, the New Jersey Supreme Court ruled in favor of plaintiff Feldman, who claimed that the drug manufacturer had failed to provide sufficient information and warnings to physicians about the potential for tooth discoloration from its tetracycline product, demeclocycline.[17] Ms. Feldman was prescribed and dispensed samples of the drug by her father, a physician and pharmacist, several times when she was an infant and toddler. The company claimed that at the time Ms. Feldman received demeclocycline, information about this side effect was not fully known, and therefore not included in the labeling and prescribing information approved by the FDA. However, abnormalities in tooth development and discoloration associated with tetracycline products were reported in published studies of laboratory animals and children with cystic fibrosis who received high doses. A lower court had found the manufacturer not liable because the company had asked the FDA for guidance on whether to include a warning in the labeling of all of its tetracycline products, but the agency advised against including this information in demeclocycline labeling based on a lack of sufficient evidence. However, the state supreme court disagreed with the lower court's decision, noting that the FDA's response did not prevent the manufacturer from providing this information or relieve the company of its responsibility to do so.

There are several unusual circumstances in this case, including uncertainty as to whether Ms. Feldman received demeclocycline or another tetracycline. Because samples were used, no prescription or dispensing records were available to confirm the plaintiff's assertion. In addition, most product-liability cases include the manufacturer and prescriber as litigants, but in this instance, legal action was directed only toward the drug manufacturer, not the prescriber (the patient's father).

In *Brown v. American Home Products Corporation Diet Drugs,* the federal courts approved a negotiated settlement in the class-action product-liability case of fenfluramine–phentermine ("fen-phen") or dexfenfluramine with phenteramine.[18] The

is trademark symbol needed here and two lines below for Redux?

class-action lawsuit found that product manufacturers for fenfluramine (marketed as Pondomin by American Home Products, Inc.) and dexfenfluramine (marketed as Redux by Wyeth) possessed extensive information, including published case reports, animal studies, case reports in patients taking drugs with similar effects on serotonin, and unpublished studies conducted by the manufacturer, showing that the drugs could cause damage to heart valves and lead to valvular regurgitation. The court found that despite having this information, the manufacturer continued to market the drug combination until the drugs were withdrawn from the market in 1997, without further investigating these reports or warning prescribers or patients through labeling or other mechanisms. The settlement created a $2.5 billion fund to compensate patients for harm and cover current and future associated health care costs based on factors such as length of therapy and extent of harm.

A 2001 U.S. Supreme Court case ruled that patients cannot sue pharmaceutical companies for withholding information during the drug-approval process in instances in which the FDA has found no evidence of fraud or failure to disclose information. However, in *Warner Lambert v. Kent*, a split decision by that court upheld a lower court decision allowing an exemption in Michigan law that permitted patients who had received troglitazone to sue the product manufacturers for punitive damages by alleging fraud, even in instances when the FDA did not allege or find evidence of fraud.[19] Similar exemptions exist in seven other states.

A decision in March 2009 by the U.S. Supreme Court may have a pronounced effect on the manner in which pharmaceutical manufacturers view and operationalize their duty to warn of significant adverse drug events in product labeling. In *Wyeth v. Levine,* the court upheld a state trial and supreme court decision that awarded damages to a Vermont woman whose arm was amputated because of gangrene that developed following administration of promethazine by intravenous (IV) push.[20] The product's FDA-approved labeling included information on the preferred route of administration (deep intramuscular injection), warnings about the potential for gangrene (especially with intraarterial or subcutaneous administration), and a preference for IV infusion administration when the drug is administered intravenously. However, the trial court found that the patient's injuries would not have occurred if the product's labeling included adequate warning, including specific information about the danger of IV push administration. The Supreme Court agreed with the trial court and disagreed with the pharmaceutical manufacturer's argument that it was protected from state-law claims because of federal labeling requirements and the FDA's approval of the existing product's label. In general, those requirements allow a manufacturer to change labeling only following FDA approval of the proposed change. However, the court noted that the manufacturer could have strengthened the safety warning through the "Changes Being Affected" regulation, which allows labeling changes that improve safety while the manufacturer is in the process of seeking the FDA's official approval of that change. In issuing its decision, the court emphasized that the pharmaceutical manufacturer, not the FDA, is ultimately responsible for the accuracy and completeness of the product labeling and that the FDA's regulatory authority is intended to be complementary to, not preemptive of, a state's role in drug safety. This decision may have far-reaching impact on other ongoing product-liability cases, including those asserting harm from altered glucose metabolism and diabetes from olanzapine use and drug-induced hepatitis associated with troglitazone use. [19,21]

Pharmacists' and Other Clinicians' Duty to Warn

According to the National Association of Chain Drug Stores, as of October 2008 there were approximately 50 state and federal lawsuits involving the pharmacist's duty to warn.[22] The majority of these cases have found that pharmacists are not liable for patient harm resulting from adverse drug events or drug-induced disease. These decisions are generally based on the learned intermediary doctrine, which assigns responsibility for drug selection to the prescriber based on his or her knowledge of the drug and the individual patient. Pharmacists have generally been considered "sellers" of the drug product or service, and the courts have considered dispensing to be an extension of the physicians' order. Several decisions have noted that if pharmacists' liability was permitted, it could undermine the physician–patient relationship by calling prescribers' authority into question.[23] Based on existing case law, it is unclear how the learned intermediary doctrine would be applied to pharmacists who select drug therapy under collaborative practice agreements or with the significant expansion of information that would be available to pharmacists from proposed national or universal electronic health records. In *Jones v. Irvin and K-Mart,* the plaintiff appellate argued that the

practice of pharmacy had changed dramatically, that the pharmacist had greater knowledge of the dangers associated with drugs than physicians, and therefore the pharmacists' duty to warn warranted new consideration. The court found that while this advanced knowledge may be true, the physician's role as learned intermediary is predominant.[24] However, future courts may take a more expansive view of the pharmacist's role.

While the learned intermediary principle has frequently shielded pharmacists and their employers from liability, it negatively affects efforts to establish pharmacists as medication experts and independent practitioners. Most importantly, pharmacists have a professional obligation to ensure safe care, regardless of legal liability. Patient education, including risk communication, is a significant component of the commitment that all pharmacists make through their education, licensure, and subsequent practice.

THE DRUG-APPROVAL PROCESS AND OTHER FACTORS THAT AFFECT DRUG-INDUCED DISEASE

The drug-approval process is expected to assess the efficacy and, to a certain extent, the safety of new drug products, but it should be noted that several characteristics of that process and the subsequent environment of drug use contribute to drug-induced disease. Patient populations in preapproval clinical trials are, by necessity, narrowly structured and defined. Strict inclusion and exclusion criteria often exclude patients with multiple diseases and advanced disease and patients of a certain sex, age, or race. Even the largest clinical trial conducted across multiple study sites evaluates a drug's use in a number of patients that is small in comparison with the broader use of the drug postapproval—use that includes individuals with characteristics not studied during the approval process.

Drug-induced disease can also be attributed to conditions of drug use postapproval, which can differ dramatically from established conditions in clinical studies. Drugs are often used for unapproved indications and for approved indications but with variations in dose or route of administration. Subtle changes in manufacturing processes can also contribute to drug-induced diseases. For example, between 1998 and 2001, there was a dramatic increase in the number of pure red-cell aplasia (PRCA) cases in patients with chronic kidney disease.[25,26] PRCA is a known, but very rare, side effect that can occur when anti-erythropoietin antibodies form in response to erythropoietin treatment. Most events occurred in patients treated with an erythropoietin product supplied by one manufacturer, but cases also occurred in patients treated with a similar product. On further analyses, the dramatic increase in adverse events was attributed to a change in the stabilizers in one manufacturer's product and subsequent storage, handling, and subcutaneous administration of that product. Education regarding proper use of the various formulations resulted in a significant decrease in the number of PRCA cases.

Product contamination has also resulted in significant morbidity and mortality, most recently in the case of serious adverse events associated with heparin that occurred from November 2007 through February 2008.[4,27] Patient events included 62 deaths, with other reports of patients experiencing allergic symptoms or symptoms of hypotension. Voluntary product recalls occurred when a pattern of serious events was determined. The adverse drug events were later linked to the presence of oversulfated chondroitin sulfate in the active pharmaceutical ingredient from an overseas plant that processes heparin from pig intestines. The contaminant was not detected in random sampling of manufacturing plants, in part because it mimics heparin in commonly used tests. Follow-up tests conducted by the FDA found that the contaminant accounted for 5% to 20% of the total mass of each sample tested. It was alleged that the contamination with chondroitin was a purposeful act.[28] Plans to increase overseas inspections and to modify current standards for assessing the purity of heparin were also announced. This incident illustrated the importance of oversight and inspection of the complete product-development process, including assessment of the raw materials. It also noted that even in a more robust system of inspections, purposeful adulteration may occur at anytime by unscrupulous suppliers of raw materials and manufacturers, as well as criminal acts by private citizens, as occurred with acetaminophen adulteration in the early 1980s.

RECOMMENDATIONS TO IMPROVE DRUG SAFETY

During the past decade a number of public and private entities have assessed drug safety efforts in the U.S. and made recommendations to improve that process. Many of these recommendations, such as development of a national database for enhanced

collection and assessment of adverse drug events and drug-induced diseases, were included in PDUFA IV, and their implementation is underway. The following describes major reports and the current status of their recommendations.

Institute of Medicine (IOM)

In its landmark 2006 report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public,* the IOM issued more than two dozen recommendations to improve drug safety.[29] The report, which focused on postmarketing safety, identified structural and procedural barriers at the FDA that hampered efforts to enhance drug safety. The report stated that preapproval data are inherently limited in their ability to identify infrequent adverse events and that existing approaches for data collection following drug approval are not adequate to address this shortcoming. The report's authors called for increased, proactive postmarketing surveillance by the FDA, as well as additional authority for the FDA to control manufacturers' postapproval marketing activities. Many of the IOM's recommendations, including strengthened authority to require REMS, were included in PDUFA IV. Strategies to better inform the public, such as establishment of an advisory committee to address communication of risks, have also been implemented. However, the IOM's recommendation to prevent potential harm by restricting direct-to-consumer advertising for a period of 2 years following drug approval, and require that labeling and marketing materials for these products contain a symbol to designate the recent approval status, were controversial and not addressed in the reauthorization of the legislation.

Other IOM reports, including *Preventing Medication Errors* (2006) and *Knowing What Works in Health Care: A Roadmap for the Nation* (2008) have also addressed drug safety.[30,31] While these reports focus on the broader context of avoidable harm from drug therapies and comparative effectiveness, respectively, they include components on drug-induced disease and postmarketing safety surveillance.

Government Accountability Office (GAO)

In 2006, the GAO issued the report, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process,* which evaluated drug safety processes based on an assessment of regulatory actions for four drugs: leflunomide (Avara), cerivastatin (Baycol), valdecoxib (Bextra), and cisapride (Propulsid).[1] Leflunomide remains available, but the other drugs were voluntarily withdrawn from the U.S. market following several safety assessments by FDA staff and subsequent regulatory actions. A major finding in the GAO report was instances in which conflicting recommendations were made by divisions within FDA's Center for Drug Evaluation and Research. As a result, decisions were either not made or were made counter to the recommendations of another FDA group without a clear process for resolving the disparate views.

The GAO identified a lack of collaboration and communication between the two predominant offices involved in drug safety—the Office of New Drugs (OND), which is responsible for drug approval and for initiating regulatory actions, and the Office of Drug Safety (ODS), which predominantly focuses on postmarketing safety. The GAO described the ODS as serving in an advisory capacity to the OND, based on its finding that the ODS had no authority to initiate a regulatory action. The report identified a lack of documented processes for decision making, including an absence of criteria to determine the appropriate regulatory action when a safety concern is identified.

Significant progress has been made to address shortcomings identified in the GAO report, such as better coordination and more frequent meetings with the ODS risk-management advisory committee and the OND's disease-specific advisory committees. Other recommendations, including the establishment of clearly defined processes to resolve conflicts of opinion between the offices, remain unresolved. The report describes a draft policy entitled "Process for Decision-making Regarding Major Postmarketing Safety-related Actions" that remains unavailable to the public at the time of this writing. While the GAO report focuses on the lack of criteria and processes, it should be noted that risk assessment and decisions about drug safety are not an exact science. It requires careful balancing of the pros and cons of providing continued availability of a drug, and is based on evidence that, by nature, is constantly evolving.

FDA

The FDA has also assessed existing processes and taken numerous steps to enhance drug safety. In late 2007, the FDA's Science Board Subcommittee on Science and Technology published, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology.*[3] The report was requested by then Commissioner Andrew von Eschenbach to review the adequacy of the agency's science and technolo-

gy resources to meet current and future challenges. The report concluded that the agency's resources had decreased, despite an increase in responsibilities that resulted from the speed of scientific discoveries, increased and more complex products, and the increasingly global nature of the drug industry. The subcommittee recommended that the existing deficits in resources in scientific research programs; recruitment, development and retention of expert staff; and information technology must be corrected in order to meet these challenges.

Among the report's specific recommendations was the need to strengthen and coordinate the science program across the FDA's centers. The need for collaboration with external scientific and research programs, including the Agency for Healthcare Research and Quality's Centers for Education and Research on Therapeutics, the Centers for Disease Control and Prevention, the National Institutes of Health, and others when the expertise is not available at the FDA was identified. It is anticipated that the Reagan–Udall Foundation, an independent organization mandated by PDUFA IV, will assist in the development of these and other public–private partnerships as part of its charge to assist the FDA in modernizing its activities to address the rapid pace of change in the scientific and regulatory environments.

Other recommendations in the report include broadening staff with the statistical and epidemiologic expertise needed to analyze collected data as well staff with expertise in risk assessment and its quantitative measurement. A major focus of the report was the need to establish information standards that permit sharing and aggregation of information from public and private postmarketing safety surveillance databases. The report noted that these standards were critical, especially with the establishment of new sciences, including pharmacogenetics, nanotechnology, and cell-based products, for which collection of the extent and types of data will not be supported by current systems.

In terms of funding these improvements, the report stated that appropriation provided by PDUFA IV provided only a small portion of that which is needed. The Science Board called for a 2009 budget to address the identified shortcomings and directed the FDA Commissioner to develop an action plan to implement the report's recommendations. Calls to increase FDA funding are echoed by health care professional, research, and consumer sectors through entities such as the Alliance for a Stronger FDA.[32] The Alliance, whose members include former Secretaries of the Department of Health and Human Services and Commissioners of the FDA, aims to build awareness about current deficits in funding and advocate for increased federal appropriations in order to decrease the FDA's reliance on user fees paid by drug manufacturers.

Other FDA efforts to enhance drug safety have included improved guidance to industry on premarketing risk assessment, development and use of risk-minimization action plans, and pharmacovigilance and pharmacoepidemiologic assessment.[33-35] Consumer awareness and education has also been a major focus, including new regulations that require inclusion of MedWatch reporting information on drug packaging and patient information leaflets for prescription and nonprescription drugs and in direct-to-consumer television advertising.[36-38]

Improving Data Collection and Use

At the core of efforts to improve drug safety, there is reliance on the extent and quality of information used to inform these decisions. Safety information gained from premarketing as well as postmarketing studies is often described as data that are unreported, underreported, and unpublished. The International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals requirement that researchers register human subjects research via www.clincialtrials.gov as a condition of publication and the editor's obligation to publish negative studies represent the combined efforts of regulatory and private entities to address these shortcomings.[39] Other efforts have focused on developing standards for reporting drug-induced diseases and other adverse drug events. The Consolidated Standards of Reporting Trials [CONSORT], in "Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement," recommends the use of standardized terminology and inclusion of harms information in the publication abstract as mechanisms to assist clinicians, researchers, and patients in the critical appraisal of clinical trial results.[40]

Public and private collaborations to improve active surveillance, including data mining in large population-based databases, are described in Chapter 4.

DRUG SAFETY CHALLENGES AND OPPORTUNITIES

As noted in the FDA Science Board report, the rapid rate of new-drug development, the evolving role of evidence-based medicine, and advancing science

and technology will offer ongoing and new challenges to our nation's drug safety system. Novel first-in-class drugs, nanotechnology, cell-based therapies, large-molecule biologics, and follow-on biologics will be among many challenges in assessing and ensuring postmarketing drug safety.

Pharmacogenomics and personalized drug therapy have the potential to improve the prediction and prevention of drug-induced disease from the perspective of both individual patients and entire populations. One of the earliest known genetic variations to result in drug-induced disease is glucose-6-phosphate dehydrogenase deficiency, which results in the breakdown of red blood cells when a person is exposed to certain drugs (e.g., antimalarial drugs, aspirin, nonsteroidal antiinflammatory drugs, quinidine, quinine, and sulfonamide antibiotics). More recent discoveries include variations in the organic anion transporter SLCO1B1 that are associated with an increased risk of statin-related myopathy.[41]

Many factors contribute to genetic variation in response to drug therapy. Polymorphisms, which can be affected by the interplay of more than one genetic variation, may lead to differences in drug disposition, including absorption, distribution, and excretion.[42] These differences can lead to decreased or increased pharmacologic effect, with the latter more frequently resulting in toxicity or undesired drug effects. Genetic differences in drug transporters also play a role in response to drug therapies. Examples of drugs, genetic variables, and the proposed associated adverse drug event are described in Table 1–2.[42,43]

Some genetic polymorphisms are more common in certain racial groups; therefore, ethnicity has been used to predict drug response in the absence of more specific genetic information for an individual patient.[44] For example, the relative risk of angioedema or cough associated with the use of angiotensin-converting–enzyme (ACE) inhibitors has been projected as 3.0 and 2.7 for blacks and East Asians, respectively, as compared with whites. Other studies, including the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico

TABLE 1–2 Examples of Drug-Induced Diseases Associated with Genetic Variation[42,43]

Drug	Genetic Variation	Adverse Drug Event or Drug-Induced Disease
Abacavir	HLA	Hypersensitivity reaction
ACE inhibitors	Bradykinin B2 receptor	ACE-induced cough and angioedema
Carbamazepine	HLA-B*1502 allele	Stevens–Johnson syndrome, toxic epidermal necrolysis
Cisplatin, carboplatin, and oxaliplatin	Changes in gene expression in the dorsal-root ganglia resulting in apoptosis (Cdkn1a, Ckap2, Bid3, S100a8, S100a9), inflammation (S100a8, S100a9, Cd163, Mmp9), and nerve growth and regeneration (Mmp9, Gfap, Fabp7)	Peripheral neurotoxicity
Digoxin	P glycoprotein 3435TT genotype	Increased drug accumulation and potential for digoxin toxicity
Mercaptopurine	Thiopurine methyltransferase polymorphism	Hematopoietic toxicity
Oral contraceptives	Variation in prothrombin and factor V	Increased risk of DVT or cerebral vascular thrombosis
Trimethoprim–sulfamethoxazole, clarithromycin, quinidine	KCNE2 variants in potassium channels	Increased QT interval prolongation, morbidity, and mortality

ACE = angiotensin-converting enzyme; DVT = deep-vein thrombosis; HLA = human leukocyte antigen.

(GUSTO)-1 trial found that intracranial hemorrhage or moderate to severe bleeding following thrombolytic therapy was more in common in black patients.[44,45] While these and other studies give credence to ethnicity as a determinant of adverse events, shortcomings in the data, including inconsistent definitions and reporting of ethnicity and adverse events, limit its application to clinical practice. Most drug-induced diseases, including ACE-inhibitor–induced cough, have been theorized as a complex interaction of ethnic and other factors such as age, sex, and comorbid disease.[46] When considered in total, these predictive factors can be used to improve drug safety by guiding drug selection and monitoring.

The inclusion of genetic biomarker information, and its clinical application, in FDA-approved drug labeling is becoming more common. However, currently there is no requirement that pharmaceutical manufacturers complete genetic studies. Whether these studies are voluntary or required, more research (including practical clinical trials) and better systems for collecting and analyzing these data are needed. Even with improved data, uncertainties will remain about the extent to which genetics affects drug response and the interplay of genetics with other variables, including concomitant therapies, diet, and other patient variables. At present, the clinical significance of genetic variation and genetic testing in drug safety and effectiveness are much debated.

As the regulatory and legal environments evolve, clinicians will continue to play a central role in improving drug safety and preventing drug-induced disease. The identification and management of adverse effects, participation in spontaneous reporting efforts, and provision of patient education that addresses both the risk and benefit of therapies are critical and core clinician-responsibilities. As illustrated by the example of thalidomide, drugs with significant safety concerns can provide great health benefits when properly managed. Medication-therapy management and other care provided by pharmacists are essential components of the drug-safety system.

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