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Liability, Litigation, and Lessons in New Drug Development

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CONTENTS

28.1	Liability: The Downside of Drug Development	490
28.2	History of Drug Liability and Milestones in Drug Regulation	493
28.2.1	History of Vaccine Regulation and Litigation	493
28.2.2	Noteworthy Fiscal Year 2003 FDA Activities	496
28.3	Classification of Adverse Drug Reactions (ADRs)	498
28.3.1	Type A Reactions: Augmentation of the Pharmacological Response	499
28.3.2	Type B Reactions: Bizarre (Idiosyncratic) Responses	499
28.4	Adverse Drug Reactions: A Major Cause of Litigation	500
28.4.1	Extent of the Problem: Incidence of Adverse Drug Reactions	500
28.4.2	Who Is Most at Risk?	500
28.4.3	Beyond Malpractice: Reasons for the High Incidence of Adverse Drug Reactions	501
28.4.3.1	Incomplete Testing	503
28.4.3.2	Inadequate Reporting	504
28.4.3.3	Inadequate Warnings	504
28.4.3.4	Investigator Fraud	506
28.4.3.5	Quality Control, Safety, Manufacturing	506
28.4.4	Types of Drugs Most Frequently Involved in Litigation	506
28.4.4.1	Vaccines	507
28.4.4.2	Fen-Phen and Other Diet Drugs	508
28.4.4.3	Nonsteroidal Anti-Inflammatories	509
28.4.4.4	Corticosteroids	511
28.4.4.5	Noteworthy Class Actions: Rezulin, Baycol	514
28.4.4.6	Drug-Induced Hepatotoxicity	515
28.5	Market Entry and Subsequent Withdrawal	516
28.6	Deep Pockets and Efforts to Limit Litigation	517
28.7	Summary and Conclusions	517
	References	518

28.1 Liability: The Downside of Drug Development

Therapeutic agents, such as vaccines and antibiotics, have changed the course of modern medicine and prolonged the average life span of the population by abating diseases that used to be associated with mortality. New classes of medications contribute to further treatment and disease modification. All drugs can, however, be harmful. Table 28.1 defines how the Food and Drug Administration (FDA) differentiates “adverse drug reactions” (ADRs) from “adverse drug events” (ADEs) and other terms.

In 1992, while researching ADRs as to how drug manufacturers respond to such reports, Glenna Fitzgerald, a former FDA employee, said,¹

The initial response of those working within an organization — particularly product champions, both technical and commercial — is that of denial. Until this moment, the whole culture within the pharmaceutical company has been positively and energetically to promote the advantage of the drug. Thus, before accepting that the drug is associated with a potentially serious disadvantage, drug champions tend, firstly, to demand proof of causality; secondly, to seek out alternative explanations for the clinical syndrome; and thirdly, to try to implicate other agents in the same drug class to diminish the impact on the specific product.

Published responses from pharmaceutical companies to ADR reports follow a similar pattern, usually containing some of the following forms of denial:

- Never admitting a causal relationship
- Never acknowledging the validity of comments in the reports
- Listing all possible alternatives however tenuous
- Never mentioning the number of cases the company has received
- Offering a long list of references, some of which seem to have little to do with the ADR
- Implying that the problem is a class effect
- Including remarks from clinicians who have been trialists or advisors to the pharmaceutical company without acknowledging the association

It is this naysay mentality that threatens the safety of medicines and exposes pharmaceutical companies to further liability.

In an editorial in the *International Journal of Risk and Safety in Medicine*, M.N.G. Dukes wrote that, “... even with western industry, one still, in the 1990s, runs into serious instances where risk data have been concealed in the interests of commerce.”² Richard Merli,³ managing editor of *Pharmaceuticals Insiders*, believes that increased public concern presents drug companies with the difficult choice of either “implementing expensive risk management strategies that might involve taking a blockbuster drug off the market or risking huge court awards and irreparable public relations damage.” Time will tell if this is what will happen with the blockbuster Vioxx, taken off the market in 2004, with predictions of liability costs approaching \$20 billion dollars. The Vioxx withdrawal and a widespread effect on the nonsteroidal anti-inflammatories (NSAIDs) market will be addressed later in this chapter.

Merli³ states that a proactive risk management plan reduces product liability lawsuits, but it can also reduce drug sales “for reasons that turn out to be ephemeral.” He warns pharmaceutical companies, however, that being defensive — such as described by Fitzgerald¹ — is extremely risky. “Ongoing product liability litigation can damage a company’s bottom

TABLE 28.1
A Glossary of Drug Misadventure Terms

Terms	Glossary
Accelerated approval	A process for speeding approval of drugs that “promise significant benefit over existing therapy for serious or life-threatening illnesses.” The FDA usually approves the drug on condition that the drug company will conduct phase 4 studies on the actual clinical benefit of the drug.
Adverse drug event (or adverse drug experience) (ADE)	Any untoward medical occurrence in a patient or clinical-investigation subject administered a pharmaceutical product. It is not necessary for the event to have a causal relationship with this treatment.
Adverse drug reaction (ADR)	A negative, undesirable, or harmful reaction to a particular drug. In marketed drugs, an ADR is an unintended reaction that happens at a normal dose. In clinical trials, where the drug is not yet approved for marketing, any and all unintended and noxious reactions to a drug are considered ADRs and reported accordingly.
Advisory Committee	A panel of outside experts convened periodically to advise FDA on safety and efficacy issues about drugs and other FDA-regulated products. FDA is not bound to take committee recommendations, but usually does.
Beers list or Beers criteria	Criteria for safe medication use in older adults — people over 65 years of age, the Beers list was first issued in 1991, and the criteria have been repeatedly revised and updated. Named for Dr. M.H. Beers, principal author of the original 1991 criteria.
Brand name drug	A brand name drug is a drug marketed under a proprietary, trademark-protected name.
Clinical trial	Any investigation in humans to identify any ADRs and to assess a drug’s safety and efficacy.
Deception	In clinical trials, intentionally misleading or withholding information about results or reactions in the trial.
Discontinued drug	A discontinued drug is one that has been removed from the market in the United States for reasons other than safety or effectiveness.
Drug interaction	An altered reaction of the body to one drug when another is taken as well. An interaction between a drug and another substance that prevents the drug from performing as expected. This definition applies to interactions of drugs with other drugs (drug–drug interactions) as well as drugs with food (drug–food interactions) and other substances.
Efficacy	The ability of a drug to produce beneficial effects on the duration or course of a disease.
Institutional review board (IRB)	An independent group that reviews and approves material about a clinical trial to ensure that the study is safe and effective and adheres to FDA regulations.
Kaplan–Meier survival analysis	A statistical technique used to test the significance of differences between the survival curves associated with two different treatments. It is often used to analyze survival (life vs. death) data when there are censored observations (observations that are unknown because a subject has not been in the study long enough for the outcome to be observed) or to analyze the effects of different treatment procedures. ¹
Label	The FDA approved label is the official description of a drug product and includes what the drug is used for; who should take its adverse events (side effects); instructions for use in pregnancy, children, and other populations; and safety information for the patient. Labels are often found inside drug product packaging.

(Continued)

TABLE 28.1 (Continued)

Terms	Glossary
Medication Guide	A medication guide is required by FDA when a drug poses serious health concerns. It contains information for patients' understanding of how to safely use a drug product.
MedWatch program	An FDA program to monitor ADRs by analyzing voluntary health professional reports and required drug manufacturer reports.
Morbidity	An adverse effect caused by a treatment. A state produced by any departure, subjective or objective, from a state of physiological or psychological well-being.
Off-label	The unauthorized use of a drug for a purpose not approved by the FDA.
Orphan drug	An FDA designation for a therapy developed to treat a rare disease (one which afflicts less than 200,000 people in the United States). Because there are fewer financial incentives for drug companies to develop these therapies, the U.S. government offers additional incentives to the companies (tax advantages and extended marketing exclusivity) that develop these drugs.
Over-the-counter drugs (OTC)	The FDA defines OTC drugs as safe and effective for use by the general public without a doctor's prescription.
Patient package insert (PPI)	A PPI contains information for patients' understanding of how to safely use a drug product.
Phase 4 study	After a drug has been approved by the FDA, Phase 4 studies are conducted to compare the drug to a competitor, explore additional patient populations, or to further study any ADRs.
Postmarketing surveillance	The FDA's ongoing safety monitoring of marketed drugs.
Risk-benefit ratio	Risk to individual patients compared with the potential benefits.
Safety	No drug is completely safe or without potential side effects. Before a drug is approved for marketing, tests that show a drug is "safe" under the conditions on the proposed label. "Safety," therefore, is determined case-by-case and reflects the risk-benefit ratio.
Serious adverse event (SAE)	Any ADE that is fatal, life-threatening, permanently disabling, or that results in hospitalization or prolonged hospital stays.
Review	A comprehensive analysis of clinical trial data and other information that forms the basis of FDA's decision to approve an application.
Serious adverse drug event	A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires in-patient hospitalization, prolongs a hospital stay, results in persistent or significant disability or incapacity, or causes a congenital anomaly or birth defect.
Supplement	An application to allow a company to make changes in a product that has already been approved. The FDA must approve all-important changes (in packaging or ingredients, for instance).
Side effects	Secondary or unwanted effects. Problems that occur when treatment affects healthy cells. For instance, the common side effects of chemotherapy include fatigue, nausea, vomiting, decreased blood cell counts, and hair loss. Most treatment-related side effects can be managed.
Unexpected adverse drug reaction	A reaction that is not consistent in nature or severity with study application.

Sources: From Informedesign, University of Minnesota, www.informedesign.umn.edu; Center Watch, www.centerwatch.com/patient/glossary.html; FDA's Drug Review Glossary, www.fda.gov/fdac/special/newdrug/bengloss.html

line for years.” He recommends companies to adopt a risk management plan that closely monitors ADRs and includes a communication channel for quick decisions if serious side effects begin to show up. “It’s much more to a company’s advantage to make a decision to voluntarily withdraw a drug from market,” says John Morris, global chair of KPMG in London, “rather than be forced to withdraw the drug.”³ Poor public relations and stiff liability verdicts for not acting quickly on ADRs or for withholding drug safety information can bankrupt a company, as was seen with asbestos and now is being experienced by several ephedra manufacturers.

For instance, in September 2004, Bayer settled 2861 product liability cases for \$1.09 billion for its cholesterol medicine cerivastatin (Baycol), which was linked to 100 deaths and withdrawn from market in 2001. In July 2004, the company settled 2771 cases for \$1.06 billion. Bayer still has 7577 additional cases to settle⁴ (see Section 28.4.4.5 for additional information). In another example, a \$1 billion jury verdict was upheld against Wyeth for its fenfluramine or dexfenfluramine and phentermine (Fen-Phen) drug combination, which was linked to primary pulmonary hypertension (PPH). Wyeth has set aside \$16.6 billion to cover future liability on the drug (see Section 28.4.4.2 for more on this case).³

28.2 History of Drug Liability and Milestones in Drug Regulation

Liability for medical and drug injuries is not new. In 2000 BC, the Babylonians decided that a physician who caused the death of a patient should lose his hands. These days, the punishment for malpractice is not quite so cruel and unusual, but medical mistakes are often career-ending errors that can cost healthcare providers millions or billions in sanctions. Table 28.2, “History and Milestones in U.S. Drug Regulation,” traces the chronology of laws, regulations, and litigation intended to ensure drug safety and efficacy in the United States.

28.2.1 History of Vaccine Regulation and Litigation

As the government has an interest in preventing the spread of diseases, vaccines have followed a somewhat different historical path than that of other drugs. Most vaccines have been hailed as major modern advances. During the 1920s, several vaccines were introduced: diphtheria and tetanus toxoids, whole-cell pertussis, and bacille Calmette-Guérin (BCG) (to protect against tuberculosis) vaccines were introduced. The chorioallantoic membrane used to culture viruses allowed a yellow fever vaccine to be developed by 1935. After World War II, many vaccines still in use today emerged, including the killed and oral polio vaccines and the measles, mumps, and rubella vaccines. But vaccine regulation and litigation has a tumultuous history.

In the early 1960s, drug companies began to lobby for government indemnity for the vaccines they developed, tested, and produced.⁵ Because so many people are vaccinated at one time, particularly school-age children, ADRs from a vaccine can carry considerable liability. As more diseases have become vaccine-preventable, more ADRs have been reported.⁶ In 1974, impetus for indemnity increased when the courts upheld a jury verdict of \$200,000 for a child who developed polio from the Sabin live-polio vaccine.⁷

After a suspected case of the 1918 Spanish flu virus (which, in a global pandemic during World War I, affected half the world’s population and killed almost 25 million people in 18 months)⁸ was identified in 1976, Congress passed the *National Swine Flu Immunization Program*,⁹ releasing manufacturers from the liability, so that a flu vaccine

TABLE 28.2

History and Milestones in U.S. Drug Regulation

1820	Physicians establish the <i>U.S. Pharmacopoeia</i> , the first U.S. drug standards.
1848	The <i>Drug Importation Act</i> passed to stop the entry of adulterated drugs.
1862	The Bureau of Chemistry, predecessor of the FDA, is created.
1880	Chief chemist Peter Collier recommends a national food and drug law; during the next 25 years, more than 100 such bills are introduced.
1883	Chief chemist Harvey W. Wiley (called the "Crusading Chemist" and "Father of the Pure Food and Drugs Act") campaigns for a federal drug safety law.
1902	<i>The Biologics Control Act</i> passes to ensure purity and safety in vaccines.
1906	The <i>Food and Drugs Act</i> prohibits interstate commerce of adulterated drugs.
1911	In <i>U.S. v Johnson</i> , the Supreme Court rules that the <i>Food and Drugs Act</i> does not prohibit false therapeutic claims.
1912	The <i>Sherley Amendment</i> passes to prohibit false therapeutic claims in medicines.
1914	The <i>Harrison Narcotic Act</i> requires prescriptions for products exceeding the allowable limit of narcotics and mandates increased record keeping for physicians and pharmacists.
1924	The <i>U.S. v 95 Barrels Alleged Apple Cider Vinegar</i> ruling says that any statement, design, or device on a label that may mislead or deceive is prohibited.
1927	Regulatory functions of the Bureau of Chemistry become the Food, Drug, and Insecticide Administration, which was shortened to Food and Drug Administration (FDA) in an agricultural appropriations act three years later.
1933	FDA recommends revision of the <i>Food and Drugs Act</i> , launching a 5-year legislative battle.
1937	Elixir of Sulfanilamide, containing a poisonous solvent, kills 107 people including children, dramatizing the need to enact the pending food and drug law.
1938	The <i>Federal Food, Drug, and Cosmetic (FD&C) Act</i> passes requiring new drugs be shown safe before marketing, eliminating the requirement in the <i>Sherley Amendment</i> that "intent to defraud" must be proven in misbranded drugs, requiring that safe tolerances be set for unavoidable poisonous substances, authorizing factory inspections, and adding injunctions to seizures and prosecution as remedies for violations.
1940	FDA is transferred from the Department of Agriculture to the Federal Security Agency, with Walter G. Campbell appointed the first Commissioner of Food and Drugs.
1941	The <i>Insulin Amendment</i> requires FDA to test and certify the purity and potency of insulin.
1943	<i>U.S. v Dotterweich</i> makes corporations and officials of corporations liable for violations without the need to prove intent or knowledge.
1944	The <i>Public Health Service Act</i> passes to regulate biological products, the control of communicable diseases, and other health issues.
1945	The <i>Penicillin Amendment</i> requires FDA to test and certify the safety and effectiveness of all penicillin products (later extended to all antibiotics).
1948	The <i>Miller Amendment</i> ensures the FD&C Act applies to all goods regulated by FDA and transported from one state to another.
1949	FDA publishes the first <i>Guidance to Industry</i> .
1950	<i>Alberty Food Products Co. v U.S.</i> finds that drug labels must include the drug's purpose.
1951	The <i>Durham-Humphrey Amendment</i> defines drugs that cannot be used without a prescription from a licensed practitioner.
1952	<i>U.S. v Cardiff</i> finds that factory inspection in the 1938 FD&C Act is too vague to be enforced as criminal law. FDA consumer consultants are appointed in each field district.
1953	The <i>Factory Inspection Amendment</i> clarifies FD&C and requires FDA to provide written inspection reports.
1955	The Division of Biologics Control becomes an independent entity within the National Institutes of Health (NIH) after a polio vaccine is linked to about 260 cases of polio.
1958	FDA publishes the first list of "Substances Generally Recognized as Safe" (GRAS), containing nearly 200 substances.
1962	The sleeping pill thalidomide causes birth defects in thousands of babies in Western Europe. News reports about FDA medical officer Dr. Frances Kelsey keeping the drug from U.S. markets arouse public support for stronger drug regulation. The <i>Kefauver-Harris Drug Amendments</i> pass to ensure drug efficacy and safety; manufacturers are required to prove the effectiveness of their drugs before marketing them.

(Continued)

TABLE 28.2 (Continued)

1966	FDA has the <i>effectiveness</i> of 4000 drugs (approved on safety only) evaluated. The <i>Fair Packaging and Labeling Act</i> requires all labels to be honest and informative.
1968	FDA becomes part of the Public Health Service (PHS). The <i>Drug Efficacy Study Implementation (DESI)</i> is FDA's response to the investigation on the effectiveness of drugs.
1970	<i>Upjohn v Finch</i> upholds enforcement of the 1962 drug effectiveness amendments by ruling that commercial success alone does not constitute substantial evidence of drug safety and efficacy. FDA requires the first patient package insert.
1972	Over-the-counter (OTC) drug review begins to ensure the safety, effectiveness, and appropriate labeling of drugs sold without prescription. Regulation of biologics (serums, vaccines, and blood products) is transferred from NIH to FDA.
1973	The Supreme Court upholds the 1962 drug effectiveness law and endorses FDA action to control classes of products by regulation rather than litigation.
1976	The <i>Medical Device Amendments</i> pass to ensure safety and effectiveness of medical devices including diagnostic products, requiring some quality control, premarket approval, and performance standards on some products.
1982	Tamper-resistant packaging required after the deaths from cyanide placed in Tylenol, and the <i>Federal Anti-Tampering Act</i> makes it a crime to tamper with packaged consumer products.
1983	The <i>Orphan Drug Act</i> passes, enabling FDA to promote research and marketing of drugs needed to treat rare diseases.
1984	<i>Fines Enhancement Laws</i> of 1984 and 1987 increase penalties for all federal crimes, with double fines for corporations. The <i>Drug Price Competition and Patent Term Restoration Act</i> expedites the availability of less-costly generic drugs by permitting FDA to approve generics without repeating the safety and effectiveness research.
1985	FDA approves the AIDS test on blood to protect patients from infected donors.
1986	The <i>Childhood Vaccine Act</i> requires vaccine makers to provide patient information, gives FDA authority to recall biologics, and authorizes civil penalties.
1987	Regulations on experimental drugs for patients with serious diseases and no alternative therapies.
1988	The <i>Food and Drug Administration Act</i> puts FDA within the Department of Health and Human Services (HHS) and spells out research, enforcement, and education requirements. The <i>Prescription Drug Marketing Act</i> prevents the resale of diverted drugs, requires drug wholesalers be licensed, restricts reimportation, and bans the sale, trade, or purchase of drug samples or counterfeit drug coupons.
1989	FDA recalls all OTC dietary supplements containing L-tryptophan because of a clear link to an outbreak of eosinophilia-myalgia syndrome (EMS). By 1990, more than 1,500 cases of EMS – 38 deaths are confirmed, with an estimated 3,000 to 10,000 unreported cases.
1990	The <i>Safe Medical Devices Act</i> requires reporting of medical devices that probably caused the death, serious illness, or injury of a patient. Postmarket surveillance on permanently implanted devices required with methods for tracing and locating patients depending on such devices. FDA is authorized to recall device product.
1991	Regulations are published to accelerate the review of drugs for life-threatening diseases.
1992	The <i>Generic Drug Enforcement Act</i> imposes debarment and other penalties for illegal acts involving abbreviated drug applications. The <i>Prescription Drug User Fee Act (PDUFA)</i> requires manufacturers of drug and biologics to pay fees for product applications and supplements. The <i>Mammography Quality Standards Act</i> requires facilities to be accredited and federally certified by 1994, with annual inspections.
1997	The <i>Food and Drug Administration Modernization Act</i> reauthorizes PDUFA and mandates accelerated reviews and regulates drug advertising of unapproved uses.
1998	The first phase begins of consolidating FDA labs from 19 facilities to nine (by 2014).

Note: From the beginning of civilization, people have been concerned about the quality and safety of their food and medicines. In 1202, King John of England proclaimed the first English food law, the Assize of Bread, which prohibited adulteration of bread with such ingredients as ground peas or beans. Food regulation in the United States started in colonial times. Federal control of the drug supply began with the inspection of imported drugs in 1848. The chronology describes some of the milestones in the history of food and drug regulations in the United States.

Source: From Milestones in U.S. Food and Drug Law History, www.fda.gov/opacom/backgrounders/miles.html

could be produced. Forty million people in the United States were vaccinated against this flu in less than 3 months.¹⁰ Adverse drug reactions were reported shortly after the massive vaccination program began, and it was found that those who had received the vaccine had a tenfold increase of Guillain Barre Syndrome (GBS). The swine flu program is a milestone in vaccine litigation history as it was a precursor to federal involvement and to no-fault vaccine compensation programs.⁵

In response to continued concerns about vaccine safety, the *National Childhood Vaccine Injury (NCVI) Act of 1986* established a no-fault compensation process for people injured by them.¹¹ The NCVI also mandated that the Institute of Medicine (IOM) reviews scientific evidence of vaccine-related ADRs in children. In 1996, the Department of Health and Human Services (HHS) made changes to the NCVI, which lessened its usefulness.⁵ In response to the problems this generated, the *Vaccine Injured Children's Compensation Act of 2001* was introduced in Congress.¹² This bill, however, also has its problems, and in April 2001, the bill was referred to the House subcommittee on health, where it still remains.¹³

Vaccine liability issues were also covered in Section 304 of the *Homeland Security Act (HSA) of 2002*,¹⁴ as amended in April 2003,¹⁵ in which Congress enacted liability protection for manufacturers of smallpox vaccines. Vaccine liability can be handled in four different ways: the government can substitute itself as the defendant, it can decide nobody need be liable and provide no-fault compensation, it can indemnify manufacturers after they have been sued and lost, or it can alter the normal rules of litigation.¹⁶ In the HSA, the government substitutes itself as the defendant if the HHS Secretary declares "an actual or potential bioterrorist incident or other actual or potential public health emergency makes advisable the administration of a covered countermeasure,"¹⁶ such as a vaccine. Secretary Tommy Thompson issued the first such declaration on January 24, 2003.

The HSA states, however, that "covered countermeasures" apply only to smallpox vaccines at this time, and although HSA protects manufacturers and others against liability, it does not directly set forth compensation procedures for vaccine recipients. Under Part C of the HSA, compensation for death benefits is capped at \$262,100. If a case does end up in court, the plaintiff must "prove culpability equal to or rising above the level of negligence."¹⁶ It seems assured that the history of vaccine regulations and litigations will continue to change for some time to come. The swine flu and other vaccine-related ADRs are discussed further in Section 28.4.4.1.

28.2.2 Noteworthy Fiscal Year 2003 FDA Activities

In the Center for Drug Evaluation and Research (CDER) report for fiscal year (FY) 2003 (October 1, 2002 to September 30, 2003),¹⁷ the agency acknowledges that the need for drug safety in the United States must be increasingly vigilant. "As Americans are increasingly receiving the benefits of important new drugs before they are available to citizens of other countries, we must be especially vigilant in our surveillance." According to Sandy Kweder, deputy director of the office of new drugs at FDA, "We have a public that is much more concerned over drug safety. Our judgments have to reflect what risks the public is willing to accept." Kweder elaborated, "There's no rule on the percentage of adverse events considered acceptable. The risks to the public must be balanced against the benefits among the patient population."³

The FDA's postmarketing surveillance of drug safety in FY 2003 includes a new database on prescribed drug use (with patient identities removed). The agency uses this database of marketed drugs to "make risk assessments and decisions about the most appropriate way to manage any new risk or new perspective on a previously known

risk.”¹⁷ Some of the risk management tools FDA uses to prevent confusion and associated drug injuries include the following techniques:

- Requiring new labeling
- Changing drug names
- Changing drug packaging
- Sending out “Dear Health Care Practitioner” letters
- Communicating special risk information
- Restricting distribution programs
- Terminating product marketing

The FDA has also signed a 2-year data-mining agreement with a commercial firm to develop software tools for quantitatively analyzing drug safety data. The goal is to increase the agency’s awareness and understanding of trends in ADRs. Yet the regulations, litigation, and databases do not prevent serious adverse drug effects. The CDER received more than 370,880 ADRs in FY 2003, a 13% increase over the previous year.¹⁷

The FDA also has a drug safety email notification system. During FY 2003, 33 drug safety alerts were sent out, and 25 to 45 notices on drug labeling changes were sent out each month. In the first 4 months of 2003, FDA placed 10 drugs on their list of “Drugs with Special Safety Restrictions,” which allows distribution only from specific facilities, limits prescribing authority to physicians with special training or expertise, or requires medical tests before prescriptions are written. The CDER also uses “Medication Guides,” which must be distributed to patients when drugs that pose serious health concerns are dispensed. In FY 2003, CDER approved Medication Guides for one innovator product mefloquine hydrochloride (Lariam; Roche Pharmaceuticals, Nutley, NJ), on generic lindane (shampoo and lotion; Pennex Pharmaceuticals, Morton grove, IL), and on isotretinoin products (Claravis; Barr Laboratories, Pomona, NY, and Sotret; Ranbaxy Pharmaceuticals, Gurgaon, India, are the generic versions of Accutane from Roche Pharmaceuticals, which already carries a Medication Guide).

During FY 2003, CDER reviewed more than 3000 cases of medication errors, half of which, they acknowledge, were a result of error-prone labeling. During the same period, FDA recalled 254 prescription drugs (29.0% lower than in FY 2002) and 88 over-the-counter (OTC) medicines (a 6.0% increase). Drug recalls can apply to one or several batches of a drug or to the complete withdrawal of the drug (although there were no safety-based drugs withdrawn during FY 2003). FDA estimates that about 2.5% of all drugs are recalled from the market each year for safety reasons, which represents \$4.5 billion in lost annual sales.³ Between January 1, 1994 and April 30, 2004, FDA approved 303 new drug products); seven (2.3%) were subsequently recalled.¹⁷ The primary reasons for drug recalls included the following problems:¹⁷

- Content uniformity failures
- Current good manufacturing practices (cGMP) deviations
- Dissolution failures
- Generic drug or new drug application discrepancies
- Label mix-ups
- Microbial contamination of nonsterile products
- Presence of a foreign substance
- pH failures
- Stability data that did not support the expiration date
- Subpotency

In other FY 2003 drug safety highlights, FDA made 1512 GMP inspections, reviewed 51 field recommendations for regulatory action, and approved 34, which included 27 warning letters, 4 injunctions, and 3 seizures. The agency also reviewed 184 foreign establishment inspection reports, resulting in one warning letter and one import alert. The CDER issued 737 drug promotion review letters (42 regulatory action letters, 185 launch campaign letters, and 510 advisory acknowledgement or closure letters). The regulatory action letters were for prescription drug promotions determined to be “false, misleading, lacking in fair balance of the risks and benefits, or promoting a product or indication before approval.”¹⁷ Warning letters are issued for more serious or repeat violations. Examples of specific types of violative promotions included promotional exhibit hall displays, oral representations, Internet sites, and journal advertisements or sales brochures. Letters for direct-to-consumer promotion violations accounted for 254 of the letters, a 26.0% increase over FY 2002.

The FDA also promulgated an OTC and prescription medicines rule, which became final in February 2004, requiring a bar code on medicines used in hospitals to ensure that health professionals gave patients “the right drugs at the appropriate dosages and at the right time.”¹⁷ Adoption of this advanced information system has, in some hospitals, reduced medication error rates by as much as 85%. The agency estimates that the rule will help prevent 500,000 adverse events and transfusion errors and save \$93 billion in health costs during the next 20 years.

Another big change in 2004 was the passage of new legislation restricting drug liability class actions. During 2004, the Bush administration had gone to court as a friend to industry to prevent lawsuits by consumers who say that they have been injured by prescription drugs and medical devices.¹⁸ This action will be discussed more extensively in Section 28.6.

That was 2003 and 2004, and of course we now know (and will read about later in the chapter) the Vioxx recall in September, 2004. A tremendous amount of renewed pressure and criticism was directed to the FDA, and the FDA has been re-examining the Agency’s methods of monitoring drug safety. Janet Woodcock MD, former director of CDER, and now Deputy Commissioner for Operations, recently gave the following remarks to the IOM:

... the agency’s system for ensuring the safety of drugs is “pretty much broken down” and it has known for a long time it needed to improve its system. “The keystone of the current system is the prescriber, and that person is the one who decides if the benefits of a drug outweigh the risks for that patient,” Dr. Woodcock said. “This system has obviously broken down to some extent, as far as the fully informed provider and the fully informed patient.”

She said the drug agency had long known that it needed to improve systems for learning about problems with drugs on the market. One way to do that, she said, is to take advantage of electronic health records from managed-care organizations. She also said the FDA had proposed this better system several years ago, but Congress declined to fund it. “The bottom line is that a lot of drug safety problems are actually preventable,” she said, because “most adverse events are from known side effects.”

(Source: From Harris, G. Drug Safety System is Broken, a Top FDA Official Says. *New York Times*, June 9, 2005)

28.3 Classification of Adverse Drug Reactions (ADRs)

An ADR is any unintended or undesirable response obtained from the appropriate dose of a drug or diagnostic agent. These reactions have been conventionally classified into six

different categories: overdose, intolerance, unexpected side effects, secondary effects, and idiosyncratic and hypersensitivity reactions. Although drug interactions are included with other ADRs, they are also classified into seven categories:

- Those that occur outside the body
- Those that occur at the site of entry
- Those that occur at storage sites within the body
- Those that occur at the site of action
- Those that inhibit enzymes from metabolizing
- Those that stimulate enzymes
- Those that affect drug excretion

Although these classifications have been used in both reviews and textbooks, it is unnecessary and confusing to separate ADRs from drug interactions.

Drug manufacturers are required to promptly report all serious or unexpected ADRs from spontaneous sources and from any clinical or epidemiological investigation — independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for instance, those found in regulatory ADR registries or in publications). There are situations in addition to single case reports of serious ADRs that may necessitate rapid communication to regulatory authorities, such as information that might materially influence the risk–benefit assessment of a medicinal product, or would be sufficient to consider changes in administering the product or in the overall conduct of a clinical investigation. Examples include clinically important increases in the rate of occurrence for an “expected,” serious ADR; significant hazards to the patient population — such as lack of efficacy with a drug used to treat a life-threatening disease; or major safety findings from a newly completed animal study (such as a study on carcinogenicity).

28.3.1 Type A Reactions: Augmentation of the Pharmacological Response

Type A reactions are those that are dose-related and that arise from the normal pharmacological action of a drug. They usually result from exaggerated but otherwise normal pharmacological actions of a drug given in the usual therapeutic doses. An example of this type of reaction would be the postural and exercise hypotension (low blood pressure) in a patient taking an adrenergic neuronal blocking agent such as guanethidine (Ismelin, Ciba Specialty Chemicals), used to treat severe high blood pressure, or drowsiness from taking phenobarbital (nonproprietary), a barbiturate used as a sedative and also as an anticonvulsant. Type A reactions are largely predictable on the basis of the known pharmacological properties of a drug. Although the incidence of morbidity in the population is often high, the mortality rate is usually low.

28.3.2 Type B Reactions: Bizarre (Idiosyncratic) Responses

Type B reactions are those that represent an abnormal or novel response to a drug. They are unusual effects that would not be expected from known pharmacological actions of a drug when given at the accepted dose to a patient whose body handles the drug in a normal manner. Example of Type B reactions includes malignant hyperthermia caused by anesthesia. Immunological (allergic hypersensitivity) reactions are Type B reactions (although these would constitute medication errors if the allergy is known). Anaphylaxis — a classic Type B hypersensitivity reaction — is one of the most serious and potentially life-threatening ADRs. This IgE-mediated reaction generally occurs within 20 min of exposure to an

antigen, usually after an injection, but it can occur with any route of administration. The symptoms of anaphylaxis are produced by a variety of chemical mediators, most notably histamine.¹⁹ Although the incidence of anaphylaxis is low, the mortality rate from these reactions — which are unpredictable and are not discovered in conventional toxicological screening — is high. The Physicians' Insurance Association of America (PIAA) medication-error study²⁰ identifies drug allergies as a problem that results in frequent suits against physicians.

28.4 Adverse Drug Reactions: A Major Cause of Litigation

The reported incidence and frequency of ADRs vary depending on the source of the report and on the methods used to describe the event. One reason for the discrepancy is that the cause of an ADR can be difficult to ascertain. ADRs listed in hospital admission reports have ranged from less than 1% up to 28%. Most studies report an incidence rate of 10 to 20%, reflecting the different methods used to detect and report ADRs.

28.4.1 Extent of the Problem: Incidence of Adverse Drug Reactions

In reviewing ADRs, Jick²¹ determined that the incidence of ADRs ranged between 1 in 10,000 (0.01%) to 1 in 200 (0.5%). ADRs with an incidence of 1 in 10,000 would be difficult to identify at the clinical trial stage, where data are usually available on only about 1000 patients. Reactions with an intermediate frequency (>1 in 10,000 but less than 1 in 200) might be identified in postmarketing surveillance studies, whereas ADRs of low frequency (<1 in 10,000) might be verified only in cohort or case-control studies. Many important ADRs are pharmacologically unpredictable with an incidence of 1 in 10,000 or less, entailing a follow-up of a cohort of drug users. This has important implications for the sample size needed in postmarketing surveillance studies. Sample-size limitations mean that serious but infrequent reactions will not be picked up unless cohort samples are of 100,000 or more.

The mortality from ADRs has been estimated within the hospitalized patient population to be in the range of 0.01 to 0.3%. Estimates of deaths annually from ADRs have ranged from 2,000 to 140,000, and annual hospitalizations due to ADRs range from 160,000 to 1.5 million.²² It is estimated that up to 30% of hospitalized patients experience an ADR.²³

28.4.2 Who Is Most at Risk?

The PIAA conducted a medication-error study in 1993²⁰ and another in 1999²⁴ to analyze high-frequency and severe malpractice claims. The data collected included loss description and causation information, expense and indemnity payments, and the demographics of policyholders, claimants, and institutions. The PIAA companies insured almost 87,000 physicians in the United States, ranging from the smallest to the largest physician-owned malpractice insurers.

The PIAA found in both 1993 and 1999 that prescriptions were the second-most frequent and second-most expensive item in the claims reported. As of June 30, 1992, there were 6646 claims involving medicine prescriptions. Payments were made in 2195 of these claims, resulting in a total indemnity payment of \$218.9 million, an average indemnity payment of \$99,721, and a median indemnity payment of \$35,000. In the 1999

report, 9,801 of the 145,287 (6.7%) closed claims were for prescription medicines, and \$438 million of the \$7.3 billion (6.0%) paid in indemnities were for prescription medicine. The authors of the study concluded that medication injury claims are a significant source of loss for malpractice carriers and the physicians they insure.

We can extrapolate from the PIAA data to determine who is most at risk of experiencing A DRs. More female than male patients were involved in the claims studied by PIAA²⁰ (ratio: 1.5 females to 1 male). Two thirds of all claims involved patients between 18 and 59 years. Although the number of claims in the 6 to 12 and 13 to 17 age brackets was predictably low, these brackets had the highest average indemnities, reflecting the serious consequences of medication errors in young patients.

The elderly represent the group taking the largest amount of drugs (one third of all medications prescribed each year)²⁵ and suffering the greatest number of ADRs. In a recent study, Curtis et al. found that 21% (162,370 of 765,423 subjects) of elderly Americans were being prescribed drugs that could possibly harm them (defined as drugs on the Beers list, see Table 28.1), 15% received two or more of these medicines, and 4% received three or more of the risky drugs.²⁵

Life expectancy — the probability of living a longer life — has increased from about 24 years for those in the Roman Empire to 30 years at the beginning of the 19th century and 50 years at the beginning of the 20th century. Now, the worldwide life expectancy is 63 years, and the average life expectancy in the United States is 77.43 years (74.63 for males and 80.36 for females), which makes it 48th in the world (Andorra has the longest at 83.5 years and Zambia has the shortest at 37.2 years). With greater life expectancy, both the number of elderly people (currently about 365 million in the United States) and the percentage of the population that is elderly (about 12.4%) increases. This means that the number of people 75 years of age and older will rise from about 10 million (4.4% of the population) in 1980 to close to 30 million (9.1% of the total population) in 2050. Whereas the population older than 85 years was about 3 million (1% of the population) in 1980, the number is anticipated to grow to about 18 million (5.2% of the population) by 2050. Those older than 85 years represent the most rapidly growing segment of the population. With the elderly experiencing the most ADRs, these statistics mean that the rate of ADRs will increase if improvements in drug safety do not increase to match it. Routine monitoring for drug safety should include patients in various subsets (the elderly, children, and patients with specific disease states, such as kidney or liver disease) where there may be a particular liability to ADRs.

The PIAA studies^{20,24} also emphasize that medication errors can cause significant injuries. A substantial percentage (42.4%) of the claims involved significant permanent injuries, with 21.1% in 1993 and 27.0% in 1999 of all claims resulting in death. Close analysis of the death claims shows that medication errors were either the direct cause or a major contributing factor in the deaths in 84.3% of the 1993 claims. The average payment for a death claim (\$188,555 in 1999) was 14.0% higher than for claims not involving death. In a 1998 study of 33 million hospital admissions, the number of serious injuries from ADRs was 2.2 million; that is, 2.1% of all in-patients experienced a serious ADR.²⁶ Lazarou and colleagues found that 4.7% of all admissions were due to serious ADRs, and fatal ADRs occurred in 0.19% of in-patients and 0.13% of admissions. The authors concluded that 106,000 deaths occur annually from ADRs.

28.4.3 Beyond Malpractice: Reasons for the High Incidence of Adverse Drug Reactions

When exploring the cause of an ADR, many syndromes and conditions can have multiple causes that occur in only a small percentage of the population and which often have vague

TABLE 28.3
 Prescription Drugs Withdrawn from Market for Safety Reasons in the United States from 1997 to 2004

Drug	Brand Name	Manufacturer	Type of Drug	Date Approved	Date Withdrawn	Time on Market	Primary Health Risk	Estimated U.S. Sales
Valdecoxib	Bextra	Pfizer, Inc.	Cox-2 inhibitor	11/1/2002	4/7/2005	2.5 years	Serious and potentially life-threatening skin reactions	(Unavailable)
Rofecoxib	Vioxx	Merck & Co.	Cox-2 Inhibitor	5/21/1999	9/30/2004	5.33 years	Heart attack and stroke	US\$2.5 billion
Cerivastatin sodium	Baycol	Bayer	Cholesterol-lowering	6/26/1997	8/8/2001	4.17 years	Rhabdomyolysis	\$554 million in 2000
Rapacuronium bromide	Raplon	Organon	Anesthetic, muscle relaxant	9/19/1999	3/30/2001	7 months	Bronchospasm	\$23 million
Alosetron hydrochloride	Lotronex	Glaxo Wellcome	Gastrointestinal	2/9/2000	11/28/2000	9 months	Ischemic colitis	\$50.4 million
Cisapride monohydrate	Propulsid	Janssen Pharmaceuticals	Heartburn	7/29/1993	7/14/2000	7 years	Heart rhythm abnormalities	US\$2.5 billion
Troglitazone	Rezulin	Warner-Lambert	Type 2 diabetes	1/29/1997	3/21/2000	2.16 years	Liver failure	US\$2.1 billion worldwide
Asternizole	Hismanal	Janssen Pharmaceuticals	Antihistamine	12/19/1988	5/18/1999	6 months	Heart rhythm abnormalities	\$23 million
Grepafloxacin	Raxar	Glaxo Wellcome	Antibiotic	11/6/1997	11/1/1999	2 years	Heart rhythm abnormalities	\$23.5 million
Mibefradil	Posicor	Roche Laboratories	Blood pressure, cardiovascular	6/20/1997	6/8/1998	1 year	Drug interaction, lowered heart rate in women	Not available
Bromfenac	Duract	Wyeth-Ayerst	Pain reliever	7/15/1997	6/22/1998	1 year	Liver failure	\$89.7 million
Terfenadine	Seldane, Seldane-D	Hoechst Marion Roussel	Antihistamine	5/8/1985	2/27/1998	2.75 years	Heart rhythm abnormalities	Not available
Fenfluramine hydrochloride	Pondimin	Wyeth-Ayerst	Appetite suppressant	6/14/1973	9/15/1997	23.25 years	Valvular heart disease	Not available
Dexfenfluramine hydrochloride	Redux	Wyeth-Ayerst	Appetite suppressant	4/29/1996	9/15/1997	1.42 years	Valvular heart disease	\$255.3 million

Source: From MedWatch Safety Reports and other online Internet records.

or obscure onsets.⁵ These data complicate the causal relationship. Often a drug has been on the market for years before its ADRs become known. In a study of the *Physicians' Desk Reference (PDR)* black box warnings,²⁷ only half of the serious ADRs were detected and documented within 7 years of the drug's approval. Half of all drug withdrawals occur within 2 years of approval.^{27,28} As mentioned, premarketing drug trials frequently miss ADRs because of their limited sample size.^{27,29,30} See Table 28.3 for a list of prescription drugs withdrawn since 1997.

28.4.3.1 Incomplete Testing

The FDA has been under fire from at least two different sides. Industry and certain patient groups argue that the agency takes far too long to approve new drugs, whereas public interest groups argue that the agency is not thorough enough in its reviews of new drugs. Before drugs can be sold in the United States, the manufacturers must apply to FDA for the right to test them in humans, submit their test results to the agency, and then apply for the right to sell the drugs.

Although most experts agree that clinical trials completed before approval cannot detect all side effects caused by a drug because of the limited population size of the studies,²¹ in some cases, serious ADRs found in premarketing trials fail to prevent a drug's release.³¹ According to Lasser and colleagues,²⁷ there were reports that alosetron hydrochloride (Lotronex, GlaxoWellcome) was associated with ischemic colitis before its approval and subsequent withdrawal. In another example, David Willman of the *Los Angeles Times*³² blamed new policies at FDA for the failure to prevent the marketing approval of grepafloxacin hydrochloride (Raxar, GlaxoWellcome, now GlaxoSmithKline), which was implicated in prolonging QT intervals (an electrocardiogram measurement), possibly leading to two deaths. Willman blamed the release and withdrawal since 1993 of seven drugs suspected in 1002 deaths on an FDA decision to "partner" with the pharmaceutical industry. After a 2-year investigation, the newspaper found "that the FDA approved each of those drugs while disregarding danger signs or blunt warnings from its own specialists."³²

The *Los Angeles Times*³² alleged that FDA often asks companies to conduct additional studies after a product is approved, if unresolved safety questions remain, but the "suggestion" is often ignored. According to research by Public Citizen,³³ in only 13% (11 of 88) of the drugs approved contingent on postmarketing studies did the companies who made those commitments actually complete the tests. Although FDA has the authority to withdraw drugs from companies that have not performed required postmarketing research, by April 2000, FDA had not withdrawn any drug because of a company's failure to complete a postapproval safety study. According to Willman,³² FDA officials conceded that they do not know how often the studies are performed.

Of the seven drugs cited in the Willman research³² that were approved then withdrawn from market, none were needed as a life-saving therapy, and all had alternatives that could have been substituted: alosetron hydrochloride (Lotronex; GlaxoSmithKline, Research Triangle Park, NC) was for irritable bowel syndrome, dexfenfluramine (Redux; Wyeth-Ayerst, Philadelphia, PA) was a diet pill, grepafloxacin (Raxar; Glaxo Wellcome, now GlaxoSmithKline, Research Triangle Park, NC) was an antibiotic, mibefradil (Posicor, Roche Laboratories, Nutley, NJ) treated high blood pressure, bromfenac (Duract; Wyeth-Ayerst, Philadelphia, PA) was a pain killer, Troglitazone (Rezulin; Warner-Lambert, now Pfizer NY, NY) was for diabetes, and cisapride (Propulsid; Janseen Cilag, Mignon, Italy) treated heartburn.³² The recent withdrawals of Vioxx and Bextra, Cox-2 specific NSAIDs, are also examples of medications that were used to treat non-life-threatening conditions, were probably overprescribed (beyond any gastro-protective effect), and now that

they are no longer in the market, other medications have readily replaced them. As Lasser and colleagues²⁷ suggest, “Some drugs represent a significant advance over existing drugs in the reduction of morbidity and mortality and warrant use despite limited experience. However, the drugs that do not represent a significant advance should be considered second-line drugs until their safety profile is better known.” But patent life, blockbuster swings, investor, and stockholder demands, direct-to-consumer advertising, and prescribing habits mean that new medicines are often rushed to market.^{27,34–40}

28.4.3.2 Inadequate Reporting

Currently, the United States has a voluntary, spontaneous reporting system called MedWatch. Healthcare professionals and drug companies report ADRs to the FDA using the MedWatch Drug Experience Report Form. Since 1962, drug manufacturers have been required to report all ADRs brought to their attention, and they file the majority of the 200,000+ ADRs reported annually. The MedWatch program allows health professionals and the public to voluntarily report serious ADRs, product quality problems, and medication errors for all FDA-regulated medical products by mail, fax, telephone, or over the Internet. Direct reports, primarily from healthcare professionals, increased 51% between 1998 and 2003. The FDA is interested in receiving reports of serious, new reactions associated with the use of drugs and biologic products used in the course of medical practice. In addition, there is interest in reactions to new drugs during their first 3 years of marketing in the United States. The FDA database currently contains over 400,000 reports, including any reports that indicate a lack of therapeutic response. The FDA does not collect reports of inappropriate use, prescriber errors, or administration errors.

The spontaneous reporting system of the United States has many good features. The input is global — covering the entire population of patients treated with a drug. It includes drugs and physicians in “real-life” situations of drug use, unlike the controlled setting of clinical drug trials. The system is inexpensive, requires a minimum of time, and does not interfere with the practice of the physician. Unfortunately, the overall effectiveness of the program has been found to be wanting.⁴¹ Delays in sounding an alert can be a function of the need to verify and initiate any regulatory action. Alerting others usually occurs through published anecdotal reports. Leading a list of the limitations of MedWatch is underreporting — few physicians fill out the report forms. Although the MedWatch system is valuable for generating “signals” and forming hypotheses for epidemiological studies, it has been estimated that 95% of ADRs go unreported.⁴² According to Schiff,⁴³ the primary reasons that doctors fail to report include complacency, fear, guilt, ambition, ignorance, diffidence, and indifference.

28.4.3.3 Inadequate Warnings

ADRs are believed to be one of the leading causes of death in the United States.^{26,44} Patient exposure from new drugs with unknown toxic effects may be extensive. For instance, nearly 20 million patients in the United States took at least one of the five drugs withdrawn from the market between September 1997 and September 1998.⁴⁵ Three of the five drugs were new, having been on the market for less than 2 years.

“Boxed warnings” on medicine labels are described in the *Code of Federal Regulations*⁴⁶ as follows:

Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.

As this description lacks adequate criteria on when boxed warnings should be required, missing and inconsistent warnings are one of the causes for the high incidence of ADRs. For instance, the antipsychotic drug ziprasidone (Geodon; Pfizer), linked to heart toxicity, was not required to have a black box warning even though such a warning was required on six other drugs with prolonged QTc intervals. Sidney Wolfe⁴⁷ writes: "Although this is a dangerous inconsistency, it is somewhat predictable given the lack of clear FDA criteria for deciding on when a black box warning is necessary."

In the *PDR* study, Lasser and colleagues²⁷ found that between 1975 and 1999, 548 new chemical entities (NCEs) were approved, and 56 (10.2%) acquired a new black box warning or were withdrawn from the market. The authors found, using a Kaplan–Meier survival analysis (see Table 18.1), that there was a 20% probability of a new drug acquiring black box warnings or being withdrawn from the market within 25 years and a 4% probability of a new drug being withdrawn from the market, half of which occurred during the first 2 years the drug was marketed. The authors also noted inconsistencies in the *PDR* safety warnings. For instance, four beta-blockers contained black box warnings about the dangers of abruptly discontinuing the drugs (which can exacerbate coronary artery disease), but three other beta-blockers had no such warning. They also found asynchronous dates on the warnings for drugs from the same class.

A relationship between inadequate warnings and liability should be clear. Since physicians rely on manufacturers' warnings, if a physician is sued for an ADR in their patient, and it is discovered that information related to precautions and warnings are deficient, the plaintiff or injured party, and the physician may in turn file litigation against a manufacturer. Indeed, in 20 years of consulting work in litigation, this author has observed that the overwhelming product liability claim against a pharmaceutical manufacturer is based on an inadequate warning, which is claimed to render the product defective. Since FDA regulations provide for manufacturers to strengthen their warning based on a reasonable association of risk, the manufacturer cannot (but frequently tries to) claim that the warnings were approved by the FDA and cannot be changed without FDA approval. The specific regulation is as follows:

21 USC 201.57 (e) Warnings. Under this section of the section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.

21 USC 314.70 (c) Supplements for changes (in labeling) that may be made before FDA approval "Special Supplement-Changes Being Effected."

... (2) changes labeling to accomplish any of the following:

- (i) to add or strengthen a contraindication, warning, precaution, or adverse reaction;
- (ii) to add or strengthen a statement about drug abuse, dependence, or overdose;
or
- (iii) to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product;
- (iv) to delete false, misleading, or unsupported indications for use or claims for effectiveness.

28.4.3.4 Investigator Fraud

Another problem in detecting and reporting ADRs has been the discovery of numerous instances of proven investigator fraud, which can vary from bewildered ignorance to deliberate dishonesty:

- Some fail to document and report what they should clearly recognize as an ADR.
- Some are so “invested” in the study drug, believing so strongly in its safety, that their enthusiasm overshadows sound scientific and regulatory standards.
- Some choose not to report ADRs — either because it requires too much effort or because they are deliberately attempting to defraud.
- Some are confused over what constitutes an ADR.
- Many ADR reports lack essential information.
- Most are weak in causality assessment (whether the drug actually caused the ADR).

28.4.3.5 Quality Control, Safety, Manufacturing

A recent book, (*Risky Business: Managing The Quality of America's Medicines*, Robert A. Rhodes, FDA News, www.fdanews.com) attracted my attention, and I quickly read it as this chapter and the book was being readied for submission to the publisher. Rhodes, a veteran of 25 years in Quality Control in the Industry and now a member of the Weinberg Group, recommends the book to anyone thinking about becoming a quality professional in an FDA-regulated industry, as a means of achieving a sufficient picture of the complexity and intricacy of what it is like, through the eyes of someone who has “been there, done that.” To me the book reads like a “what ever could go wrong, will go wrong,” and quality systems in manufacturing and distribution are established and necessary to help protect the integrity of the product and the safety of the patient, which will ultimately help protect the Company, which could suffer serious financial and reputation setbacks for a defective product. As stated elsewhere, while most drug liability litigation flows out of inadequate warnings, from time-to-time, ineffective manufacturing controls and procedures are to be blamed for product failure, patient injury, and litigation and regulatory actions against the pharmaceutical manufacturer. I strongly recommend this book to anyone working in the pharmaceutical industry, not just those involved in “Quality.”

28.4.4 Types of Drugs Most Frequently Involved in Litigation

Although almost any drug can cause an adverse reaction of varying severity in at least some individuals, a number of drugs can be singled out as causing approximately 90% of reported drug reactions: adrenal steroids, aminoglycosides, anticoagulants, antimicrobials, antineoplastics, aspirin, bronchodilators, digitalis, diuretics, insulin, and NSAIDs. These agents have commonly been cited for the past 20 years. With the exception of digitalis, the use of which is declining, the “usual suspects” continue to be drawn from the same drug classes. Certain drug categories routinely appear in ADR studies.⁴⁸ Examples are:

- Anticoagulants (heparin, warfarin)
- Antimicrobials (penicillins, cephalosporins, sulfonamides)
- Cardiac agents (digoxin, diuretics, hypotensives, quinidine)
- Central nervous system agents (analgesics, anticonvulsants, sedative-hypnotics)
- Diagnostic agents (radiocontrast media)
- Hormones (corticosteroids, insulin)

As a rule, it has been this writer's observation that the longer the drug is on the market, the more we learn about the drug, and the more information is in the package insert, the less the drug company or manufacturer faces liability for inadequate warnings. The new drugs are usually the subjects of product liability suits.

The PIAA studies^{20,24} found that the most frequent drug classes and errors involved in its claims were antibiotics (failure to note documented allergy, most appropriate drug not used, drug inappropriate for medical condition); glucocorticoids (incorrect dosage, communication failure between physician and patient, failure to monitor for drug side effects); and narcotic and non-narcotic analgesics or narcotic antagonists (drug inappropriate for medical condition, incorrect dosage, failure to monitor for drug side effects, drug dependence).⁴⁹ The following sections describe drugs of note — those that have been the subject of large or highly publicized lawsuits.

28.4.4.1 Vaccines

Although vaccines are relatively safe, they have caused problems in the past, and any vaccine can cause an ADR in a "predisposed individual."⁵ As mentioned, the government has an interest in controlling disease outbreaks, so vaccines are routinely given to millions of people within months of each other. With that many people receiving a vaccine, even very low incidence of an ADR can still result in high rates of litigation, and as children receive a large number of vaccines (often several vaccines at once), jury awards can be high (see Section 28.2.1).

The production of vaccines has marched hand-in-hand with production mistakes, medication errors, and ADRs. For example, in October 1954, the National Foundation for Infantile Paralysis, which had paid for the development of the Salk vaccine to prevent polio, announced it was ordering enough of the drug to vaccinate 9 million children — without waiting for the results of a field trial.⁵⁰ This became the famous "Cutter Incident," when the doctor who conducted the field trials stated the vaccine was 60 to 90% effective, assuming that it was ineffective for the children in the trial who developed polio. Newspapers, parades, air-raid sirens, and erroneous statements all helped create the euphoria over the treatment. After vaccine shortages, conspiracy charges, and somewhat unregulated manufacturing to increase production, postinoculation polio was seen in children inoculated by vaccine from the Cutter Laboratories (Berkeley, CA, U.S.A.) which turned out to have live polio virus in some of its batches.

In 1976, another vaccine case illustrated how dangerous a mistake involving vaccines can be. Between October 1, 1976 and December 14, 1976, more than 40 million people were vaccinated against swine flu (a virus similar to the 1918 Spanish flu virus that killed so many during World War I). The feared epidemic never manifested, but there was a tenfold increase in GBS (in which the body's immune system attacks its peripheral nerves), which thousands of people contracted.

Numerous other vaccines have been linked to a variety of MedWatch — The FDA Safety Information and Adverse Event Reporting Program FDA has requested that sponsors of all NSAIDs make labeling changes to their products. The FDA recommended proposed labeling for both the prescription and OTC NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. The FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health

concern. Read the complete MedWatch 2005 Safety summary, including a link to the updated Drug Information Page and Medication Guide at <http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#NSAID>. Autoimmune disorders, such as encephalitis, lupus-like reactions, arthritis syndromes, arthropathies, and transverse myelitis.⁵ Other vaccines have been linked to ADRs:

- *Rotavirus* — the most common cause of severe diarrhea in infants, with approximately 125 million cases worldwide per year and 600,000 deaths — vaccines have been linked with intussusceptions (a problem with the intestine in which one portion of the bowel slides into the next) at a rate of between 1 in 5000 and 1 in 11,000 infants.⁵¹ The only rotavirus vaccine approved in the United States, RotaShield (Wyeth–Ayerst), was withdrawn from market on October 22, 1999, about 1 year after licensure.
- The *diphtheria, pertussis, and tetanus (DPT)* vaccine, which has prevented more than 95% morbidity from these diseases, has been linked with convulsions, encephalitis, and sudden infant death syndrome.⁵²
- The *hepatitis B* vaccine has been linked to anaphylaxis.
- The *measles* vaccine has been linked to thrombocytopenia and anaphylaxis.
- *Tetanus* toxoid-containing vaccines to GBS, brachial neuritis, and anaphylaxis.

What is, perhaps, most disturbing is the assertion by Coulter and Fisher⁵³ in 1985 that the ADRs from DPT should not have happened. They document that Japan switched to an acellular form of the DPT virus in 1981, which was just as effective in preventing the diseases but had fewer ADRs. Shoemaker⁵ reports that “In Japan, the Ministry of Health, instead of trying to cover up problems with the vaccines, chose to find a solution.” According to Shoemaker, it took almost 20 years for the United States to stop using the whole-cell version of the vaccine, and manufacturers are still distributing the whole-cell version in third-world countries “undoubtedly because it is cheaper to make.”⁵⁵

Vaccines are currently in development for allergies, anticholesterol, behavioral addictions, cancer, *Candida albicans*, cat allergy, *Chlamydia trachomatis*, cytomegalovirus, *Escherichia coli*, genital herpes, gonorrhea, *Helicobacter pylori*, hepatitis C, hepatitis E, herpes simplex, juvenile diabetes, *Listeria monocytogenes*, malaria, multiple sclerosis, nicotine, peanut allergies, periodontal disease, ragweed, respiratory syncytial virus (RSV), rheumatoid arthritis, ringworm, *Staphylococcus aureus*, *Streptococcus* genus, syphilis, and tuberculosis.

28.4.4.2 Fen–Phen and Other Diet Drugs

The use of drugs to treat obesity has had limited success because of the danger of unintended side effects. Some of these side effects are, at worst, a nuisance, but some of them can be life threatening. Compounding the risk of taking diet drugs as directed is by taking them in doses exceeding the recommended amount or in an “off-label” manner. Using larger doses, extending the duration of treatment, or combining two or more drugs to enhance the same effect are examples of this practice. The Fen–Phen diet is an example of combining two drugs for assistance in achieving weight loss. Each had been tested and approved as safe and effective for short-term use in morbidly obese subjects. The combined therapy proved to be so well received that millions of prescriptions were written for two drugs that were not approved or tested for safety in combined use. In addition, the duration of therapy was arbitrarily extended from the approved 6 to 8 weeks (short term), to more than 1 year. The result was that a population experiment in which a potentially deadly adverse effect, PPH, was discovered after millions of doses had been prescribed and administered.

PPH was a problem in Europe in the 1960s for an appetite suppressant, Aminorex. There is no method for screening potential dexfenfluramine patients for susceptibility to PPH: it is a silent killer, with no early symptoms, affects predominately women in their early 30s and 40s, and that there is no cure.⁵⁴ The risk of PPH among anorexic agents is significantly elevated, but the absolute incidence is still small: 28 cases per million person-years of exposure, comparable to the fatality risk from penicillin-caused anaphylaxis. The risk of death from untreated obesity is perhaps 20 times higher than the estimated mortality from PPH among patients given appetite-suppressant drugs.⁵⁵

The Chairman of FDA's Advisory Committee commented on the risk of death from developing PPH. "We have had what I think appears to be a reasonable estimate of the risk of deaths from pulmonary hypertension. We need to understand clearly that if a million patients take this drug, at least a couple dozen of them will die annually as a result of this complication. That seems the best estimate. This is something that has to be weighed seriously." The appearance of heart valvulopathies in otherwise asymptomatic people in their thirties or forties was unexpected and caught patients and practitioners by surprise. Both fenfluramine and phentermine cause an increase in the amount of serotonin available in the body, which can cause cardiac valvulopathies.

On September 15, 1997, FDA asked the manufacturers of dexfenfluramine (Redux; manufactured for Interneuron Pharmaceuticals by Wyeth–Ayerst) and fenfluramine (Pondimin; Wyeth–Ayerst) to voluntarily withdraw both treatments from the market because of findings that indicate approximately 30% of patients taking the combined drugs had abnormal echocardiograms, even if they had no symptoms. Both companies agreed. FDA is not requesting the withdrawal of phentermine, the third widely used medication for obesity.

Additional ADRs linked to diet pills include psychosis,⁵⁶ myocardial ischemia,⁵⁷ drug interactions, such as the interaction of fenfluramine with imipramine, fenfluramine with amitriptyline or desipramine, or the toxic reaction between fluoxetine and phentermine; and the release of serotonin while inhibiting its reuptake,⁵⁸ contributing to hyperserotonin reactions. When the next craze takes hold of patients and their physicians, hopefully physicians and pharmacists will take a more vocal position and recommend restraint, until some proof of efficacy and lack of toxicity is shown for new faddish off-label combinations.

28.4.4.3 Nonsteroidal Anti-Inflammatories

The efficacy of NSAIDs in the treatment of a wide variety of disorders is well established. An estimated 1.2% of the U.S. population takes NSAIDs regularly, and more people take them intermittently. NSAIDs have also been involved in the prescription-to-OTC shift (Motrin to Advil; Naprosyn to Aleve) and so more — and more potent — NSAIDs are being used. The NSAIDs, according to FDA, account for the largest number of ADR reports.

Gastrointestinal effects are the most frequently reported ADRs associated with NSAIDs and include nausea, vomiting, dyspepsia, and diarrhea. Gastrointestinal bleeding, ulceration of the GI tract, and renal toxicity in predisposed patients are also common. The NSAIDs are also linked to cholestatic hepatitis and GI hemorrhage, which may be fatal. Salt and water retention with edema is a well-known effect of NSAIDs. Hyperkalemia and reduced excretion of potassium have also been reported. Most NSAIDs can inhibit platelet aggregation and prolong bleeding time. Elderly patients excrete the drug more slowly, putting them at greater risk of bleeding.

The NSAIDs have been increasingly incriminated in chronic peptic ulcerations. Patients on short- and long-term therapy should be instructed on the signs of GI bleeding and ulcer perforation, and periodic monitoring of renal function is advisable. In *"The Seven Pillars of Foolishness,"* Dukes,⁵⁹ gives an account of some past disasters occurring from the use of NSAIDs class. One of the NSAIDs Dukes discusses is Benoxaprofen, introduced in the

early 1980s. A discussion of the Benoxaprofen problem will be presented to give a historical focus to some recent problems with the NSAIDs. Four NSAIDs that have caused concern recently include rofecoxib, valdecoxib, benoxaprofen, and ketorolac.

Rofecoxib, a Cox-2 specific inhibitor NSAID, is one of the drugs most recently withdrawn from market (Table 28.3). Rofecoxib (Vioxx; Merck & Co.) was voluntarily withdrawn from the U.S. and worldwide markets on September 30, 2004, because of an increased risk of heart attacks and strokes confirmed during investigations to determine if the Rofecoxib was effective in preventing the recurrence of colon polyps. A postwithdrawal Advisory Committee questioned the need to withdraw the drug, and the Company has released statements suggesting that Vioxx may be re-introduced to the market. This COX-2 selective NSAID has been on the market for more than 5 years for treating osteoarthritis, rheumatoid arthritis, acute pain, and menstrual symptoms. On approval, it had gone through an expedited (6 months) "priority review" because the drug "potentially provided a significant therapeutic advantage over existing approved drugs due to fewer gastrointestinal side effects, including bleeding," according to FDA.

The original safety database on Vioxx included approximately 5000 patients on rofecoxib and did not show an increased risk of heart attack or stroke. A June 2000 study, VIGOR (VIOXX GI Outcomes Research), was primarily designed to look at the effects of rofecoxib on ADRs such as stomach ulcers and bleeding. The study showed that patients taking rofecoxib had fewer of the side effects than patients taking naproxen. The study also showed a greater number of heart attacks in patients taking rofecoxib. The FDA's response to the VIGOR study was to include new safety information on the Vioxx label in April 2002. Merck then began to conduct longer-term trials to obtain more data on the risk for heart attack and stroke with chronic use of Vioxx. Additional information on Vioxx is available at www.fda.gov/cder/drug/infopage/vioxx.

Valdecoxib (Bextra; Pfizer), a second COX-2 specific inhibitor NSAID was taken off the market a few months after Vioxx. In addition to a higher risk of serious skin toxicity, patients given Vioxx after Coronary Bypass Surgery had a higher rate of myocardial infarctions.

In the aftermath of the Vioxx and Bextra withdrawals, the FDA studied the CV and GI risks in great detail. A very recent request for strengthening the warnings and precautions on all NSAID products was released, and reads as follows:

MedWatch — The FDA Safety Information and Adverse Event Reporting Program

FDA has requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products. FDA recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health concern.

Read the complete MedWatch 2005 Safety summary, including a link to the updated Drug Information Page and Medication Guide at <http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#NSAID>

Benoxaprofen was an antirheumatic drug compound that early clinical studies suggested might relieve gastric problems associated with the class. This agent was approved for marketing in the early 1980s and touted as a new miracle drug, thought by some to improve the arthritis disease, in addition to serving its proven efficacy of acting as an anti-inflammatory.

When the real problems with benoxaprofen emerged, however, they were more serious: It was apparently killing elderly patients with hepatic disorders, inducing massive photosensitivity, and causing onycholysis (separation of the nail plate from the bed) in about 15% of patients. It seems probable that at least 70 elderly patients died, and many more people suffered.⁶⁰ Shortly after its well-publicized entry into the U.S. market, the manufacturer of benoxaprofen voluntarily withdrew its product as it caused fatal cholestatic hepatitis.⁶⁰⁻⁶³ This action immediately followed news of suspension of the license to sell benoxaprofen in the United Kingdom.⁶⁴

Ketorolac, in both injection and tablet form, has had its safety questioned. Even short-term parenteral treatment with ketorolac can cause gastric ulceration. According to the manufacturer (Syntex) by December 1992, approximately 16 million patients worldwide had received all formulations of ketorolac.⁶⁵ By 1993, there had been a total of 923 reports of serious ADRs from ketorolac, 838 from the United States, including GI ($n = 203$), hematological ($n = 181$), renal ($n = 124$), hypersensitivity ($n = 107$), and neurological ($n = 111$) reactions. Fatal outcomes were reported in 97 cases worldwide by April 1993, and by that time, 26 million patients had received the drug. Death resulted from GI bleeding and perforation ($n = 47$), renal insufficiency ($n = 20$), anaphylaxis and asthma ($n = 7$), hemorrhagic reactions ($n = 4$), miscellaneous causes ($n = 13$), and unexplained ($n = 6$) reactions. These data have prompted different reactions in different countries, ranging from no action (except for updating the prescribing information sheet) in the United States to limiting its use in many countries to a request for withdrawal from market in Germany and France. Other NSAIDs that have been introduced into the market and removed for safety reasons include Zomax, Suprol, and Duract.

28.4.4.4 Corticosteroids

Corticosteroid therapy can be of great benefit; they are the strongest drugs available for reducing inflammation. They are used to treat arthritis, multiple sclerosis, chronic obstructive pulmonary disease, and certain emergencies (asthma attacks, anaphylaxis, and brain swelling, for instance). They can have phenomenal success in treating tough skin conditions, such as eczema and psoriasis. When inflammation is severe, corticosteroids can save lives, but adverse effects from their use appear frequently in the medical literature — as might be expected from a group of drugs that exert many pharmacological effects and are routinely used or tried experimentally for a variety of pathological conditions. The long-term use of corticosteroids is often limited by Cushingoid side effects, which include the well-known facial puffiness and weight gain, among other complications such as activation of tuberculosis, cataracts, diabetes, ecchymosis, hirsutism, hypertension, infections, obesity, osteoporosis, phlebitis, poor healing, and renal lithiasis.

Short-term use of glucocorticoids, even in massive dosages, is less likely to produce harmful reactions. They can, however, produce a variety of effects that are neither limited to high doses nor to long-term therapy. When a low dose of steroids (prednisone) was given for several months to a 38-year-old man to treat eczema of his hands and feet, he developed bilateral avascular necrosis (AVN) of the femur. He therefore had total bilateral hip replacement, and several experts have attributed his AVN to the steroid administration. The man sued his allergist, who settled the lawsuit shortly before trial for approximately \$400,000. Most practitioners, however, are unaware of the risk of short-term or low-dose steroids. Yet many of these cases can be found in the courts, the literature, and the MedWatch databases.

Topical corticosteroids produce anti-inflammatory, anti-itching, and vasoconstricting effects. A wide variety is available (described in detail in *Drug Information 2004*⁶⁶ and other references and compendia). Such steroids are classified into five categories that reflect a

TABLE 28.4
Systemic Disorders That Can Occur with the Use of Corticosteroids

Disorders	Glossary
Cardiovascular disorders	Hypertension is one of the Cushingoid effects of corticosteroids.
Dermatological disorders	Various dermal manifestations have also been reported. Topical steroids may cause facial edema (moon-face) atrophy or thinning of the epidermis and dermal collagen, drying of the skin, telangiectasis, fragility of the skin blood vessels, purpura (easy bruising), and atrophic striae.
Endocrine and metabolic disorders	The exogenous administration of glucocorticoids can result in hypothalamic-pituitary-adrenal axis (HPA) suppression, which may subsequently lead to adrenal atrophy. ^{66,67} The degree of adrenal suppression is dependent on the dosage, duration, frequency, time, and route of administration of the specific glucocorticoids. At least one patient who received prednisone for neurological symptoms developed Cushing's syndrome. ⁶⁸
Genitourinary disorders	Steroid use has been linked to renal lithiasis.
Gastrointestinal disorders	Corticosteroid ADRs include the development, reactivation, perforation, hemorrhage, and delayed healing of peptic ulcers.
Immunological disorders	Delayed or poor wound healing, increased susceptibility to infections, masking of the symptoms of infections, thrush infections of the mouth and anaphylactoid reactions have been reported.
Musculoskeletal and connective tissue disorders	Steroid use may cause muscle wasting, pain and weakness, and atrophy of the protein matrix of bone, which can lead to osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and other pathologic fractures of the long bones. AVN has been reported following short courses (1 week). Local injections into a patient's joint (intra-articular) can produce systemic as well as local effects. Patients who have received a local injection aimed right into a joint should be given careful instructions not to overuse those joints, even after symptomatic relief of the pain. The repeated administration of intra-articular injections may result in damage to joint tissues. Septic arthritis — which includes pain, local swelling, further restriction of joint movement, fever, and malaise — is also possible. Because there is latency between the end of steroid therapy and the onset of symptoms of AVN, patients should be informed of the potential risk of osteonecrosis following the use of steroid medication. Complaints of hip pain in people who have previously been prescribed steroids should produce a high index of suspicion for underlying osteonecrosis of the femoral head.

Neurological disorders	Ischemic neuropathy, restlessness, and seizures are possible neurological ADRs.
Nutritional disorders	The primary nutritional ADR from corticosteroids is weight gain and obesity.
Obstetrical disorders	Small birth weight and necrotizing enterocolitis of a fetus resulted from the mother's use of a corticosteroid.
Ophthalmological disorders	Ocular complications following local or systemic administration of steroids include glaucoma, cataracts, adverse influence on specific ocular infections, pseudotumor cerebri, ptosis, mydriasis, subjective visual complaints, visual field defects, systemic absorption of the topical medication, conjunctival and palpebral petechiae, epithelial punctate keratitis, and, possibly, corneal and scleromalacia. ⁶⁹
Psychiatric disorders	Glucocorticoids are known to produce mental changes that range from moderate mood changes, severe depression, and euphoria to psychosis. Steroid psychosis is characterized by a delirium and a clouded sensorium. The onset of symptoms usually occurs within 5 to 30 days after therapy is initiated. The incidence rate appears to correlate closely with dosage level (a rate of 1.3% when the dose was 40 mg or less; 4.6% when it was between 41 and 80 mg; and 18.4% when it was 80 mg or more).
Withdrawal symptoms	The abrupt discontinuance of steroids in long-term therapy patients can result in withdrawal syndrome, even without evidence of adrenal suppression. To minimize morbidity associated with adrenal insufficiency, discontinuing corticosteroid therapy must be gradual. During withdrawal therapy, increased supplementation may be necessary during times of stress. Symptoms of adrenal insufficiency that result from too rapid withdrawal include nausea, fatigue, anorexia, dyspnea, hypotension, hypoglycemia, myalgia, and arthralgia. Continued supervision after therapy termination is essential because a sudden reappearance of a severe manifestation of the disease being treated can occur. Whether or not there is improvement in the disorder that is being treated, clinicians frequently attempt to withdraw patient from glucocorticoid therapy before such therapy has gone on for very long. ⁷⁰

steroid's vasoconstricting effects and its action on psoriasis. In general, an application of topical steroids does not demonstrate systemic effects. However, systemic ADRs can occur when the drugs are used on large skin areas, for prolonged periods of time, with occlusive dressings that prevent evaporation of moisture and drive the drug into the dermis, when more potent preparations are applied to areas of greater than average absorptive abilities (for example, scrotum, scalp, macerated skin), or when they are used on infants and children. In addition, recent evidence suggests that excessive or prolonged use of topical fluorinated steroids (for example, triamcinolone) during pregnancy can affect the intrauterine growth of the fetus.

Corticosteroids can produce a variety of devastating and systemic effects. Some of the ADRs associated with corticosteroids are listed in Table 28.4.

28.4.4.5 Noteworthy Class Actions: Rezulin, Baycol

Rezulin (troglitazone, Warner Lambert, now Pfizer) was approved in January 1997 to treat adult-onset diabetes and was hailed as a drug to treat patients who have failed other therapies (untreated diabetes can cause heart and kidney failure, blindness, and other problems). It was a "fast track" drug with an approval process that took only 6 months, despite objections from several FDA scientists and the death from liver failure of one of the study participants. The FDA received reports of liver failure and in December 1997, it was banned in Great Britain. The FDA, at that time, however, only ordered stronger liver toxicity warnings on the drug label — the warning was strengthened four times between 1997 and June 1999 — even though several patients who had monthly liver tests still experienced sudden liver failure and died.⁶⁷ In March 1999, an FDA epidemiologist warned that "Rezulin was among the most dangerous drugs on the American market," and that "patient monitoring would not protect them from liver failure."⁶⁷ An advisory committee recommended the drug be made available only to patients whose diabetes was not well controlled by other drugs. In March 2000, an FDA official Robert Misbin wrote to Congress, "I am writing to enlist your aid in convincing my superiors at FDA that Rezulin should be removed from the market because of its unacceptably high risk of causing liver failure."⁶⁸

Even the efficacy of troglitazone was in suspect. After the drug was removed from the market, one FDA official wrote that it had been approved and kept on the market so long because it was "shown to reduce or delay long-term serious effects of diabetes, including death." But when asked about the basis of that claim, an FDA spokesperson said "those findings were not intended as definitive scientific observations."⁶⁷ With the help (and possible conflicts of interest) of FDA officials and the physicians carrying out a National Institutes of Health (NIH) study,⁶⁹ the drug manufacturer was able to keep FDA from banning troglitazone for 27 months.⁷⁰ The drug was eventually withdrawn from the market in the United States on March 21, 2000, but keeping the drug on the market as long as possible was profitable. At its peak sales in January 1999, 488,000 prescriptions were filled, and during its 3 years on the U.S. market, troglitazone generated \$2.1 billion for Warner Lambert.

The withdrawal of troglitazone came only after a whistleblower shared his findings and internal email with a *Los Angeles Times* reporter. A series of articles by David Willman,^{32,69,71} raised questions about irregularities and conflicts of interest in the study and approval of the drug. Litigation over troglitazone is still ongoing. In 2003, an appeals court overturned a lower court, which had denied class action status to Rezulin cases. In January 2004, Pfizer set aside \$975 million to cover 35,000 settled or withdrawn injury claims. In March 2004, a federal grand jury requested testimony from former Warner-Lambert employees. In April 2004, a jury awarded \$2 million as compensatory damages to a woman. In June 2004, a Los Angeles jury found that facts about the drug did not support responsibility for the death of two patients and the injury of another. In July 2004, an Illinois class action

lawsuit was settled for \$60 million, and an \$11.55 million award was upheld for a man who died 1 month after starting the drug.⁷²

28.4.4.6 Drug-Induced Hepatotoxicity

Of course, Rezulin is not the only drug implicated in liver toxicity. In fact, the FDA recently posted a notice on its website (<http://fda.gov/>), describing a special interest and monitoring of drug-induced hepatotoxicity:

Drug-Induced Liver Toxicity

Momentum and interest continue to grow concerning the rising incidence of liver toxicity, uncommon but serious, caused by prescription drugs, over-the-counter medications, or dietary supplements that are often combined with special diets and alcohol consumption, in addition to environmental chemicals. The liver is a most marvelous organ that usually protects us against injury from foreign substances, and is very robust in its capacity to withstand damage and heal itself. In a few people, the ability to resist and heal is not adequate, or the injury is so great that serious liver damage results, with progression to acute failure, and to death or transplantation. Drug-induced liver injury has become the most frequent cause of acute liver failure in the United States, exceeding all other causes combined. Drug-induced liver injury also remains the major single reason for regulatory actions concerning drugs, including failure to approve, withdrawal from the market, restrictions on use, and warnings to physicians. (*emphasis added*).

This web site is sponsored by the Hepatotoxicity Steering Committee, (HepToxSC) jointly made up of interested persons from the Food and Drug Administration Center for Drug Evaluation and Research (FDA/CDER), the Pharmaceutical Research and Manufacturers of America (PhRMA), and the American Association for the Study of Liver Diseases (AASLD). Members of this regulatory-industry-academic research group have been meeting annually for several years since the first public conference in Chantilly VA in February 2001, with additional quarterly telephone conferences. Material from the most recent annual meeting, January 28, 2005, is shown here; the older material is available in the background by clicking on the underlined listings.

We call attention also to the web site for the Drug-Induced Liver Injury Network (DILIN) sponsored since 2003 by the National Institutes of Health (NIH), Liver Disease Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

We encourage you to contribute your ideas and comments about this topic. Please send your thoughts to John R. Senior, M.D. (john.senior@fda.gov) or Lana Pauls, M.P.H. (lane.pauls@fda.gov).

The reader should note the emphasis in the above paragraphs: drug-induced hepatotoxicity is the leading cause of acute liver failure and the number one reason for regulatory actions against drugs in the United States!

Baycol (cerivastatin, sold as Lipobay in Europe, Bayer) is a statin, a class of cholesterol-lower drugs. Statins are the most prescribed drugs in the United States, with more than 12 million people taking them, and more than 700,000 people in the United States taking cerivastatin.⁷³ It received marketing approval on June 26, 1997 and was voluntarily removed from the market on August 8, 2001 because of its link to 100 deaths and several injuries from potentially the muscle disease rhabdomyolysis. The other statins — lovastatin (Mevacor; Merck); pravastatin (Pravachol; Bristol-Myers Squibb); simvastatin (Zocor; Merck); fluvastatin (Lescol; Novartis); atorvastatin (Lipitor; Parke-Davis); rosuvastatin

(Crestor; Astra-Zeneca); and lovastatin + niacin (Advicor; Kos Pharmaceutical) — that can also cause rhabdomyolysis remain on the market. Although scientists agree that the other statins “seem to have essentially identical safety profiles and benefit–risk ratios,”⁷⁷ FDA said the ADRs associated with Baycol “have been reported significantly more frequently than for other approved statins.”⁷⁴

When initially recommending cerivastatin for approval, after testing in 3343 patients from the United States, Japan, and China, an FDA official cited rhabdomyolysis as one of four potentially serious ADRs. After approval, a warning was added in 1999, and the labeling was changed again in June 2001. Just 2 months later, Baycol was withdrawn from the market. In 2003, the first Baycol lawsuit went on trial in Texas and involved a victim who did not die or require kidney transplant;⁷⁴ the verdict favored Bayer. The primary legal complaint in subsequent lawsuits is that the manufacturer failed to adequately warn of the known dangers and complications of the drug. “In clinical trials, there is a “filtering” of adverse events in drug-treated groups in that if the principal investigator expresses the opinion that the adverse event was not related to the drug, one researcher says, “the adverse event is excluded from analysis.”⁷⁴ Kauffman,⁷⁵ discussing Lipitor, suggests that the cost–benefit analysis of statins is another possible area of litigation, saying, “The absolute risk reduction is ... one in 667 per year. The cost of a month’s supply of Lipitor at 40 mg/day is \$1,500/year, reflecting a cost of \$1 million to prevent one death among 667 people taking the drug for one year.”⁷⁵

In March 2004, Bayer settled with its insurance carriers, eliminating the insurers rights of litigation and settlement and setting the limits of liability at \$1.2 billion. In July 2004, the company settled 2771 cases for \$1.06 billion. In September 2004, Bayer settled another 2861 product liability cases for \$1.09 billion. There are still 7577 such suits pending.⁴

28.5 Market Entry and Subsequent Withdrawal

In 1997, 39 new drugs were approved by the FDA. Now, five of them have been taken off the market (see Table 28.4) and an additional two have new boxed warnings. Thus, seven drugs approved that year (18%) have already been withdrawn or had a black box warning 4 years after approval. According to one study, 20% of drugs will be withdrawn or have a black box warning within 25 years of coming on the market.²⁷

In 10 years (1988 to 1998) the number of drugs approved first-in-the-world by the FDA jumped from 4 to 66%. The FDA approved 80% of the new drug applications at the end of the 1990s, but only 60% at the beginning of the decade. The FDA has recently been slow in removing drugs that have already been withdrawn in Europe. There are increasing reports of drug approvals after FDA scientists and drug advisory committees have recommended against approval. Charges have been made that researchers and advisory committee members deciding on a drug’s safety and approval often have conflicts of interests. Several medical researchers have concluded that new drugs should only be given with extreme caution. The FDA argues that many good therapies are lost as physicians fail to read and heed the drug warnings it issues. There are many reasons that drugs might be approved and later withdrawn, and there are many people and groups pointing fingers at others. A New Drug Safety Board has been appointed, constituted by members primarily from the agency, and Congress has substantially increased the funding for FDA safety monitoring.

Many drugs are simply discontinued for reasons that may not have to do with safety. The OTC drugs and drug products used as a compound in other drugs may also be withdrawn.

So occasionally different numbers of withdrawn drugs are reported. Table 28.3 lists prescription drugs withdrawn from market for safety reasons between 1997 and 2004.

28.6 Deep Pockets and Efforts to Limit Litigation

The Bush administration is now asking the courts to decide whether consumers can recover damages for ADRs. In what it admits is a policy shift, the Department of Justice now suggests that consumers cannot recover damages as the drugs involved were approved by FDA. The administration contends that allowing such lawsuits undermines public health and interferes with the federal regulation of drugs and devices by allowing juries and judges to second-guess FDA experts.¹⁸ It also argues that if such lawsuits succeed, good products might be removed from the market. The federal court of appeals in Philadelphia agreed with the administration in the case of a defective heart pump case.⁷⁶ In *Horn v Thoratec Corp.* the company argued that the plaintiff's claims were preempted by the Medical Device Amendments (MDA) to the *Food, Drug, and Cosmetic Act*. The Third Circuit agreed and affirmed the district court opinion. Five other circuit courts have found that personal injury suits are improper for FDA-approved medical devices. One circuit court found to the contrary.⁷⁶ Although the Supreme Court weighed in on this issue in 2001,⁷⁷ that decision was based on the Court's finding that Congress had vested enforcement authority solely to the FDA in the MDA changes to the FD&C law. The MDA preemptions will probably be revisited by the Supreme Court, which previously ruled that FDA regulation does not preempt state law or local regulation.⁷⁸ These changes have only been applied to medical devices, not to drugs, at this time.

In 2002, the administration shifted the federal government's previous policy by making FDA a party in product liability lawsuits. The administration believes that consumer lawsuits are a burden on the economy and increase the cost of healthcare. Senator John Edwards, who was a plaintiffs' attorney, disagrees, and that is why he helped draft a bill defining patients' rights, including the right to sue. Although the bill passed the Senate (S-283), threats of a veto stalled it. A Bush-Norwood compromise was passed in the House that would allow patients to sue their insurers in state court but pain-and-suffering and punitive damages would be capped at \$1.5 million each. The bill, however, never became law.⁷⁹

Canada limits lawsuits against drug manufacturers. According to one estimate, one third to one half of the drug price difference between the United States and Canada is a result of the reduced litigation in Canada.⁸⁰ Maurice D. Hinchey, the New York representative to Congress, however, believes that the Bush administration has gone too far, saying it has "taken the FDA in a radical new direction, seeking to protect drug companies instead of the public." He recently persuaded the House to cut \$500,000 from the FDA chief counsel budget to slow its "aggressive opposition to consumer lawsuits."⁸¹

28.7 Summary and Conclusions

Clearly, ADRs continue to induce injury and harm to patients, despite careful prescribing, dispensing, and administering. New drugs represent unknown risks and require intense scrutiny and monitoring in their early-market stages. Poor monitoring, selecting more toxic drugs, or taking poor patient histories increases a patient's risk of partially reversible morbidity and mortality. Careful monitoring by pharmaceutical manufacturers during

clinical trials, early post marketing use, and throughout the life of the product, with labeling updates and promulgated adequate warnings to prescribers and patients will improve the safety of medicines and limit the liability of the pharmaceutical manufacturers.

The best science in the world, as evidenced and described in this book, has to be balanced and tempered with thorough safety monitoring in order to safely provide the new drug discoveries with patients.

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