

2000

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Recommended Citation

49 Cath. U. L. Rev. 449 (2000)

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ADVERSE DRUG REACTIONS: HARNESSING EXPERIENTIAL DATA TO PROMOTE PATIENT WELFARE

Barbara A. Noah*

A wise man should consider that health is the greatest of human blessings, and learn how by his own thought to derive benefit from his illnesses. —Hippocrates¹

In the last two years, five prescription drugs have been withdrawn from the market and several others have been the subject of intensified warnings to physicians and consumers, all due to the discovery of previously unforeseen side effects associated with their use. For instance, the Food and Drug Administration (FDA) recalled two diet drugs because they appeared to cause heart valve problems, and it recently withdrew its approval of a prescription painkiller because of reports associating that drug with acute liver failure.²

Although such occasional incidents may attract widespread attention, the problem of adverse drug reactions is pervasive and longstanding. A 1998 study concluded that over 100,000 people die in the United States each year from adverse reactions to medications,³ making them the fourth leading statistical cause of death in this country.⁴ Many of these

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1. HIPPOCRATES, 9 REGIMEN IN HEALTH.

2. See Sheryl Gay Stolberg, *New Painkiller is Withdrawn After 4 Deaths*, N.Y. TIMES, June 23, 1998, at A1.

3. See Denise Grady, *Study Says Thousands Die from Reaction to Medicine*, N.Y. TIMES, Apr. 15, 1998, at A1 (describing a *Journal of the American Medical Association* study that found an additional 2.2 million nonfatal adverse drug reactions in 1994); see also U.S. GEN. ACCOUNTING OFFICE, PUB. NO. GAO/PEMID-90-15, FDA DRUG REVIEW: POSTAPPROVAL RISKS 1976-85 3 (1990) [hereinafter FDA DRUG REVIEW] (estimating that over 50% of all new drugs approved by the FDA during the studied years had serious risks that remained undiscovered until after marketing). Experts disagree about the accuracy with which the risk of adverse drug events can be predicted. See U.S. GEN. ACCOUNTING OFFICE, PUB. NO. GAO/HEHS-00-21, ADVERSE DRUG EVENTS: THE MAGNITUDE OF HEALTH RISK IS UNCERTAIN BECAUSE OF LIMITED INCIDENCE DATA 2 (2000).

4. See Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized*

reactions can be attributed to the expected side effects of potent therapeutic agents, but some of these adverse reactions come as a surprise. In addition to causing significant rates of morbidity and mortality, adverse drug reactions tend to prolong hospital stays, resulting in increased economic burdens on patients and on the health care system. They also have significant implications for the overall quality of patient care.⁵

The concept of managed care has transformed the health care system in the past decade. Managed care magnifies the conflict between health care resources allocated to individual patients and those remaining for the total group of potential beneficiaries because the system demands pre-authorization for the utilization of resources for any individual within the group.⁶ This pre-approval mechanism can interfere with a physician's ability to select treatments based solely on the individual patient's needs and instead requires that the physician work within standards intended to serve the needs of the entire group of which the patient is a member.⁷ Providers have strongly protested the allocation of health services on a population-wide basis under managed care.⁸ Perhaps population-based

Patients: A Meta-analysis of Prospective Studies, 279 JAMA 1200, 1202 (1998); see also John A. Anderson, *Allergic Reactions to Drugs and Biological Agents*, 268 JAMA 2845, 2845 (1992) (noting that an estimated 2% to 5% of all hospitalizations result from adverse drug reactions, and that up to 30% of hospitalized patients experience some form of adverse drug reaction). At the same time, two of the leading causes of death have declined dramatically. See Gina Kolata, *Vast Advance is Reported in Preventing Heart Illnesses*, N.Y. TIMES, Aug. 6, 1999, at A15 (noting that mortality rates from heart attacks and strokes are falling). As the population ages and consequently increases its use of prescription medications, adverse drug reactions will account for an even greater share of deaths in this country. See Barbara A. Noah & David Brushwood, *Adverse Drug Reactions in Elderly Patients: A Systems Approach to Promoting Patient Welfare* (Feb. 2000) (unpublished manuscript, on file with the *Catholic University Law Review*).

5. See David C. Classen et al., *Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality*, 277 JAMA 301, 301, 305 (1997) (concluding that adverse drug events complicated 2.43% of hospital admissions during the studied period, and that the ADEs increased the length of hospital stays an average of 1.91 days with a resulting increased average cost of \$2262); see also David W. Bates et al., *The Costs of Adverse Drug Events in Hospitalized Patients*, 277 JAMA 307, 307, 311 (1997) (finding a 2.2 day average additional length of stay for patients with ADEs, resulting in an increased average cost of \$2595 by analyzing 4108 random hospital admissions).

6. See William M. Sage, *Physicians as Advocates*, 35 HOUS. L. REV. 1529, 1536 (1999).

7. See George J. Annas, *A National Bill of Patients' Rights*, 338 NEW ENG. J. MED. 695, 696-97 (1998) (describing the "core response to the perception that health plans had gone too far . . . [and] an attempt to put the power to make decisions back in the context of a consensual and informed doctor-patient relationship freed from financial conflicts of interest").

8. See, e.g., Jerome P. Kassirer, Editorial, *Managing Care—Should We Adopt a New Ethic?*, 339 NEW ENG. J. MED. 397, 397-98 (1998) ("I believe that intentionally providing minimally acceptable care to some for the benefit of others in an arbitrary group—let

medicine threatens the integrity and quality of medical care, but the collection, analysis, and dissemination of information relating to adverse drug reactions demands an emphasis on population-based outcomes and utility. In order to improve the quality of patient care that utilizes prescription drugs, the health care system must have access to meaningful safety data derived from large population trials and records of clinical outcomes. This Article will suggest ways to increase both the quality and quantity of drug safety data.

Recent changes in the marketing of pharmaceutical products will exacerbate drug safety problems in the future. With the advent of direct advertising to consumers,⁹ patients increasingly demand and receive new prescription drugs immediately upon initial FDA approval.¹⁰ Even if physicians manage to resist patients anxious for the latest, and therefore, least time-tested pharmaceuticals, overall use will increase in response to sophisticated advertising campaigns. As the consumer demand for old and new prescription drugs continues to rise,¹¹ the importance of post-

alone for the benefit of the bottom line—is wrong . . .”). Dr. Kassirer opined that “[i]f we capitulate to an ethic of the group rather than the individual . . . we risk becoming economic agents instead of health professionals.” *Id.* at 398.

9. See Elyse Tanouye, *Drug Dependency: U.S. Has Developed an Expensive Habit; Now, How to Pay for It?*, WALL ST. J., Nov. 16, 1998, at A1 (noting that drug marketers spent \$1.3 billion on consumer advertising in 1998, a seven-fold increase over spending five years before and that, since 1997, the FDA has permitted full-scale television advertising of prescription drugs directly to consumers); see also Center for Drug Evaluation & Research, FDA, *Guidance for Industry: Consumer-Directed Broadcast Advertisements* (last modified Aug. 8, 1997) <<http://www.fda.gov/cder/guidance/index.htm>> (providing that television advertisements may specify the indications for use of a prescription drug if accompanied by warnings of the product's main risks and a cross-reference to more detailed cautionary information in printed form); Draft Guidance for Industry; Consumer-Directed Broadcast Advertisements; Availability, 62 Fed. Reg. 43,171, 43,172 (1997) (“This draft guidance is intended to provide consumers with adequate communication of required risk information, while facilitating the process used by sponsors to advertise their products to consumers.”). The FDA recently finalized the draft guidance, with minor changes. See *Guidance for Industry on Consumer-Directed Advertisements; Availability*, 64 Fed. Reg. 43,197 (1999). For a thorough discussion of this development, see Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141 (1997).

10. See Charles Marwick, *Drug Safety Takes Cooperation*, 282 JAMA 315, 316 (1999) (noting that direct-to-consumer advertising of prescription drugs has accelerated widespread use of drugs, especially new ones); see also Thomas M. Burton & Yumiko Ono, *Campaign for Prozac Targets Consumers*, WALL ST. J., July 1, 1997, at B1 (reporting that consumer demand for certain types of drugs, such as obesity treatments, Viagra for erectile dysfunction, anti-depressants, hair growth drugs, and certain allergy medications has increased dramatically); *Viagra by the Numbers*, HEALTH ADVOC., Summer 1999, at 8 (noting that physicians wrote 598,000 prescriptions for Viagra in the first month of its marketing although the manufacturer tested the drug on only approximately 3000 men during clinical trials).

11. See Tanouye, *supra* note 9, at A1 (stating that consumer demand for drugs such as

approval monitoring for adverse drug reactions will continue to grow.

Drug safety monitoring is, by necessity, a cooperative venture among the FDA, pharmaceutical manufacturers, physicians, and patients. Even so, many physicians and members of the general public have begun to question why the FDA failed to detect some of these recent problems before approving the drugs for marketing.¹² Critics also suggest that the FDA's traditional emphasis on pre-approval review comes at the expense of adequate post-approval surveillance. Each year, the FDA receives approximately 230,000 reports of possible adverse drug reactions, and approximately ten percent of these reports raise concerns about serious reactions that pre-approval clinical trials failed to detect.¹³ Yet the FDA only devotes the equivalent of fifty-five full-time employees to post-approval surveillance, as compared with over 1700 full-time equivalents engaged in pre-market review of new drug applications.¹⁴ Moreover, only a small percentage of those employees responsible for post-approval review have advanced degrees in a specialty relevant to the surveillance of pharmaceutical products, such as epidemiology or biostatistics.¹⁵

Another recent development may magnify the drug surveillance problem. Even if this allocation of scarce regulatory resources worked rela-

Viagra and Claritin caused drug sales to rise 16.6% in 1998, an increase that was more than four times that of overall health care spending); *see also* *Americans Hooked on Prescriptions?*, ATLANTA J. & CONST., Aug. 30, 1999, at 12A (predicting that an estimated three billion prescriptions will be filled in 1999, an increase of 9% over 1998).

12. *See* Denise Grady, *In a Survey, the F.D.A. is Accused of Hasty Approval of Drugs*, N.Y. TIMES, Dec. 3, 1998, at A25 (describing a survey of FDA-employed physicians who expressed concerns that the agency had succumbed to public interest and industry pressures to approve new drugs too quickly and/or inappropriately); Gina Kolata, *The F.D.A. Approves a Drug: Then What?*, N.Y. TIMES, Oct. 7, 1997, at F1 (noting criticism of the reporting system from a leading epidemiologist who suggested that, although reports from physicians are the leading means for informing the FDA about drug reactions, "most doctors don't know the system exists"); *see also* Teresa Moran Schwartz, *Punitive Damages and Regulated Products*, 42 AM. U. L. REV. 1335, 1347-52 (1993) (describing how the FDA approved a number of dangerous prescription drug products for marketing, and criticizing the FDA's licensing process for drugs).

13. *See* CENTER FOR DRUG EVALUATION & RESEARCH, U.S. DEP'T OF HEALTH & HUMAN SERVS., 1998 REPORT TO THE NATION 22 (1998) [hereinafter CDER REPORT TO THE NATION], available in <<http://www.fda.gov/cder/reports/rptntn98.pdf>> (noting that in fiscal year 1998, the FDA received approximately 232,470 reports of suspected drug-related adverse events); *see also* Kolata, *supra* note 12, at F8 (describing how the agency responds to reports about serious drug reactions by researching computer databases such as Medicare's patient files to determine whether the reaction is common and by consulting with a private company that tabulates information about drug sales to provide the basis for a frequency analysis).

14. *See* CENTER FOR DRUG EVALUATION & RESEARCH, FDA, FACT BOOK 1997 32 (1997), available in <<http://www.fda.gov/cder/reports/cderfact.pdf>>.

15. *See* Kolata, *supra* note 12, at F8.

tively well in the past, the FDA has responded to pressures from patient advocates and the pharmaceutical industry to accelerate the drug approval process. The new fast-track approval system, combined with new user fees that provide an economic incentive to approve new drugs more quickly, has increased the pressure on an already inadequate adverse drug reaction monitoring system.¹⁶ Although many new drug applications now pass through the FDA review process in significantly less time, and sometimes under relaxed regulatory standards, Congress has not provided for any enhanced post-approval resources to monitor the safety of the rapidly increasing stream of new drugs entering the market.¹⁷

In May 1999, the FDA released a lengthy report on this subject, entitled *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*.¹⁸ In part a response to widespread criticisms prompted by the FDA's recent string of highly publicized drug withdrawals, the report includes a detailed audit of the agency's performance in monitoring spontaneous reports of adverse product events. Although a fuller discussion of its findings will appear later in this Article, the report generally paints a favorable picture of the FDA's performance. It suggests moderate reforms, asks Congress for additional resources, and implores health professionals and pharmaceutical manufacturers to take their obligations to patients seriously.¹⁹ The FDA makes important concessions in the report about weaknesses in the post-approval reporting system, but its overall message appears designed to reassure.

This Article suggests a less optimistic vision of the status quo. Part I evaluates the pre-approval and post-approval regulatory framework governing prescription drugs, and the FDA's spontaneous reporting system for adverse events, as it contrasts that system with the regulatory mechanisms used to monitor risks associated with other products. Part II summarizes the recent series of prescription drug marketing withdrawals

16. FDA scientists recently concluded that the shortened review times could not account for the removal of five prescription drugs from the market during a 12-month period and that the FDA's pre- and post-approval drug review procedures currently are adequate. See Michael A. Friedman et al., *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There is a Problem?*, 281 JAMA 1728, 1728, 1730, 1733-34 (1999). Although the authors may be correct in their assertion that this particular cluster of drug withdrawals is unrelated to accelerated review procedures, this does not prove the obverse assertion—that the post-approval monitoring procedures adequately address problems of unexpected adverse drug reactions.

17. See *infra* Part I.B.3.

18. FDA U.S. DEP'T OF HEALTH & HUMAN SERVS., *MANAGING THE RISKS FROM MEDICAL PRODUCT USE: CREATING A RISK MANAGEMENT FRAMEWORK*, available in <<http://www.fda.gov/oc/tfirm/1999report.html>> [hereinafter RISK MANAGEMENT FRAMEWORK].

19. See *id.* at 12-15, 22, 53, 67.

prompted by reports of unexpected adverse reactions. Finally, Part III offers some possible solutions designed to improve the efficiency of post-approval surveillance so that fewer patients will suffer the consequences of unexpected adverse drug reactions and interactions. This Article concludes that the existing regulatory system requires fundamental reprioritization and more substantial structural reforms in order to avoid a troubling replay of recent prescription drug withdrawals. The proposed reforms may help to enhance a physician's ability to provide quality patient care based on optimal knowledge of the safety and efficacy of pharmaceutical products.

I. THE REGULATORY FRAMEWORK

When filing a new drug application (NDA) with the FDA, the sponsor must submit evidence of the new drug's safety and effectiveness. The NDA must include all known information about the drug, including evidence from animal studies and human clinical trials about safety risks or ineffectiveness. The FDA then directs one of its advisory committees to consider the application and to recommend approval or disapproval of the NDA based on the committee's assessment of the drug's safety and effectiveness. This evaluation calls for a weighing of the risks and benefits of use. Once an approved drug becomes available on the market, the sponsor must submit reports of any adverse events associated with the drug and may be required to make labeling changes to reflect new risk information.

Drugs may cause unwanted side effects in patients for a variety of reasons. Obviously, potent therapeutic agents entail some intrinsic risks. In addition, a drug may interact in an unforeseen way with another drug taken by a patient, or it may cause a reaction due to some particular sensitivity of the patient. Patients may also, because of a medication error, receive either the wrong drug or an improper dosage of the correct drug, and either event may result in unforeseen side effects.²⁰ Adverse effects also arise with the use of other therapeutic interventions, such as medical devices, or from ordinary consumer products, such as foods and cosmetics. Although this Article draws brief comparisons to the safety monitoring systems for several other classes of products, it focuses on prescription drugs.

Pharmaceutical products may cause undesirable side effects for a vari-

20. See Ashish K. Jha et al., *Identifying Adverse Drug Events: Development of a Computer-based Monitor and Comparison with Chart Review and Stimulated Voluntary Report*, 5 J. AM. MED. INFORMATICS ASS'N 305, 306-07 (1998) (describing methods for detecting preventable adverse drug events, including medication errors).

ety of reasons, but not all of these effects qualify as adverse reactions. The World Health Organization defines an "adverse drug reaction" (ADR) as "an effect which is noxious and unintended, and which occurs at doses used in many for prophylaxis, diagnosis, or therapy."²¹ This definition excludes prescribing and dispensing errors and overdoses. The more inclusive term "adverse drug event" (ADE) refers to "an injury resulting from medical intervention related to a drug," including unpredictable side effects of drugs (such as a skin rash or anaphalaxis), foreseeable side effects such as nausea with chemotherapy, and unwanted effects resulting from errors in prescribing, dispensing, or administering drugs.²² This Article focuses on the narrower category of adverse drug reactions, and particularly on previously unknown ADRs associated with new drugs.

All prescription drugs have side effects.²³ Most of the time, the therapeutic benefits of a drug outweigh its potential detrimental effects. This risk-benefit calculus constitutes a fundamental part of the overall decision about whether to permit the marketing of a new drug. Once a drug becomes available for sale, the health care provider makes an assessment about the likely usefulness of the drug for the particular patient, including a determination of whether the drug might be contraindicated for use in that patient due to some other health problem. In addition, the health care provider attempts to determine whether the drug may interact with other drugs that the patient is taking. Much of the prescribing decision is based on a combination of trust in the rigor of the pre-approval process and the physician's understanding of the drug's safety and effectiveness

21. See *id.* at 306.

22. See *id.*; see also Lazarou et al., *supra* note 4, at 1200 (describing the definitions of "adverse drug event" and "adverse drug reaction," and choosing to focus on ADRs in order to exclude from consideration injuries caused by drugs that were improperly prescribed or administered). The FDA defines an adverse drug experience as:

Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

21 C.F.R. § 314.80(a)(1999).

23. Cf. 21 U.S.C. § 353(b)(1)(1994) (providing that a drug which, "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such a drug . . . shall be dispensed only" by prescription); ALFRED G. GILMAN ET AL., *GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS* 1083 (8th ed. 1990) (describing anaphylactic reactions to penicillin that occur in approximately 300 people—0.001% of treated patients—each year).

based on clinical experience and on the relevant medical literature.²⁴

A. Pre-approval Process

Tremendous effort goes into the preparation and review of applications for the approval of new drugs in this country. Pharmaceutical manufacturers may spend up to \$500 million to develop a new drug, with human clinical trials accounting for at least thirty percent of the total research budget.²⁵ After investing a substantial amount of time and resources in animal studies and other preliminary data gathering, a pharmaceutical company must see the drug through controlled clinical trials as required by the FDA's new drug approval process. The development process for a new drug takes an average of 14.7 years, from the early research and pre-clinical trials through the multi-stage clinical trials process and FDA approval of the NDA.²⁶ The following section briefly describes the NDA procedure along with some of the recent amendments to the FDA's enabling statute that permit accelerated new drug approval under certain circumstances.

1. Basic Licensing Requirements

Beginning in 1938, the FDA's governing statute has required that the agency review all "new drugs" for safety prior to marketing.²⁷ Under the original provision, applications for approval to market new drugs auto-

24. See Lars Noah, *Sanctifying Scientific Peer Review: Publication as a Proxy for Regulatory Decisionmaking*, 59 U. PITT. L. REV. 677, 695 n.77, 704 n.117 (1998). In a sense, the FDA's formal system of monitoring and reporting is supplemented by an informal discourse within the medical community about the apparent side effects associated with newly-marketed drugs. See, e.g., *Sildenafil in the Treatment of Erectile Dysfunction*, 339 NEW ENG. J. MED. 699, 699-702 (1998) (series of letters to the editor from physicians discussing early clinical experience with Viagra).

25. See Robert Langreth, *Recall of a Popular Roche Drug Raises Questions on Testing, Approval Process*, WALL ST. J., June 10, 1998, at B16; see also Robert Langreth, *Drug Marketing Drives Many Clinical Trials*, WALL ST. J., Nov. 16, 1998, at A10 (reporting that clinical-trial costs increased to \$7 billion, or almost 40% of the annual U.S. industry research budget). In 1998, analysts estimated that drug companies would spend approximately \$21 billion on research and development costs and would earn approximately \$100 billion at the retail level. See Tanouye, *supra* note 9, at A1.

26. See Richard J. Findlay, *Originator Drug Development*, 54 FOOD & DRUG L.J. 227, 227-28 (1999) (describing the new drug development process, and providing a timeline depicting the length of the various development stages).

27. The Food, Drug, and Cosmetic Act (FD&C Act) defined a "new drug" as "[a]ny drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." Pub. L. No. 75-717, ch. 675, § 201(p)(1), 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 321(p)(1) (1994)).

matically went into effect after sixty days, unless the FDA extended the review period and notified the applicant.²⁸ In 1962, Congress amended the original Act to create a pre-approval system for new chemical entities under which the NDA sponsor must prove the new drug's safety and effectiveness for its intended use prior to marketing.²⁹ Most importantly, the 1962 Amendments require that the manufacturers prove the safety and effectiveness of a drug by "substantial evidence," defined in the statute as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified . . . to evaluate the effectiveness of the drug involved."³⁰

New drugs typically must pass through several phases of development and testing in order to satisfy the NDA requirements. First, the sponsor must perform a variety of pre-clinical tests to evaluate the drug's toxicity and pharmacokinetic properties. Once the sponsor has gathered this preliminary data, it can apply for investigational new drug (IND) designation,³¹ which allows the sponsor to begin clinical trials.³² The sponsor must conduct three phases of pre-approval clinical trials in order to satisfy the NDA requirements. During Phase I, the sponsor tests the drug for safety in humans with an emphasis on determining the pharmacological action of the drug. If a new chemical entity passes this initial hurdle, Phase II trials study the drug in patients with the relevant disease in or-

28. See *id.* § 505(c), 52 Stat. at 1052; see also David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 LAW & CONTEMP. PROBS. 2, 40 n.232 (1939).

29. See Drug Amendments of 1962, Pub. L. No. 87-781, § 102(d), 76 Stat. 780, 781 (codified as amended in scattered sections of 21 U.S.C.). Congress passed the 1962 Amendments in response to the Thalidomide tragedy of the early 1960s. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 191 n.45, 192 (1971). The FDA also subjected drugs first marketed prior to 1962 to a complex retrospective review procedure as a prerequisite for continued marketing. This brief summary of the law governing the new drug approval process focuses on the law applicable to drugs that are new to the market; it does not include a discussion of the law governing the continued marketing or safety monitoring of drugs first introduced prior to 1962. For a detailed discussion of how the current new drug approval process evolved from earlier approaches, see Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1761-76 (1996).

30. 21 U.S.C. § 355(d) (1994). Adequate and well-controlled studies generally must include independent, double-blind clinical trials. See 21 C.F.R. § 314.126(b)(2)(i) (1999) ("A placebo-controlled study . . . usually includes randomization and blinding of patients or investigators, or both.").

31. See 21 C.F.R. § 312.23 (providing the IND application content and format). The IND application must contain, among other things, all information about the drug's safety and effectiveness based on animal studies and trials or marketing experience in other countries. See *id.* § 312.23(a)(3)-(5).

32. See Findlay, *supra* note 26, at 227 (describing the early drug research process).

der to identify the lowest effective doses that will produce the desired result. Finally, Phase III trials study the drug's efficacy and side effects in a larger study population, typically from several hundred to several thousand subjects. The information derived from Phase III studies provides the basis for FDA reviewers to evaluate the risk-benefit ratio for the drug.³³ In performing the risk-benefit calculus, the FDA recognizes that even efficacious and relatively safe drugs carry the risk of side effects for some patients, but that a small overall risk may be justified if the new drug promises significant potential benefits to the targeted class of patients.³⁴

2. *Inherent Limitations*

The FDA acknowledges that pre-marketing human clinical studies have inherent limitations. Their relatively short duration, narrow subject population, and small size, among other things, limit the ability of these studies to uncover rare or delayed adverse reactions or drug interactions.³⁵ "It is simply not possible to identify all the side effects of drugs before they are marketed. The difficulty is not a failure of the . . . drug approval process; it is the expected consequence of the biologic diversity

33. See 21 C.F.R. § 312.21 (describing clinical trials phases); see also Findlay, *supra* note 26, at 227-28 (describing the clinical trials phases and providing estimates for the length of time typically required to complete each phase).

34. See Peter Huber, *Safety and the Second Best: The Hazards of Public Risk Management in the Courts*, 85 COLUM. L. REV. 277, 304-05 (1985) (discussing how the overall benefits from a drug outweigh the drug's small risks because the alternative of keeping the drug off the market will harm a greater number of patients).

35. See FDA, *The Clinical Impact of Adverse Event Reporting* (visited Feb. 21, 2000) <<http://www.fda.gov/medwatch/articles/medcont/postmkt.htm>> [hereinafter *Medwatch Postmarketing Surveillance*] (describing the "intrinsic limitations to pre-marketing human clinical trials with respect to their ability to detect adverse events"). The typical pre-approval clinical trial by definition cannot detect delayed or long latency adverse reactions. See, e.g., Arthur L. Herbst et al., *Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women*, 284 NEW ENG. J. MED. 878, 880 (1971) (describing the latent effect of DES on the daughters of women who took the drug while pregnant, and speculating that more tumors may occur in the exposed population as it matures). Some drug manufacturers choose to engage in additional pre- and post-marketing human trials in order to gain FDA approval of new uses to make favorable claims about the relative efficacy of the newly-approved drug compared to others available in its class. See Langreth, *supra* note 25, at A10. Although the number of these kinds of trials appears to be growing, such trials focus on efficacy rather than safety, see Joseph A. DiMasi et al., *New Indications for Already Approved Drugs: An Analysis of Regulatory Review Times*, 31 J. CLIN. PHARMACOL. 205, 205 (1991) (explaining that "extensive toxicity and safety evaluation would generally not be required for supplemental indication reviews"), and the trend does not appear to have contributed to an improved safety record for new pharmaceutical products.

of humans”³⁶ The FDA’s regulations classify side effects as “rare” if they occur at a frequency of less than 1-in-1000.³⁷ According to the FDA’s statistics, in order to have a ninety-five percent chance of detecting an adverse reaction with an incidence of 1-in-1000, a study must enroll at least 3000 patients. Because clinical trials typically involve no more than 3000 to 4000 individuals prior to marketing, the studies will only detect adverse reactions that occur at a rate of 1-in-1000 or higher.³⁸

In contrast, post-approval monitoring detects problems that do not arise in the carefully controlled environment of pre-market clinical trials. Once a drug becomes available for general use, a wide variety of patients with varying health conditions may take the drug, often in combination with other prescriptions. In particular, post-approval (Phase IV) studies can be useful for a variety of purposes, including (1) identifying and adjusting optimal dosage for the drug product; (2) confirming the safety of the product and identifying new risks; (3) evaluating the product’s safety and efficacy in special populations such as pediatric or elderly patients; and (4) discovering new uses for the product.³⁹

In many instances, these studies may provide the first point at which health care providers, manufacturers, and the FDA can gather meaningful information about potential drug safety problems in large patient populations.⁴⁰ The problem of drug interactions, along with other con-

36. Alastair J.J. Wood et al., *Making Medicines Safer—The Need for an Independent Drug Safety Board*, 339 NEW ENG. J. MED. 1851, 1852 (1998).

37. See 21 C.F.R. § 201.57(g)(2) (1999). The FDA has, on occasion, taken regulatory action in response to adverse reactions occurring at a frequency of less than 1 in 1000. For example, the agency has determined that toxic shock syndrome (TSS) associated with tampon use occurs at the rate of approximately 1 in 10,000 tampon users annually. See *Menstrual Tampons*; User Labeling, 47 Fed. Reg. 26,982 (1982). Though a TSS reaction is “rare” by FDA standards, the agency requires consumer warnings about the risks. See 21 C.F.R. § 801.430(c)-(d) (1999) (providing for tampon package warnings).

38. See *id.*; see also American Med. Ass’n, *Reporting Adverse Drug and Medical Device Events: Report of the AMA’s Council on Ethical and Judicial Affairs*, 49 FOOD & DRUG L.J. 359, 360 (1994) (noting that, “in order to detect the difference between an adverse reaction incidence rate of 1/5000 and 1/10,000, approximately 306,000 patients would have to be observed,” and emphasizing the importance of spontaneous adverse reporting by physicians); RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 43 (describing the International Conference for Harmonization (ICH) recommendation of a baseline patient sample size of 1500 participants studied over a six-month period to identify adverse reactions that occur at a level of one percent).

39. See Raymond Woosley, *Opportunities in Phase IV to Improve Drug Development*, 52 FOOD & DRUG L.J. 185, 185 (1997). It is unclear whether the FDA has the authority to require Phase IV studies from sponsors as a condition of NDA approval. The agency asserts such authority, however, with regard to drugs on the market without an approved NDA. See 21 C.F.R. § 310.303(b).

40. See *New Drug and Antibiotic Regulations*, 50 Fed. Reg. 7452, 7471 (1985) (“The

founding variables such as patient lifestyle habits (e.g., alcohol use and smoking) or multiple disease conditions, also becomes much more pronounced and traceable once a drug is generally marketed or studied formally in large Phase IV trials. As a bonus, such improved monitoring might also help to uncover what might be called “beneficial drug reactions”—previously unknown beneficial uses of prescription drugs that clinicians discover serendipitously.⁴¹

Wholly apart from the problems associated with small numbers of enrollees, pre-approval clinical trials have historically enrolled unrepresentative samples of patient populations. Researchers traditionally excluded—or included only in very limited numbers—women, minorities, children, and the elderly in clinical studies of new drugs.⁴² Although the FDA now recognizes this limitation and encourages greater diversity in clinical trial subjects,⁴³ the overall numbers of subjects enrolled in a study have not increased. Indeed, with this fractionalization, infrequent ADRs that do not arise with the same frequency in minority or vulnerable populations will prove even more elusive and difficult to predict or detect for any group of patients.⁴⁴

Thus, the product’s labeling at the time of marketing approval only

much larger patient population and longer period of use associated with the marketing of a drug provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects, some of which may be serious.”).

41. See Gina Kolata, *Drugs that Deliver More than Originally Promised*, N.Y. TIMES, Apr. 5, 1998, § 4, at 3; *Use of Approved Drugs for Unlabeled Indications*, FDA DRUG BUL., Apr. 1982, at 4-6. For example, the drug minoxidil was originally indicated for use in treating certain heart conditions; patients then realized that the drug had the additional effect of inhibiting hair loss. See *id.* The drug is now marketed for hair loss prevention under the brand name Rogaine. See Gina Kolata, *Hair-Growth Drug Approved, the First Cleared in the U.S.*, N.Y. TIMES, Aug. 18, 1988, at A1.

42. See Barbara A. Noah, *Racial Disparities in the Delivery of Health Care*, 35 SAN DIEGO L. REV. 135, 152-54 (1998) (describing the difficulties of extrapolating information about a drug’s safety for the population at-large from data derived from white males).

43. See, e.g., CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDELINE FOR INDUSTRY, STUDIES IN SUPPORT OF SPECIAL POPULATIONS: GERIATRICS 3 (1994); CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. DEP’T OF HEALTH & HUMAN SERVS., GUIDELINE FOR THE STUDY OF DRUGS LIKELY TO BE USED IN THE ELDERLY 6-7 (1989); FDA, *Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (Docket No. 93D-0236) (1993), available in <<http://www.nih.gov/grants/oprr/humansubjects/guidance/58fr39406.htm>>; Robert Pear, *President to Order Drug Makers to Conduct Pediatric Studies*, N.Y. TIMES, Aug. 13, 1997, at A17 (noting that only 42% of drugs routinely used in treating children have been studied in pediatric trials).

44. In other words, a clinical trial that studies 3000 white males will detect more infrequent ADRs in this relatively large and homogenous group. By comparison, a study that consists of 1800 white males, 900 white females, 200 African-American males, and 100 African-American females will generate far less sensitive results for infrequent ADRs within each subgroup.

represents what is known about the drug's risks and side effects based on the narrow parameters of relatively small clinical trials.⁴⁵ The FDA, industry, and health care providers obviously must monitor new drugs carefully and track adverse events associated with these drugs once they become generally available. As experience accumulates, the FDA may demand labeling revisions to reflect newly-discovered side effects or interactions with other prescription or nonprescription drugs, including disclosure of side effects occurring at much lower frequencies.⁴⁶ Although the American public predictably recoils at any suggestion that patients continue to act as "guinea pigs" after new drug approval, real world use by a large and diverse patient population over a longer period of time provides the only true test of a drug's safety.⁴⁷

3. Recent Developments

Several relatively recent revisions to the FDA's regulations and enabling statute now allow for the accelerated review of NDAs under certain circumstances. In 1996 and 1997, the agency approved ninety-two new drugs, almost double the number of approvals in the previous year.⁴⁸ During 1998 and 1999, five prescription drugs were removed from the market, a record number for this short period of time, and critics blame the accelerated review process for creating this consumer hazard.⁴⁹ The mechanisms described below that accelerate the pre-approval process increase the rate at which new drugs enter the market each year and, there-

45. See *Medwatch Postmarketing Surveillance*, *supra* note 35, at 1-2; see also Annetine C. Gelijns et al., *Capturing the Unexpected Benefits of Medical Research*, 339 NEW ENG. J. MED. 693, 693-98 (1998) ("The end of the research-and-development process does not entail the elimination of all, or even most, of the uncertainties surrounding medical innovation.").

46. See Lars Noah, *The Imperative to Warn: Disentangling the "Right to Know" from the "Need to Know" About Consumer Product Hazards*, 11 YALE J. ON REG. 293, 327-30 (1994).

47. According to a General Accounting Office (GAO) report, approximately half of the 198 drugs approved by the FDA between 1976 and 1985 were accompanied by the discovery of serious post-approval risks, based on labeling changes. Yet, all but six of the drugs were still on the market in 1989 because of the FDA's determination that the drugs' benefits continued to outweigh their risks. See FDA DRUG REVIEW, *supra* note 3, at 3.

48. See Wood et al., *supra* note 36, at 1851.

49. See John Schwartz, *Is FDA Too Quick to Clear Drugs?*, WASH. POST, Mar. 23, 1999, at A1. The FDA responded to this concern by pointing out that it has not lowered its safety standards, adding that it is impossible to eliminate the risks associated with prescription drugs. See *id.* Another commentator, who directs the Tufts University Center for the Study of Drug Development, has noted that the number of drugs recalled recently is consistent with the historic two to three percent withdrawal rate for new drugs. See *id.* at A8.

fore, provide patients and their physicians with an increased number of treatment options. At the same time, however, the post-approval safety monitoring system attempts to capture and respond to the increased number of reports of adverse reactions associated with these new drugs. Therefore, some of the recent revisions to the new drug approval process may exacerbate the existing problems associated with detecting adverse reactions and interactions unintentionally. Although statutory changes have improved the efficiency of the NDA process, these accelerated review procedures and incentives place an increased burden on the FDA's post-approval safety review mechanisms that the agency may not be equipped to handle.

First, in 1988, the FDA promulgated regulations to establish an expedited new drug approval process for certain types of drug therapies.⁵⁰ Under these procedures, new drugs intended to treat life-threatening and seriously debilitating illnesses (such as AIDS and cancer) may receive provisional marketing approval with a weaker body of evidence demonstrating effectiveness than normally required in the NDA process.⁵¹ Under this expedited approval system, qualifying drugs may reach the market after two, instead of three, phases of human clinical trials;⁵² although the FDA can demand post-approval studies to discover additional information about the drug's safety and optimal use.⁵³ This approach represents a willingness to accept less data demonstrating effectiveness in circumstances where patients desperately need new alternative therapies to survive. The FDA focuses primarily on ensuring safety with the hope that the drugs will prove efficacious as well. Foregoing Phase III trials, however, reduces the quantum of safety data. Phase III trials perform an essential function by enrolling the largest numbers of patients, and studying both efficacy and safety. Accordingly, these studies typically provide valuable safety data on new drugs.⁵⁴

In 1992, the FDA promulgated regulations that allowed for the accelerated approval of drugs to treat serious or life-threatening illnesses "that provide meaningful therapeutic benefit to patients over existing treatments."⁵⁵ The FDA permits the use of "surrogate marker evidence"

50. See Investigational New Drug Application, 53 Fed. Reg. 41,516, 41,523-24 (1998) (codified at 21 C.F.R. pt. 312(E) (1999)).

51. See 21 C.F.R. § 312.80 (1999) (noting that accelerated review is especially appropriate where "no satisfactory alternative therapy exists").

52. See *id.* § 312.82.

53. See *id.* § 312.85.

54. See *id.* § 312.21.

55. Applications for FDA Approval to Market a New Drug, 57 Fed. Reg. 58,942, 58,958 (1992) (codified at 21 C.F.R. pts. 314 & 601 (1999)).

for these drugs during Phase III trials.⁵⁶ The agency predicates its willingness to relax its scientific evidence requirements in these cases on, among other things, a requirement that the sponsor conducts post-approval studies relating the surrogate markers to clinical endpoints.⁵⁷ Manufacturers must conduct these studies with "due diligence" and use the data obtained to: (1) verify the drug's clinical benefit; (2) describe in greater detail the relationship between the surrogate endpoint and the intended benefit; or (3) simply explain how the intended clinical benefit, if achieved, affects long-term patient outcomes.⁵⁸ In 1997, Congress belatedly authorized these "fast-track" procedures.⁵⁹ These procedures, like the expedited approval regulations described above, could increase the likelihood of errors or omissions in the pre-approval process. The requirement for structured post-approval trials, however, creates an additional safeguard over the traditional NDA approval model.

Congress also has altered the relative allocation of resources to the drug approval process in ways that may burden the FDA's post-approval monitoring system. Under the Prescription Drug User Fee Act of 1992 (PDUFA),⁶⁰ NDA sponsors pay a substantial user fee.⁶¹ In exchange for the authority to collect user fees, the agency agreed to spend user fee

56. See *id.* at 58,943-44 (responding to comments, and noting that "approval based on surrogate endpoints is not new, although the issue has not previously been considered in regulations"). The term "surrogate marker" refers to a clinical indicator, such as CD4 cell counts in AIDS patients, that can be used to predict the overall effectiveness of a given drug therapy for a targeted condition. See 21 C.F.R. §§ 314.510, 601.41 (1999).

57. See 21 C.F.R. § 314.510 (describing approval based on adequate and well-controlled clinical trials "establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely . . . to predict clinical benefit"); see also Larry R. Versteegh, *Science and Regulatory Rituals Associated with the Drug Development Process*, 52 FOOD & DRUG L.J. 155, 157 (1997) (explaining how surrogate markers affect the tradeoff between safety and drug availability). This process has accelerated the number of drug approvals and, consequently, benefited patients who suffer from the AIDS virus as well as some cancers. See Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 115 (1999) (citing the fast-track approval of the protease inhibitor ritonavir, which took approximately 10 weeks after the NDA application date).

58. See 21 C.F.R. § 314.510 (1999).

59. See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 112, 111 Stat. 2296, 2309-10 (codified at 21 U.S.C. § 356 (Supp. III 1997)).

60. Pub. L. No. 102-571, 106 Stat. 4491 (1992) (codified as amended at 21 U.S.C. §§ 379g-h (1994 & Supp. III 1997)).

61. PDUFA created a fee schedule based on the amount of FDA resources required to review various types of marketing applications, and it provided for inflation-based increases in the fees throughout the five-year period in which the fee system was initially in effect. See 21 U.S.C. § 379h (Supp. III 1997). In the first five years, the FDA expected to receive over \$325 million in user fees. See John Henkel, *User Fees to Fund Faster Reviews*, FDA CONSUMER, Oct. 1993, at 19, 19-20.

proceeds on hiring and training new personnel to participate in the NDA review process.⁶² They also informally promised to reduce significantly the NDA processing time.⁶³ In fact, the FDA has employed more than 240 new reviewers and completes reviews of standard NDAs within twelve months.⁶⁴ Interestingly, the statute prevents the FDA from diverting any of these user fees to handle the increasing load of post-approval reports generated by this accelerated pace of NDA review.⁶⁵ Adding to these concerns, the Food and Drug Administration Modernization Act of 1997 (FDAMA),⁶⁶ which reauthorized PDUFA, relaxed the "substantial evidence" standard.⁶⁷ NDA sponsors can now submit one instead of two adequate and well-controlled clinical trials.⁶⁸ This may translate into the enrollment of fewer total patients as subjects. Thus, these pre-approval studies may become even less likely to uncover low

62. The agreement to direct the user fee proceeds toward accelerating the new drug approval process represented a hard-fought compromise between the FDA and the pharmaceutical industry. At first, the industry opposed user fees, and the agency feared that a fee arrangement would make it "beholden" to the industry. Eventually, the FDA and the industry supported the user fee scheme on the condition that the proceeds supplement existing agency resources for NDA reviews. See Bruce N. Kuhlik, *Industry Funding of Improvements to the FDA's New Drug Approval Process: The Prescription Drug User Fee Act of 1992*, 47 FOOD & DRUG L.J. 483, 485 n.12, 486-91 (1992) (describing the history of the user fee proposals).

63. See Merrill, *supra* note 29, at 1795. Since the enactment of PDUFA, the average time from submission to approval of new drug applications has dropped from approximately 30 months to 12 months. See RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 17.

64. See Merrill, *supra* note 29, at 1840. With PDUFA in place, the FDA now approves 40% more new drugs each year, an increase from an average of 70 to 97 approvals annually. See RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 17. Although the user fee amendments expired in October 1997, Congress extended the fee system for five more years. See Food and Drug Administration Modernization Act, Pub. L. No. 105-115, § 103(a)(1), 111 Stat. 2296, 2299-2304 (1997).

65. See 21 U.S.C. § 379h(g)(2)(B) (Supp. III 1997); see also Kuhlik, *supra* note 62, at 499-500.

66. Pub. L. No. 105-115, 111 Stat. 2296 (codified in scattered sections of 21 U.S.C.).

67. See *id.* § 115(a), 111 Stat. at 2313 (codified at 21 U.S.C. § 355(d) (Supp. III 1997)); see also Jennifer Kulynych, *Will FDA Relinquish the "Gold Standard" for New Drug Approval? Redefining "Substantial Evidence" in the FDA Modernization Act of 1997*, 54 FOOD & DRUG L.J. 127, 146 (1999) (noting that section 115 of FDAMA uses permissive rather than presumptive or mandatory language to revise the standard, and stating that pharmaceutical manufacturers may establish substantial evidence of effectiveness with data from one adequate and well-controlled clinical study if the FDA determines that such data are sufficient).

68. See 21 U.S.C. § 355(d) (Supp. III 1997) ("If the Secretary determines, based on relevant science, that the data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence . . .").

frequency or longer latency ADRs.

For years, critics blamed the FDA's lengthy pre-approval process for creating a "drug lag" that delayed drugs approved in Europe from reaching the American market.⁶⁹ This lag in approval time, however, created an unintended safety benefit because applicants must provide any available foreign marketing data with a NDA.⁷⁰ Consequently, the agency received a greater quantum of data on which to base its review, rather than relying solely on pre-approval clinical trials.⁷¹ In the case of thalidomide, at least, the "lag" meant that the drug's terrible side effects became apparent prior to approval for marketing in the United States.⁷²

The speedier review system has the benefit of making innovative new drugs available to the consumer more quickly,⁷³ but it may increase the odds that the NDA process will fail to detect dangers associated with new drugs.⁷⁴ In general, the FDA has not relaxed its standards for proof of safety and effectiveness, except in the limited fashion described above. In fact, the FDA has asserted that, since implementation of PDUFA and the accompanying acceleration of the NDA approval process, the rate of serious, unanticipated ADRs has actually decreased.⁷⁵ The debate over

69. See William M. Wardell, *A Close Inspection of the "Calm Look": Rhetorical Amnesia and Selective Amnesia at the Food and Drug Administration*, 239 JAMA 2004, 2004-05 (1978) (criticizing the FDA's position on the drug lag and parodying the Commissioner's position as follows: "The drug lag does not exist; nevertheless I will abolish it"); see also Kenneth I. Kaitin et al., *The Drug Lag: An Update of New Drug Introductions in the United States and in the United Kingdom, 1977 Through 1987*, 46 CLIN. PHARMACOLOGY & THERAPEUTICS 121, 133 (1989).

70. See 21 C.F.R. § 314.50(c)(2)(ii) (1999).

71. According to one FDA expert, the number of new drugs marketed first in the United States (rather than in a foreign market) has risen from approximately 3% in the early 1980s to 60% in 1998. See Friedman et al., *supra* note 16, at 1732.

72. See PETER BARTON HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW* 478, 582 (2d ed. 1991) (describing the Thalidomide tragedy); Morton Mintz, *The Cure That Could Kill You; FDA Reforms Are Bad Medicine*, WASH. POST, July 14, 1996, at C1 (describing how the FDA's delay in approving Thalidomide for use in the United States prevented thousands of profound birth defects). *But cf.* Wardell, *supra* note 69, at 2005 (describing and criticizing another commentator's claim that the "drug lag" benefits and protects patients).

73. See Salbu, *supra* note 57, at 119-20 (noting FDA claims that PDUFA has enabled the agency to "reduce to 15 months the 30-month average time . . . [previously] required for a drug review").

74. See Schwartz, *supra* note 49, at A1 (describing consumer advocates' concerns that the FDA "has become too cozy with the pharmaceutical industry and too lax," and discussing experts' concerns that increasing approval rates might mean that "more problems are bound to make it onto the market").

75. See RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 35. The FDA compared data from a 1990 GAO report that tracked serious adverse reactions during the postmarketing period for drugs that were approved between 1976 and 1985. The GAO

the tradeoff between lengthy scrutiny of NDAs and the consequent delay in market availability is not a new one,⁷⁶ but these recent statutory changes increase the frequency with which new drugs reach the market after shorter review periods, and with lower levels of foreign marketing data or reduced data from clinical trials.

A number of FDA employees involved with the NDA process have recognized the gravity of the hazard that these changes to the approval process pose, as well as the weaknesses inherent in the traditional model for evaluating new drugs. In a few cases, particular reviewers have vocally opposed approvals that later came back to haunt the agency.⁷⁷ In fact, several scientists have chosen to leave the FDA rather than continue to participate in what they regard as a sloppy approval process.⁷⁸ This intra-agency dissension reflects the broader conflict between concerns about drug safety and drug availability that have always existed and will probably never fully be resolved. The FDA has, however, recently paid renewed attention to the back end of the approval process. They have begun to work towards creating new systems to manage the risks associated with drug products at various stages of development and marketing.⁷⁹

B. Post-approval Requirements

The FDA has created a system of mandatory manufacturer ADR reporting, coupled with voluntary health care professional reporting, to monitor the safety of new prescription drug products once they enter the market. The agency's post-approval risk monitoring programs attempt

defined "serious," for purposes of the report, as adverse reactions that resulted in: (1) withdrawal of the drug; (2) new warnings; (3) significant labeling changes; or (4) issuance of a "Dear Healthcare Professional" letter to inform physicians about important new drug safety information and labeling changes. The FDA took similar data for drugs approved under PDUFA during a narrower time period (1994-1997) and concluded that the incentives created by PDUFA did not cause any increase in drug withdrawals or serious adverse reactions. *See id.* at 34-36, app. A. Although there may be methodological flaws associated with the comparison between these two data sets, the FDA appears confident that PDUFA-related acceleration of the NDA approval process has not caused serious safety problems. The agency acknowledges, however, that 30% of new drugs required significant postmarket label changes, which "still raises the question of why these serious risks are not discovered before marketing." *Id.* at 36.

76. *See* HUTT & MERRILL, *supra* note 72, at 580-83 (describing this risk-tradeoff debate in the context of the Drug Amendments of 1962).

77. *See, e.g.,* Schwartz, *supra* note 49, at A8 (describing the FDA lead reviewer's opposition to approval of Rezulin, the agency's decision to remove the reviewer from the committee, and the subsequent safety problems with the drug once it entered the market).

78. *See* Grady, *supra* note 3, at A21.

79. *See* RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 77-82.

to: (1) detect previously unknown adverse reactions associated with a drug product; (2) evaluate in more detail the product's known risks; (3) uncover adverse reactions that arise from product interactions; (4) uncover adverse reactions peculiar to particular segments of the patient population; and (5) attempt to identify causal connections between marketed drug products and patient problems.⁸⁰ The FDA enters information gathered from mandatory and voluntary reporting into a database, and a "postmarketing safety evaluator" processes the information.⁸¹ Based on the apparent gravity of the risk, the FDA may issue a medical alert to health professionals, require labeling changes to reflect new information, require boxed warnings in labeling to emphasize particularly important warnings, or require that the product be withdrawn from the market altogether.⁸²

Given the enormous potential risks posed by new prescription drugs, existing systems for the post-approval surveillance of pharmaceutical products deserve close scrutiny. In contrast to the FDA, which allocates very limited resources to the task of post-approval monitoring,⁸³ many foreign drug approval systems provide significant resources for detecting problems with drugs during the post-approval stage, in recognition of the fact that it often takes widespread use to uncover serious, but less common, problems associated with drug products.⁸⁴ Recently, however, the

80. See *id.* at 52.

81. See John Henkel, *MedWatch: FDA's "Heads Up" on Medical Product Safety*, FDA CONSUMER, Nov.-Dec. 1998, at 11, 15.

82. See *id.* at 15 (describing various examples, including the withdrawal of Redux and Pondimin from the market).

83. See RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 30 ("The majority of FDA program resources are devoted to premarketing scientific risk identification and assessment and approval or nonapproval. Significant, but substantially fewer, resources are devoted to postmarketing surveillance and risk assessment activities."). One commentator has suggested that the FDA's decision to reduce resource-intensive activities, such as inspections of pharmaceutical company facilities, results from the increasing number of ADR reports that the agency now receives. Such reports may allow the FDA to utilize its enforcement resources more efficiently. See Mary Olson, *Substitution in Regulatory Agencies: FDA Enforcement Alternatives*, 12 J.L. ECON. & ORG. 376, 404 (1996).

84. See, e.g., Harvey Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 579 (1985) (describing the "fundamental difference of regulatory philosophy" between the United States and England). The United Kingdom places a heavier emphasis on monitoring post-approval adverse reactions. See *id.* The U.K. "has more readily accommodated to the unpalatable truth that . . . serious, rare side effects will not necessarily manifest themselves until a drug has been used by a far greater proportion of the population than is feasible even with extensive premarket testing." *Id.*; see also Evelynne Friedel & Michael Freundlich, *European Community Harmonization of the Licensing and Manufacturing of Medicinal Products*, 49 FOOD & DRUG L.J. 141, 168-70 (1994) (describing the pharmacovigilance system used by member states of the EC under

FDA has recognized the importance of modernizing the system, in terms of both the scope and coordination of information collection and analysis.⁸⁵ The new Commissioner recently testified at a congressional appropriations hearing about the need for an "integrated system for the reporting, monitoring, and evaluation of all FDA regulated product-related injuries."⁸⁶

1. Regulatory Requirements

The Food, Drug and Cosmetic Act requires the holder of an NDA to report any data relating to clinical experiences with the drug that the FDA decides to require by regulation.⁸⁷ The FDA has only gradually taken up this congressional data collection assignment. It initially promulgated implementing regulations in 1963 to require that companies maintain records and submit annual reports concerning information or developments not previously submitted as part of the NDA or not previously encountered during clinical trials of the drug.⁸⁸ Unless the information suggested an "unexpected" adverse drug experience, which had to be reported to the FDA on an expedited basis, periodic reports only had to include information from clinical and nonclinical experience and

the guidance of the Committee for Proprietary Medicinal Products, and noting that the CPMP is developing procedures to *require* physicians to report serious unanticipated adverse reactions). The rate of spontaneous reporting in the United States compares unfavorably with that of other countries. The U.S. rate averages about 25% of the rate in Denmark, 40% of the rate in Canada, and half of the reporting rate in the United Kingdom. See Stanley A. Edlavitch, *Adverse Drug Event Reporting: Improving the Low U.S. Reporting Rates*, 148 ARCHIVES OF INTERNAL MED. 1499, 1499 (1988). There are important distinctions between regulatory systems that emphasize premarket screening and those that focus on standard-setting enforced through after-the-fact policing. See Peter Huber, *The Old-New Division in Risk Regulation*, 69 VA. L. REV. 1025, 1033-37 (1983).

85. See CDER REPORT TO THE NATION, *supra* note 13, at 23, 30-32.

86. *FDA to Release Study on How to Better Assess Safety, Efficacy of Drugs, Devices*, 8 Health L. Rep. (BNA) 725 (May 6, 1999) (quoting Commissioner Jane Henney's congressional testimony).

87. See 21 U.S.C. § 355(k)(1) (1994).

88. See 21 C.F.R. § 130.13 (1968). The original regulation required maintenance of the following records:

[C]linical experience, studies, investigations, and tests conducted by the applicant or reported to him by any person, including the drug that is the subject of the application and related drugs, and reports in the scientific literature involving the drug that is the subject of the application. (The applicant must identify at the time of each report submission each drug he considers related to the subject drug.)

Id. § 130.13(a)(1). Manufacturers of drugs subject to an approved NDA were required to report adverse drug experiences to the FDA beginning, with certain exceptions, in 1963. See 29 Fed. Reg. 7019, 7020 (1964); 28 Fed. Reg. 6381, 6381-82 (1963); see also *Stanton v. Astra Pharm. Prods., Inc.*, 718 F.2d 553, 560-63 (3d Cir. 1983) (untangling these confusing requirements).

studies received or obtained by the applicant during that reporting interval.⁸⁹

Because of regulatory ambiguity and disappointing results, the FDA substantially revised its original reporting regulations in 1985.⁹⁰ For drugs marketed under an approved NDA, the rules require that manufacturers submit several types of reports. The regulations do not require manufacturers actively to seek out safety information about their products. Instead, the current regulations require manufacturers to submit adverse experience reports whenever a health care professional or consumer spontaneously notifies it of "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug-related."⁹¹ Thus the "mandatory" system is only as effective as the degree of voluntary participation permits.⁹² Even if pharmaceutical manufacturers comply fully with mandatory ADR reporting requirements, these reports represent only the proverbial tip of the iceberg of drug reactions and interactions. Manufacturers only submit reports of adverse events based on what physicians send to them,⁹³ and these reports comprise only a small fraction of the total number of adverse drug reactions that occur.⁹⁴

89. See 21 C.F.R. § 130.13(b)(3)(iii) (1967) (later redesignated as 21 C.F.R. § 130.13(b)(4)(iv) (1968)). These requirements applied only to drugs approved on or after June 20, 1963, and the FDA subsequently promulgated a separate regulation extending these requirements to drugs that it had approved before that date. See 21 C.F.R. § 130.35 (1968).

90. See *New Drug and Antibiotic Regulations*, 50 Fed. Reg. 7452 (1985).

91. 21 C.F.R. § 314.80 (1999); see also *New Drug and Antibiotic Regulations*, 50 Fed. Reg. at 7471 (noting that the ADR system was created as a mechanism to warn the FDA and health care professionals about significant safety problems associated with prescription drugs).

92. Spontaneous, or unsolicited, reports include all reports from manufacturers or health care professionals (as well as consumers) but do not include reports arising from formal clinical studies. See Gerald A. Faich, *Adverse Drug-Reaction Monitoring*, 314 NEW ENG. J. MED. 1589, 1589-90 (1986).

93. Drug manufacturers may also become aware of ADRs through less formal contacts with health care providers. See Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 FOOD & DRUG L.J. 309, 314-15 (1992) (recognizing that members of a sales force "can provide an early warning system for adverse drug reactions or less serious practical difficulties encountered by physicians that might otherwise not come to the company's attention as quickly").

94. The full extent of underreporting of adverse reactions remains unknown, but several estimates suggest that the underreporting problem is enormous. One U.S. study estimated that physicians report less than one percent of serious ADRs to the FDA. See H.D. Scott et al., *Rhode Island Physicians' Recognition and Reporting of Adverse Drug Reactions*, 70 R.I. MED. J. 311, 311-16 (1987). In Britain, the estimates suggest that no more than 10% of serious ADRs and 2%-4% of non-serious ADRs are processed through the spontaneous reporting system there. See CENTER FOR DRUG EVALUATION AND

Because the spontaneous reporting numerator represents only a tiny fraction of the actual number of ADRs, it remains difficult to estimate accurately the incidence of safety problems with many prescription drugs.⁹⁵

The agency now defines an "adverse drug experience" as "any adverse event associated with the use of a drug in humans, whether or not considered drug related."⁹⁶ The speed with which a manufacturer must file reports depends on whether the adverse event is "unexpected," a term that has remained definitionally stable over time, but that has engendered some confusion. Within fifteen days, manufacturers must submit reports of all adverse drug experiences that are both "serious" and "unexpected"⁹⁷ and they must "promptly investigate" all such adverse experiences.⁹⁸

By contrast, manufacturers need only submit periodic reports for non-serious or expected adverse events.⁹⁹ The periodic reports must contain

RESEARCH, FDA, THE CLINICAL IMPACT OF ADVERSE EVENT REPORTING 5 (1996), available in <<http://www.fda.gov/medwatch>>; see also B.L. Strom & P. Tugwell, *Pharmacoeconomics: Current Status, Prospects, and Problems*, 113 ANNALS OF INTERNAL MED. 179, 179-81 (1990). The reporting rates for medical devices appear to be equally low. See UNITED STATES GEN. ACCOUNTING OFFICE, GAO/PEMD-87-1, MEDICAL DEVICES: EARLY WARNING OF PROBLEMS IS HAMPERED BY SEVERE UNDERREPORTING 3 (1986) (finding that less than one percent of adverse events associated with the use of medical devices in hospitals were reported to the FDA and that more serious events were less likely to be reported).

95. To further complicate the drug safety picture, the FDA lacks useful data about the numbers of patients who take particular drugs as well as about length and degree of exposure to these drugs. These data are necessary to determine the denominator for purposes of calculating the incidence of drug safety problems. See CENTER FOR DRUG EVALUATION AND RESEARCH, *supra* note 94, at 5.

96. 21 C.F.R. § 314.80(a) (1999).

97. The regulations define the term "[s]erious adverse drug experience" as:

Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require serious hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Id. The regulations define an "unexpected adverse drug experience" as "[a]ny adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity."
Id.

98. See *id.* § 314.80(c)(1)(i)-(ii).

99. Until recently, the FDA required NDA holders to submit periodic reports of the frequency of ADRs associated with their products, as well as reports within 15 working

summaries of all fifteen-day reports, along with reports of other adverse experiences, and explanations of any action that the manufacturer has taken in response to reported information.¹⁰⁰ The regulations also require that holders of an approved NDA submit quarterly adverse drug experience reports for the first three years of marketing and annual reports afterwards.¹⁰¹ The initial close scrutiny during the first three years of a drug's marketing reflects an understanding that, during this time period, physicians are less familiar with the product and its known side effects. It also reflects the reality that the drug's safety profile will continue to develop as more patients take the product. Some industry insiders refer to this early marketing period as "the red zone." Finally, additional regulations for new drugs require that manufacturers submit a brief summary of new information accumulated during the preceding year that "might affect the safety, effectiveness, or labeling of the drug product" along with a description of the manufacturer's intended response to this information.¹⁰²

Recently, the FDA redefined some of the other regulatory terms that previously caused confusion. For example, the agency has gradually narrowed and clarified the definition of "serious," thereby shrinking the subset of all adverse drug events about which manufacturers must provide information.¹⁰³ The vagueness of certain terms used in the definition of "serious," such as "disability" and "life-threatening," has, however, led

days of "any significant increase in frequency" of ADRs. *See* 21 C.F.R. § 314.80(c)(1)(ii), (2) (1996). Effective June 29, 1992, the FDA also required reports of any significant increases in "therapeutic failure (lack of effect)" detected by a manufacturer. *See* 21 C.F.R. § 314.80(c)(1)(ii) (1996). The FDA recently revoked the increased frequency reporting requirement, stating that it had not generated additional useful information on which the agency could base post-approval safety decisions. *See* Postmarketing Expedited Adverse Experience Reporting for Human Drug and Licensed Biological Products; Increased Frequency Reports, 62 Fed. Reg. 34,166 (1997). At the same time, the FDA also eliminated the reporting requirement for increases in therapeutic failures. *See id.* at 34,168.

100. *See* 21 C.F.R. § 314.80(c)(2)(ii) (1999).

101. *See id.* § 314.80(c)(2)(i). In addition, the FDA may require the continued submission of quarterly reports after the three year period has expired if deemed appropriate. *See id.* Finally, the regulations for drugs with an approved NDA demand more detailed information in the periodic reports than the regulations governing reports for drugs marketed without an approved NDA. *Compare id.* § 314.80(c)(2)(ii), *with id.* § 310.305(c).

102. *See id.* § 314.81(b)(2)(i). The regulations also require the annual submission of distribution data for approved new drugs. *See id.* § 314.81(b)(2)(ii).

103. For example, one previous definition of "serious" included a reference to adverse reactions "requir[ing] prescription drug therapy." *See* New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7500 (1985). The subsequent deletion of this component of the definition may have reduced confusion because, although many serious reactions undoubtedly require prescription drug treatment, non-serious reactions may require such treatment as well.

to some disagreements between manufacturers and the FDA about the reach of the fifteen-day reporting requirements.¹⁰⁴

The FDA also has issued guidelines to clarify further the meaning of several important terms relating to post-approval reporting, though ultimately these guidelines may not have accomplished this goal. For example, in 1995, the agency released a guideline applicable to reporting requirements for drugs subject to an approved NDA. This document elaborates on scenarios outside the definition of "serious" that might still trigger expedited reporting.¹⁰⁵ More recently, the FDA issued a guideline that specifically listed four elements that an NDA holder should obtain before reporting an adverse event relating to a drug: (1) an identifiable patient; (2) an identifiable reporter; (3) a suspect drug product; and (4) an adverse event or fatal outcome.¹⁰⁶ Interestingly, in another apparent

104. In 1997, the agency issued a final rule that, among other things, defined previously undefined terms in the regulations and clarified the definitions of other previously defined terms. See 62 Fed. Reg. 52,237, 52,249-51 (1997) (codified at 21 C.F.R. §§ 310.305, 314.80 (1999)). For example, the term "disability" (as used in 21 C.F.R. §§ 310.305(b) & 314.80(a)) is now defined to mean "a substantial disruption of a person's ability to conduct normal life functions." The term "life-threatening" (as used in 21 C.F.R. §§ 310.305(b) & 314.80(a)) is now defined as "any adverse drug experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred."

105. See FDA, CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING 5 (1995), available in <<http://www.fda.gov>>. The FDA notes that "medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations." *Id.* These other situations include "important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition These should also usually be considered serious." *Id.* Such amendatory interpretations of previously-issued regulations illustrate the continued problem with definitional instability. Other commentators have also noted that spontaneous reporting systems must have clearly stated objectives in order to function well, and they have pointed out the confusion created by inconsistent regulatory definitions. See, e.g., Edlavitch, *supra* note 84, at 1500 (describing inconsistencies between the 1985 regulatory definition of "serious" and a variety of interpretations of that term in government guidance documents and medical journal articles). The FDA also issued a previous guideline, applicable to both new approved drugs and drugs not subject to approved NDAs, in 1992. See Guideline for Postmarketing Reporting of Adverse Drug Experiences; Availability, 57 Fed. Reg. 61,437 (1992). Such guidelines do not, however, bind regulated entities or the agency. See Lars Noah, *The FDA's New Policy on Guidelines: Having Your Cake and Eating It Too*, 47 CATH. U. L. REV. 113, 116-18 (1997) (describing the agency's attempt to differentiate between binding and non-binding statements of regulatory policy).

106. See generally FDA, GUIDANCE FOR INDUSTRY, POSTMARKETING ADVERSE EXPERIENCE REPORTING FOR HUMAN DRUGS AND LICENSED BIOLOGICAL PRODUCTS: CLARIFICATION OF WHAT TO REPORT (1997), available in <<http://www.fda.gov/cder/guidance.htm>> (strongly discouraging manufacturers from submitting reports if any of the four elements of information is unavailable).

attempt to reduce the number of reports of non-serious, labeled reactions, the FDA now discourages submission of adverse event information obtained by manufacturers during the course of sponsored patient support or disease management programs.¹⁰⁷ The agency clearly continues to struggle with the volume of reports received and appears to be announcing its regulatory priorities to manufacturers in order to reduce the flow of lower-priority ADR reports. As the FDA refines its definition of the class of events that it wants reported in order to focus its resources on the most serious events, however, there may be some increased risk of missing important early warning reports at the fringes.

Even more importantly, the obligation to file ADR reports, in theory, does not depend on a causality assessment. The FDA's regulations make it clear that manufacturers should not report only those adverse events "caused" by their drug; a suspected association will suffice. However, the FDA's guidance on the causation assessment may create more confusion than illumination.¹⁰⁸ One of the most problematic aspects of both the required reporting system and the voluntary MedWatch system¹⁰⁹ is the process of determining whether a particular symptom or effect arises from the patient's medication, from the underlying disease, or from some other, extraneous cause, such as diet or alcohol intake.¹¹⁰ When the FDA states that no proof of causation is needed to trigger the obligation to re-

107. *See id.* (noting that such information should be treated like other safety information obtained from postmarketing studies, unless the adverse events in question would trigger a 15 day report). The FDA also now encourages NDA holders to request agency permission to waive the requirement for submitting reports of "nonserious and labeled" adverse events. *See id.*

108. *See, e.g.*, Revision of Rules Governing Postmarketing Reporting of Adverse Drug Reactions, 51 Fed. Reg. 47,028, 47,030 (1986) (explaining that, in spontaneous post-approval reporting, "the reporter presumably exercises discretion in deciding whether to report, withholding reports of events that seem obviously not to be caused by the drug," which suggests that the FDA assumes manufacturers will and should make some sort of causality assessment).

109. *See infra* Part I.B.2.

110. Patients taking prescription medications may recognize that they are experiencing an unpleasant or painful symptom (such as dizziness, racing of the heart, headache, or nausea); these patients may, however, attribute such symptoms to their disease. Not realizing that their symptoms arise from their medication, these patients may not report the symptoms to their physicians. *See* Grady, *supra* note 3, at A21. In the context of securities litigation, some courts have appreciated the complexity of the causation questions surrounding adverse drug reactions. *See, e.g., In re Carter-Wallace, Inc. Sec. Litig.*, 150 F.3d 153, 157 (2d Cir. 1998) (holding that only when reports of adverse effects "provide statistically significant evidence that the ill effects may be caused by—rather than randomly associated with—use of the drug" must pharmaceutical companies disclose the information in securities filings; anecdotal or isolated reports of adverse effects need not be included in filings); *see also* Ellen L. Rosen, *Drug Co. Ads Can Be Basis for 10(b) Suit*, NAT'L L.J., July 27, 1998, at B1.

port, in effect, the agency assumes that health professionals have already made a rough assessment of causality. In other words, the FDA assumes it is likely that the physician concluded that the drug in question may have caused the patient's problem because the physician would not otherwise have reported the suspected adverse reaction to the manufacturer or the FDA.¹¹¹ Thus, the ambiguity surrounding both the causality assessment and the circumstances triggering the fifteen-day reporting requirement leave room for interpretation on the part of the reporter. Recent amendments and guidelines attempting to clarify the regulations represent only a partial response to the definitional problems that the ADR reporting regulations pose.

Other reasons also account for the FDA's position that causality assessments do not factor into ADR requirements. Manufacturers have an incentive to underestimate the likelihood of a causal relationship between their products and patient ADRs. Premature assessments of causality (or lack of causality) can, however, potentially distort the statistics relating to how frequently the ADR occurs in the patient population using the drug. Further complicating the causation question, some adverse reactions occur at just slightly above the background rate (the rate at which a condition manifests itself in a given population without exposure to the drug in question) in the treated population.¹¹² Because frequency analysis contributes to a population-wide causality assessment, it is important not to discard suspected individual ADRs prematurely.

Moreover, pharmaceutical manufacturers sometimes have incentives to repackage adverse drug event information for the FDA's consumption. Concerns about market competition and liability may affect the manner in which manufacturers present drug-related data to the agency. For instance, in drug products liability litigation, plaintiffs may pursue negligence per se claims by alleging non-compliance with ADR reporting

111. The physician who initially reports to the manufacturer need not resolve the causation question; indeed, this question frequently remains unresolvable for a single patient. See Henkel, *supra* note 81, at 12 (noting that the FDA emphasizes that it is "not necessary to prove that a medical product caused an adverse reaction—a suspected association is sufficient reason to make a report"); see also FDA, *Clinical Therapeutics and the Recognition of Drug-Induced Disease* (1995), available in <<http://www.fda.gov/medwatch/articles/dig/recognit.htm#>>. The FDA describes a six-step process for assessing a possible drug-related event, including verification of the interval between the beginning of drug treatment and the onset of the adverse reaction, dechallenging (i.e. stopping the drug therapy to look for improvement in the patient's symptoms) and rechallenging (i.e. restarting the drug therapy, if appropriate) and monitoring the patient to determine whether the adverse reaction recurs.

112. See RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 44.

requirements.¹¹³ Because the FDA's reporting requirements traditionally have suffered from ambiguities, litigants could always find a way to argue that manufacturers had violated the regulations. Invariably, no matter how conscientious the behavior of the manufacturer, an ADR or published study will slip through the cracks. The fear of negligence per se claims may, therefore, encourage defensive manufacturers to err on the side of over-reporting ADRs. This, in turn, interferes with the efficiency and efficacy of the post-approval surveillance regulatory system.

Nonetheless, a number of disincentives to spontaneous reporting of adverse drug events may provide a counterweight to the incentives created by the fear of tort liability.¹¹⁴ At one level, pharmaceutical manufacturers would prefer to ignore red flags signaling problems with a product in order to keep the product on the market.¹¹⁵ They will resist filing ADR reports that appear to concede that their product caused a particular injury.¹¹⁶ The FDA reporting regulations contain a disclaimer for manufacturers that states that the submission of required reports does not constitute an admission or conclusion by the manufacturer or the

113. See, e.g., *Stanton v. Astra Pharm. Prods., Inc.*, 718 F.2d 553, 558 (3d Cir. 1983) (holding that there was sufficient evidence to conclude that the manufacturer's failure to file annual reports concerning adverse drug reactions with the FDA was negligence per se); *Toole v. Richardson-Merrell, Inc.*, 60 Cal. Rptr. 398, 409 (Ct. App. 1967) (rejecting a drug manufacturer's argument that there is a "difference between violation of the labeling and marketing provisions and violation of the reporting provisions, because the labeling provisions of the statute are designed to protect the public, whereas the reporting provisions of the statute are concerned merely with raw data comprehensible only to scientists in the FDA"); *Carnoto v. Sandoz Pharm. Corp.*, Fla. Cir. Ct. No. 95-9076 (Apr. 14, 1999) (finding that Sandoz "ignore[d], suppress[ed], and/or underreport[ed] adverse reaction reports" concerning Parlodel, a lactation suppressant, and awarding punitive damages to the plaintiff); see also *Benedi v. McNeil-P.P.C., Inc.*, 66 F.3d 1378, 1379 (4th Cir. 1995) (holding that the defendant's withholding of adverse reaction reports over a period of eight years justified awarding punitive damages).

114. See Michael D. Green, *Statutory Compliance and Tort Liability: Examining the Strongest Case*, 30 U. MICH. J.L. REFORM 461, 499 (1997) ("The marketing and profit incentives for a pharmaceutical manufacturer are contrary to thorough and accurate gathering and reporting of ADRs."); Morton Mintz, *The Cure That Could Kill You: FDA Reforms Are Bad Medicine*, WASH. POST, July 14, 1996, at C1 (reporting that numerous drug manufacturers have missed ADR reporting deadlines in recent years).

115. See MICHAEL D. GREEN, *BENEDICTIN AND BIRTH DEFECTS: THE CHALLENGES OF MASS TOXIC SUBSTANCES LITIGATION* 54-56 (1996).

116. See Patricia L. Andel, *Inapplicability of the Self-Critical Analysis Privilege to the Drug and Medical Device Industry*, 34 SAN DIEGO L. REV. 93, 94-95, 145 (1997) (arguing that it is inappropriate to apply the privilege, which protects against disclosure of "self-evaluative material," in the context of drug safety reporting when the public's need to know is outweighed by the public interest in confidentiality, and that the privilege is unnecessary in this context because the drug industry has other "strong incentives to investigate thoroughly . . . the safety and effectiveness of its products" in order to avoid products liability exposure).

agency that the drug in question caused the adverse reaction.¹¹⁷ Nothing prevents the admission of such reports at trials, however, so manufacturers may take little comfort in the disclaimer.¹¹⁸

At this level, the process of detecting and compiling information about adverse drug events among very sick patients taking multiple drugs represents a far more complex problem than that posed by the venal drug manufacturer who will do anything for a profit.¹¹⁹ The latter may, in calculating potential costs, determine that it is most cost effective to respond quickly to fairly obvious patterns of adverse reactions associated with a marketed product rather than face a massive class action lawsuit at some point in the future. Already, the withdrawn diet drugs have generated numerous suits, and entrepreneurial plaintiffs' lawyers anxiously await the next prescription drug debacle.¹²⁰ The tort system, however, is not an adequate substitute for a rigorous reporting and monitoring system, when the goal is to detect subtler problems of drug reactions or interactions in large groups of patients who may have multiple or serious

117. See 21 C.F.R. § 314.80(k) (1999) (noting that "[a] report or information submitted by an applicant under this section . . . does not necessarily reflect a conclusion by the applicant or FDA that . . . the drug caused or contributed to an adverse effect," and that "[a]n applicant need not admit, and may deny, that the report . . . constitutes an admission that the drug caused or contributed to an adverse effect").

118. With regard to the effect of these reports on the outcome of litigation, the FDA has commented that, "although the FDA does not intend for such a report to be viewed as an admission of liability, whether a court will treat a submission to FDA as an admission will depend on factors outside of the agency's control, such as the contents of the report itself." New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7476 (1985).

119. Manufacturers have certainly, however, attempted to manipulate the requirements of the ADR reporting system to protect profits or to avoid responsibility for safety problems associated with a prescription drug. See, e.g., GREEN, *supra* note 115, at 129 (describing a situation in which a drug manufacturer encouraged physicians who called to report birth defects associated with maternal use of an anti-nausea drug to describe those contacts as "inquiries" rather than "reports" in order to avoid having to forward the information to the FDA); Teresa Moran Schwartz, *Punitive Damages and Regulated Products*, 42 AM. U. L. REV. 1335, 1348-52 (1993) (cataloging nearly a dozen instances of apparent withholding of relevant information by drug and device manufacturers during the pre-approval or post-approval stages); see also Laura Johannes & Robert Langreth, *Marketer of Redux Mulling Settlement, Sees Plaintiffs' Hand*, WALL ST. J., Sept. 28, 1999, at A1 (describing testimony in the class action suit about the manufacturer's instructions to employees to delay processing of reports of heart valve defects associated with Redux); *Drug Maker Pleads Guilty Over Lethal Side Effects*, N.Y. TIMES, Dec. 14, 1984, at A23 (describing a manufacturer's failure to report ADRs appropriately and the hundreds of serious ADRs that occurred as a result); Philip Shenon, *Lily Pleads Guilty to Oraflex Charges*, N.Y. TIMES, Aug. 22, 1985, at A16 (describing a manufacturer's failure to report ADRs and the criminal sanctions imposed on the manufacturer).

120. See Bob Van Voris, *A Drug Maker's Legal Migraine*, NAT'L L.J., Aug. 23, 1999, at B20 (describing a class action lawsuit alleging that fen-phen's manufacturer concealed evidence that the drugs can cause pulmonary hypertension and heart valve problems).

health problems.

2. *The MedWatch System*

Health care providers have an ethical, though not legal, obligation to identify and report adverse drug reactions to the FDA.¹²¹ The American Medical Association (AMA) has emphasized the importance of continued physician participation in the ADR reporting system, noting that the FDA pays particular attention to reports received directly from physicians (as opposed to reports from patients).¹²² Because a substantial number of physician reports concern serious reactions resulting in hospitalization or death, these voluntary physician reports tend to generate the highest proportion of drug labeling changes.¹²³ The FDA has gone so far as to assert that, once new drugs are cleared for marketing, “ensuring safety is principally the responsibility of healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis.”¹²⁴ Although physicians certainly make prescribing decisions based on the individual needs of their patients, the FDA continues to re-

121. See AMERICAN MED. ASS'N, *Principles of Medical Ethics: Principle V*, in COUNCIL ON ETHICAL & JUDICIAL AFFS., CODE OF MEDICAL ETHICS: CURRENT OPINIONS WITH ANNOTATIONS (1999) [hereinafter CODE OF MEDICAL ETHICS] (“A physician shall continue to study, apply and advance scientific knowledge, make relevant information available to patients, colleagues, and the public.”). There are only two exceptions to the voluntary reporting scheme. The first is for vaccine-related injuries. See 42 U.S.C. § 300aa-14, -25 (1994) (requiring reporting of all vaccine-related injuries). The second applies to adverse events associated with medical devices that cause serious injury or death. See 21 U.S.C. § 360i(b)-(c)(1) (1994) (requiring that device user facilities such as hospitals submit reports in such cases, but exempting individual health care providers).

122. See American Med. Ass'n, *supra* note 38, at 362. A recent opinion from the AMA's Council on Ethical and Judicial Affairs clearly states the physician's ethical obligation to report suspected problems with prescription drugs:

A physician who suspects the occurrence of an adverse reaction to a drug . . . has an obligation to communicate that information to the broader medical community (e.g., through submitting a report or letter to a medical journal or informing the manufacturer of the suspect drug . . .). In the case of a serious adverse event, the event should be reported to the [FDA]. Spontaneous reports of adverse events are irreplaceable as a source of valuable information about drugs . . . particularly their rare or delayed effects, as well as their safety in vulnerable patient populations. Although premarketing and mandated postmarketing studies provide basic safeguards for the public health, they suffer from inherent deficiencies that limit their ability to detect rare or unexpected consequences of drug . . . use.

AMERICAN MED. ASS'N, *Opinion 9.032: Reporting Adverse Drug or Device Events*, in CODE OF MEDICAL ETHICS, *supra* note 121; see also American Med. Ass'n, *supra* note 38, at 363-65 (discussing physicians' ethical and professional obligations to participate in systems designed to detect adverse drug reactions).

123. See American Med. Ass'n, *supra* note 38, at 363-65.

124. RISK MANAGEMENT FRAMEWORK, *supra* note 18, at 4.

tain the responsibility for providing physicians with the most complete and accurate population-based safety information on which to base their individualized decisions.

In 1993, the FDA created a system to bypass the pharmaceutical manufacturer and encourage direct reporting to the agency of suspected adverse reactions. To facilitate provider reporting of suspected medical product problems (including problems with drugs, biologics, medical devices and medical foods), the FDA established the "MedWatch Medical Products Reporting Program."¹²⁵ The MedWatch program represents the FDA's first concerted effort to involve physicians more formally in the post-approval drug monitoring process.¹²⁶ According to the FDA, the program has several important goals, including clarifying what adverse events should be reported, increasing awareness about serious adverse drug reactions, facilitating the reporting process, and providing consumers with information about product safety issues.¹²⁷

MedWatch provides a simple, one-page form for physician use in reporting suspected problems with human drugs.¹²⁸ The system requests, but does not require, that the reporting physician or other health professional complete a form in response to all serious adverse reactions, including death, life-threatening reactions requiring hospitalization, disability, birth defects, miscarriage, or other reactions requiring medical intervention to avoid permanent damage to the patient.¹²⁹ The request for reports includes "expected" ADRs. The program seeks to gather data across a wide field of patients taking a particular drug in order to detect patterns of adverse events.

The early returns paint a moderately favorable picture about the effectiveness and quality of physician participation in the MedWatch program. Overall, the quantity of adverse drug reaction reports to the FDA has increased dramatically, from approximately 40,000 in 1985¹³⁰ to nearly

125. See David A. Kessler, *Introducing MedWatch: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems*, 269 JAMA 2765 (1993).

126. See *id.* at 2765 ("Unfortunately, many health professionals do not think to report adverse events that might be associated with medications . . . to the [FDA] or to the manufacturer. That needs to change, and the FDA is taking steps to encourage that to happen.").

127. See Henkel, *supra* note 81, at 11-12. The MedWatch program also covers biologics, medical devices, dietary supplements, infant formulas, medical foods, and food additives. See *id.*

128. See *id.* at 13 (reproducing a sample reporting form).

129. See *id.* at 11-12 (noting the existence of the separate mandatory reporting systems for medical device manufacturers).

130. See New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7473 (1985).

160,000 in 1996.¹³¹ Health professionals submitted 58% of the total reports received in 1996, though only 9% of these were reported directly to the FDA. Although reports from health professionals have increased in absolute numbers in recent years, the percentage of total ADR reports received from health professionals has actually decreased, from 72% in 1993 to 58% by 1996.¹³² A recent study of trends in the reporting of serious adverse reactions confirms that, although the quality of such reports increased after the launching of MedWatch, the overall numbers of reports have decreased.¹³³ The FDA also has noted a curious trend in ADR reporting—spontaneous reporting of ADRs peaks at the end of the second year of a drug's marketing but then declines dramatically, even though the prescribing of the drug and the ADR rates apparently remain relatively stable.¹³⁴

The reason for decreased physician participation in the reporting system remains unclear, though, in the era of managed care, reliance on voluntary reporting may be increasingly unrealistic. Patients change physicians far more frequently under managed care, and the duration of the average physician-patient relationship has decreased substantially in recent years. These changes negatively impact a physician's ability to become familiar with a patient's overall medical condition, resulting in lost or overlooked medical information and decreased communication between doctor and patient. Moreover, managed care cost controls exert pressure on physicians to spend less time for each patient visit,¹³⁵ and to prescribe more pharmaceutical products to manage chronic disease.¹³⁶ A spontaneous reporting system like MedWatch depends entirely on medical professionals for its effectiveness. Health care providers, however,

131. See FDA, Center for Drug Evaluation and Research, *Annual Adverse Drug Experience Report: 1996* (last modified Oct. 30, 1997) <<http://www.fda.gov/cder/dpe/annrep96/index.htm>>.

132. See *id.*

133. See T. Piazza-Hepp & D.L. Kennedy, *Reporting of Adverse Events to MedWatch*, 52 AM. J. HEALTH SYS. PHARM. 1436, 1436-39 (1995) (comparing reporting trends before and after the June 1993 implementation of MedWatch, and finding that the proportion of "serious" reports increased from 34% in 1992 to 49% in 1994).

134. See CENTER FOR DRUG EVALUATION AND RESEARCH, *supra* note 94, at 5.

135. See Sheryl Gay Stolberg, *Faulty Warning Labels Add to Risk in Prescription Drugs*, N.Y. TIMES, June 4, 1999, at A27 (describing how managed care has reduced the amount of time doctors have to spend with their patients); see also Nancy K. Plant, *The Learned Intermediary Doctrine: Some New Medicine for an Old Ailment*, 81 IOWA L. REV. 1007, 1023-32 (1996) (arguing that managed care has constrained physician practice to the point that prescribing decisions may be less informed and therefore potentially more detrimental to patient safety).

136. See J.D. Kleinke & Scott Gottlieb, *Is the FDA Approving Drugs Too Fast?*, 317 BRIT. MED. J. 899 (1998).

may find it increasingly difficult to detect, and therefore report, relevant information when they are less familiar with their patients.

Conversely, structured utilization reviews undertaken by managed care organizations (MCOs) may promote the routine collection and analysis of ADR information.¹³⁷ MCOs may have the potential to assist in the collection of information concerning adverse drug reactions because these organizations have the capability of collecting and analyzing masses of data, and they regularly perform outcomes research that demonstrates this ability.¹³⁸ Similar data collection using enhanced links with external databases for ADRs associated with drugs that are paid for by managed care may help to identify patterns of problems that are not apparent to individual practitioners, no matter how well they know their patients.¹³⁹ Ideally, MCOs would share this information with the FDA.

The Centers for Disease Control and Prevention (CDC) also play a supporting role in tracking adverse events. Although the CDC's work primarily concerns non-drug-related events such as outbreaks of food-borne illnesses or new infectious agents, it also addresses problems relating to prescription and non-prescription drugs and vaccines.¹⁴⁰ Working in conjunction with the FDA, the CDC's evaluation of drug side effects has helped to uncover previously undetected problems associated with marketed drug products.¹⁴¹ For example, the CDC recently played

137. For example, in 1993, when Merck acquired Medco, a drug discount and mail-order company, Merck stated that it planned to use Medco's data on the 33 million patients in its managed care plans to uncover patterns of medical effectiveness in order to increase sales. See Milt Freudenheim, *Merck's Big Gamble on a Merger*, N.Y. TIMES, Aug. 5, 1993, at D1. Such data, including information about drug safety, might prove extremely useful in uncovering patterns of ADRs. See *id.*

138. See Ron Winslow, *Limiting Drugs a Doctor Orders May Cost More*, WALL ST. J., Mar. 20, 1996, at B1.

139. See Woosley, *supra* note 39, at 187. Of course, the FDA's collection of data from such sources will only prove useful if the medical community changes its practices in response to new safety information. For example, one pharmacologist described a situation in which data from six HMO databases indicated that the antihistamine drugs terfenadine and astemizole could cause major cardiac toxicity when used in combination with certain other drugs. The data became available in 1990, and a FDA advisory committee issued warnings about the potential lethal interaction to physicians and pharmacists. See *id.* One year later, there was no discernable change in prescribing or dispensing practices, and only after repeated scholarly papers were published and an additional warning issued did the prescribing rate for the dangerous combinations decrease (from an average of 5 prescriptions per month to 2.3 prescriptions per month). See *id.*

140. See ELIZABETH W. ETHERIDGE, *SENTINEL FOR HEALTH: A HISTORY OF THE CENTERS FOR DISEASE CONTROL* 341-43 (1992).

141. See, e.g., 21 C.F.R. § 201.314(h)(1) (1999) (requiring a warning of the association between Reye syndrome and aspirin use in children); *id.* § 801.430(c) (requiring a warning of the association between toxic shock syndrome and tampons).

an instrumental role in discovering a causal connection between a new vaccine for rotavirus and an unusually high incidence of bowel obstruction in infants. CDC epidemiologists, acting on reports from state health officials, analyzed an apparent pattern of this complication among infants in several states and used data from state health agencies and the vaccine's manufacturer to make the connection.¹⁴² The FDA then recommended a temporary halt in the use of the vaccines, and the manufacturer, based on ninety-six reported cases of this adverse event, eventually opted to withdraw the product from the market while further controlled studies progressed.¹⁴³ Because the CDC has representatives around the country who work in a variety of settings, including quarantine facilities and local health offices, the organization is sometimes in a unique position to detect and help investigate suspected problems with medical products.¹⁴⁴

3. Other Safety Monitoring Systems

The FDA has been forced to make difficult choices in allocating its resources in the monitoring of other products under its regulatory jurisdiction. Two contrasting examples provide some context in which to consider the FDA's approach to drug safety monitoring. In comparison to prescription drug surveillance, the FDA's approach to market surveillance of medical devices generally represents a more proportionate response to the relative risks posed by this category of products than its approach to prescription drugs. The FDA's mechanisms for tracking adverse effects associated with dietary supplements, by comparison appears inadequate given the increasing popularity of the products and their potential for harm.

A number of differences exist between the systems that regulate safety of drugs and medical devices. For approved medical devices, the statute until recently required structured post-marketing surveillance for certain devices that may cause serious adverse consequences.¹⁴⁵ FDAMA re-

142. See Lawrence K. Altman, *U.S. in a Push to Bar Vaccine Given to Infants*, N.Y. TIMES, July 16, 1999, at A1; see also ETHERIDGE, *supra* note 140, at 73-80 (describing how the CDC tracked cases of polio caused by the new polio vaccine in 1955).

143. See Lawrence K. Altman, *Vaccine for Infant Diarrhea Is Withdrawn as Health Risk*, N.Y. TIMES, Oct. 16, 1999, at A10 (noting that "[t]he developments are highly embarrassing to Federal health officials," and that "even before the FDA licensed the vaccine . . . the CDC promoted it as a new weapon against rotavirus").

144. See Centers for Disease Control and Prevention, *About CDC* (visited Nov. 13, 1999) <<http://www.cdc.gov/aboutcdc.htm>> (describing the CDC's organizational structure and general operations).

145. See 21 U.S.C. § 360l (1994), amended by 21 U.S.C. § 360l (Supp. III 1997) (re-

laxed some of these reporting requirements, however, by repealing mandatory safety surveillance for certain devices and giving the FDA discretion over the decision about whether to order safety monitoring.¹⁴⁶

The medical device statute also requires spontaneous reporting. A device manufacturer must file a Medical Device Report (MDR) whenever it receives information that suggests that its device "may have caused or contributed to a death or serious injury, or has malfunctioned" in a way that might cause serious injury.¹⁴⁷ In addition, the medical device reporting provision *requires* reporting from both device manufacturers and certain device user facilities, such as hospitals.¹⁴⁸ Whenever a user facility becomes aware that a device may have caused or contributed to the death or serious injury of a patient in the facility, the user must submit a report to the FDA within ten working days.¹⁴⁹ In contrast, the ADR system requires reporting from manufacturers, but it only *requests* reports from physicians who utilize the drug products for their patients.

The FDA's definition of "serious injury" in the implementing regulations poses some of the same ambiguities that the corresponding definitions create in the drug context. For medical devices, an injury is "serious" if it is "(i) life-threatening; (ii) results in permanent impairment of a body function or permanent damage to body structure; or (iii) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure."¹⁵⁰ These regulations require reporting within thirty days for most situations¹⁵¹ and within five days if the manufacturer becomes aware of a device-related reportable event that "necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health."¹⁵²

quiring postmarket surveillance for any device that "is a permanent implant the failure of which may cause serious, adverse health consequences or death, . . . or potentially presents a serious risk to human health," and permitting postmarket surveillance for other devices if such surveillance is "necessary to protect the public health or to provide safety or effectiveness data for the device"). The surveillance regulations for these types of devices also require that the manufacturer conduct the equivalent of Phase IV trials for the device. See 21 C.F.R. § 814.82(a)(2) (1999).

146. See 21 U.S.C. § 360l (Supp. III 1997).

147. See 21 U.S.C. § 360i(a)(1)(A)-(B) (1994).

148. See *id.* § 360i(b) (defining user facilities as hospitals, ambulatory surgical facilities, nursing homes, and outpatient treatment facilities, but excluding physicians' offices).

149. See *id.* (requiring annual summary reports of all serious or fatal adverse events).

150. 21 C.F.R. § 803.3(aa)(1) (1999).

151. See *id.* § 803.20(b)(3)(i)-(ii) (requiring reporting "[w]ithin 30 days of becoming aware of information that reasonably suggests that a device has or may have contributed to a death or serious injury").

152. The FDA may also request the submission of five-day reports. See *id.* § 803.53(b) (requiring a manufacturer to submit a five-day report when it becomes aware of "a report-

Overall, the medical device reporting requirements appear better suited to the task of monitoring medical device safety, in large part because the FDA has the regulatory authority to require that users of high-risk devices, as well as manufacturers of such devices, submit timely reports of adverse events. Interestingly, however, the FDA had opposed the statutory user facility reporting requirement, fearing that it would receive and have to process excessive and unreliable information.¹⁵³ The FDA suggested instead that voluntary reporting from physicians would accomplish the goal of improving medical device safety.¹⁵⁴

In contrast, dietary supplements and herbal products, which may pose significant safety concerns, face essentially no postmarketing scrutiny. For instance, it appears that certain dietary supplements may cause adverse reactions or interactions when taken with various prescription drugs.¹⁵⁵ At one point, the FDA treated such products as food additives or drugs, but with the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994,¹⁵⁶ these products now receive far less

able . . . event . . . from any information, including any trend analysis, [that] necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health"); see also *id.* § 803.3(q) (defining "reportable event"). For an overview of early medical device reporting requirements, see Edward M. Basile, *Medical Device Reporting: The Good, the Bad, and the Ugly*, 42 FOOD DRUG COSM. L.J. 83 (1987). Other agencies impose stricter reporting requirements with shorter deadlines. See, e.g., 30 C.F.R. § 50.20(a) (1999) (requiring mine operators to report to the Mine Safety and Health Administration "each accident, occupational injury, or occupational illness" occurring at a mine within 10 days of the accident or diagnosis).

153. See Edward M. Basile, *The Safe Medical Devices Act of 1990: Postmarket Surveillance, MDR, and Other Postmarket Issues*, 46 FOOD DRUG COSM. L.J. 165, 166 (1991) (describing legislative history of the statute, and quoting a FDA official's statement during hearings that user reporting requirements "would serve only to inundate the agency with data of unmanageable quantity, dubious quality and enormous expense").

154. See *id.*

155. For example, the FDA recently warned consumers about a dietary supplement that is chemically related to "GHB" (gamma hydroxybutyrate), and noted that it had been associated with 55 adverse reactions, including some interactions with prescription drugs. See *Don't Use Dangerous GHB-Related Product, Agency Warns*, FDA CONSUMER, May/June 1999, available in <http://www.fda.gov/fdac/departs/1999/399_upd.html>. Another product, "herbal ecstasy," has caused death and injuries, resulting in a FDA proposal to limit the content of ephedrine alkaloids in dietary supplement products. See *Dietary Supplements Containing Ephedrine Alkaloids*, 62 Fed. Reg. 30,678 (1997).

156. Pub. L. No. 103-417, 108 Stat. 4325 (codified as amended at scattered sections of 21 U.S.C.). For products on the market prior to 1994, the FDA can bring a court action against any supplement that presents a "significant or unreasonable risk" of harm. See 21 U.S.C. § 342(f) (1994). The affirmative burden on the FDA to prove a product's "significant or unreasonable risk" represents a resource-intensive task that the agency is unlikely to undertake frequently. See Margaret Gilhooley, *Herbal Remedies and Dietary Supplements: The Boundaries of Drug Claims and Freedom of Choice*, 49 FLA. L. REV. 663, 702 (1997).

scrutiny. Under the terms of DSHEA, manufacturers of dietary supplements need not demonstrate the safety or efficacy of their products prior to marketing, unless the product contains a new ingredient.¹⁵⁷ Moreover, the statute does not require that manufacturers report adverse reactions associated with the products to the FDA. The agency must detect patterns of problems associated with a dietary supplement based on anecdotal evidence voluntarily submitted by physicians and consumers before deciding to demand the removal of such a product from the market.¹⁵⁸ As the popularity of dietary supplements and herbal remedies continues to increase,¹⁵⁹ the potential for adverse reactions and interactions with prescription drugs grows proportionately.

As the volume of new drugs entering the market continues to grow, the pressure on the FDA's limited post-approval surveillance resources will no doubt increase. The magnitude of the problems arising from unanticipated ADRs associated with new drugs deserves a proportionately serious response, and the FDA and Congress should consider redesigning the regulatory structure governing post-approval safety monitoring. A discussion of alternative approaches is reserved for Part III.

II. CASE STUDIES

Many of the recently-approved drugs for which the FDA has opted to withdraw marketing approval enjoyed phenomenal sales during their brief periods of availability. Consumer demand for some of the newer diet drugs, for example, predictably led to widespread prescribing for patients who did not meet the physiological criteria for which the FDA approved the drugs. Other recently withdrawn drugs appeared safe at the time of their approval but showed an alarming tendency to interact with other commonly prescribed drugs, causing adverse events in a significant number of patients. Another group of drugs causes serious and permanent liver damage in some patients, despite appearing relatively safe during clinical trials. By necessity, pre-approval clinical studies are fairly limited in scope and duration. The real test of a drug's safety and effectiveness begins with the drug's widespread use in a patient population.

The following case studies describe both recalled drugs and drugs still

157. See 21 U.S.C. § 350b(c) (1994).

158. See Jane E. Brody, *Dietary Supplements May Test Consumers' Health*, N.Y. TIMES, Sept. 22, 1998, at F7 (noting that patients are sometimes reluctant to admit to their physicians that they take dietary supplements); see also Denise Grady, *Articles Question Safety of Dietary Supplements*, N.Y. TIMES, Sept. 17, 1998, at A24.

159. See Michael Higgins, *Hard to Swallow*, A.B.A. J., June 1999, at 60, 60-62 (noting that sales of dietary supplements reached \$12 billion in 1997, up 30% from 1995).

on the market. They also demonstrate the variety of problems that can arise after the FDA decides, based on the pre-approval clinical trials, that a new drug is safe and effective for use by the public. Although the FDA approved none of the recently withdrawn drugs under either the expedited or accelerated review procedures, the recent cluster of drug withdrawals in the wake of the implementation of these regulations has generated alarm among observers from the scientific community and the public.

A. Weight-Loss Medications

In September 1997, the FDA recalled the popular diet drug Redux (dexfenfluramine) from the market after physicians and the agency linked it with heart valve abnormalities in a substantial percentage of women who took the drug.¹⁶⁰ As part of the pre-approval process, an independent panel of scientific experts typically evaluates the drug's safety and effectiveness and votes whether to recommend approval to the FDA. In the case of Redux, the FDA and members of its advisory committee initially expressed reluctance about approving Redux because clinical studies demonstrated an association between the drug and primary pulmonary hypertension.¹⁶¹ At a second meeting in April 1996, the advisory committee recommended marketing the drug.¹⁶² After the drug received marketing approval, the FDA discovered that the drug's manufacturer had received reports of prior marketing experience in Europe that appeared to implicate the drug in a series of unexplained heart valve problems, and that the manufacturer had not conveyed this information to the FDA.¹⁶³

160. See Friedman et al., *supra* note 16, at 1728.

161. See Una D. McCann et al., *Brain Serotonin Neurotoxicity and Primary Pulmonary Hypertension from Fenfluramine and Dexfenfluramine: A Systematic Review of the Evidence*, 278 JAMA 666, 669 (1997) (describing the link between these drugs and pulmonary hypertension—a rare but serious, and often fatal, disease).

162. See Alicia Ault, *Anti-Obesity Drugs Recalled from Global Market*, 350 LANCET 867, 867 (1997) (describing the timeline of events for the approval and marketing of Pondimin and Redux).

163. See Laura Johannes & Steve Stecklow, *Early Warning: Heart-Valve Problem That Felled Diet Pills Had Arisen Previously*, WALL ST. J., Dec. 11, 1997, at A1. The drug's manufacturer, American Home Products, originally submitted the application for marketing approval to the FDA in May 1993. The drug was already available in Europe. Later that year, a Belgian cardiologist discovered that six of his patients who were taking a combination of dexfenfluramine and fenfluramine had developed a valvular heart disorder. The company apparently received reports of this information. See *AHP Stock Falls 4 Percent Following News Reports that Heart Valve Problems Were Not Reported to FDA*, MEALEY'S LITIG. REP.: DRUGS & MED. DEVICES, Dec. 19, 1997, available in LEXIS, Health Library, MEADMD file (suggesting that physicians in Belgium had detected pat-

The weight-conscious American society created a substantial demand for the drug.¹⁶⁴ Some physicians began to prescribe Redux for long-term use despite label warnings about the dangers of exceeding the usage periods tested in the pre-approval trials.¹⁶⁵ As ominous data about side effects began to accumulate, however, the FDA grew increasingly concerned. Citing the previously understood link between Redux and pulmonary hypertension, as well as severe heart problems and brain damage, the FDA requested a voluntary withdraw of the drug.¹⁶⁶

The term “fen-phen” refers to a frequently-prescribed combination of one of two diet drugs, Pondimin (fenfluramine) or Redux (dexfenfluramine), with the amphetamine phentermine. Although the two drugs received approval individually, the FDA never reviewed the combination, which makes it an “off-label,” though lawful, use.¹⁶⁷ During the same period in 1997 when problems with Redux (used alone) became apparent, physicians at the Mayo Clinic noted that women taking Pondimin or Redux in combination with phentermine were developing serious and unusual heart valve problems.¹⁶⁸ The physicians reported their findings to the FDA, which then called for reports of similar cases and received

terns of heart valve damage associated with Redux use by 1994); *Questions Arise About FDA's Previous Approval of Diet Drugs*, MED. INDUS. TODAY, Sept. 17, 1997, at 1.

164. See Gregory D. Curfman, Editorial, *Diet Pills Redux*, 337 NEW ENG. J. MED. 629, 630 (1997) (recommending that physicians prescribe diet drugs only for patients with “legitimate health indication[s] for the use of the drugs” and not for patients who seek to lose weight “principally for cosmetic reasons”); Sue Miller, *Quick Fix: Do Diet Pills Work?*, NEWSWEEK, Apr. 21, 1997, at 64 (noting that more than 18 million prescriptions for fen-phen and over 3 million prescriptions for Redux were filled in one recent year).

165. See Salbu, *supra* note 57, at 127-28 (1999) (describing patterns of “indiscriminate use” of obesity drugs and the American obsession with thinness).

166. See Centers for Disease Control, *Cardiac Valvulopathy Associated with Exposure to Fenfluramine or Dexfenfluramine: U.S. Department of Health and Human Services Interim Public Health Recommendations, November 1997*, 278 JAMA 1729 (1997) [hereinafter *CDC Recommendations*] (describing 144 reports received from health care providers describing heart valve problems in patients taking one or both components of fen-phen, 113 of which were considered abnormal, and noting that 27 cases required valve replacement surgery and that three patients died after surgery).

167. See Lars Noah, *Constraints on the Off-Label Uses of Prescription Drug Products*, 16 J. PRODS. & TOXICS LIAB. 139, 157 (1994) (noting that the FDA has in the past attempted to combat such uses of approved thyroid drugs for weight loss by requiring warnings); see also Salbu, *supra* note 57, at 14-25 (noting that neither of these drugs is new to the market—the FDA approved phentermine in 1959 and fenfluramine in 1973). In fact, the drug combination was never studied for safety and efficacy in animals or humans. See Heidi M. Connolly et al., *Valvular Heart Disease Associated with Fenfluramine-Phentermine*, 337 NEW ENG. J. MED. 581, 588 (1997).

168. See Friedman et al., *supra* note 16, at 1728 (describing a report from Mayo Clinic researchers of 24 cases of valvular disease and aortic and mitral valve regurgitation in patients taking the drug combination).

nearly 100 responses.¹⁶⁹ Additional studies conducted at five separate universities found that one-third of patients taking the drug combination had heart valve damage, though subsequent reports suggested lower frequencies.¹⁷⁰ The FDA then requested voluntary withdrawal of Pondimin from the market.¹⁷¹

The eventual detection of heart valve defects associated with fen-phen prompted concern within the medical community. Because the FDA knew prior to approval that both Pondimin and Redux could cause pulmonary hypertension, a rare but deadly side-effect, critics of the post-approval monitoring system questioned why the agency had not required, as a condition of its marketing, that physicians and epidemiology centers more closely monitor and report problems with the drug.¹⁷² The clinical experience and professional intuition of health care professionals treating their obese patients appears to have been the primary factor leading to the discovery of the link between these diet drugs and heart valve damage. Although the FDA received the initial voluntary physician reports and then called for more information that eventually led to the drugs' removal from the market, the regulatory system that mandates manufacturer reporting seems to have played only a minor role in the ultimate outcome. It may be reasonable, therefore, to question whether the FDA's heavy reliance on voluntary physician reporting makes sense, or whether some restructuring of the system might represent a more appropriate approach.

169. See Kolata, *supra* note 12, at F8.

170. See Curfman, *supra* note 164, at 629 (summarizing recent findings, and explaining the poorly understood mechanisms that may cause damage to heart valves in patients taking the drugs).

171. See Gina Kolata, *How Fen-Phen, A Diet "Miracle," Rose and Fell*, N.Y. TIMES, Sept. 23, 1997, at F1; see also *CDC Recommendations*, *supra* note 166, at 1729-30 (recommending that health care practitioners continue reporting heart valve problems associated with these drugs to the FDA and "strongly consider" performing an echocardiogram on patients who have taken either drug combination). Technically, the FDA can only encourage, but not mandate, a recall. See Lars Noah, *Administrative Arm-Twisting in the Shadow of Congressional Delegations of Authority*, 1997 WIS. L. REV. 873, 887-88 (describing significant limitations on the FDA's mandatory recall authority). Although the FDA recalled fenfluramine, phentermine remains on the market even though some commentators suggest that it was the primary culprit. See Denise Grady, *Search for Cause of Diet Pill's Risk Yields New Warning*, N.Y. TIMES, Jan. 5, 1999, at F2.

172. See Kolata, *supra* note 12, at F8; see also McCann et al., *supra* note 161, at 670 (supporting a planned phase IV study to help identify patient factors likely to lead to pulmonary hypertension from use of fen-phen, and advocating a more careful risk/benefit assessment during the prescribing process).

B. Liver Toxicity Problems

Measures of liver function are a significant indicator of how the body metabolizes many types of medications. When the liver cannot, for some reason, properly break down a drug, the patient may experience some form of liver failure. More typically, a patient experiences a problem with liver function such as an elevated level of liver transaminase enzymes, or symptoms such as jaundice, nausea, vomiting, abdominal pain, loss of appetite, or dark urine. In severe cases, the liver may fail completely and require transplantation.¹⁷³ Because of the serious risks associated with drugs that affect liver function, researchers use metabolic studies and clinical trials to detect liver problems associated with new drugs so that physicians can prescribe these products safely.

The painkiller Duract (bromfenac sodium) first entered the market in July 1997. By the time the FDA withdrew approval for marketing in June 1998, the drug apparently had caused four deaths due to liver toxicity and required liver transplants in eight other patients.¹⁷⁴ During clinical trials of Duract, researchers discovered an unexpectedly high incidence of elevated liver enzymes in patients who took the drug for relatively long periods, but experts disagreed about the significance of these problems.¹⁷⁵ One FDA medical officer expressed serious concerns about the drug's potential to produce liver toxicity, and he argued in favor of attaching the agency's most stringent warnings to the drug's labeling at the outset.¹⁷⁶ The FDA chose to approve the product only for short-term use (ten days or less), and included information about elevated liver enzymes in the product labeling.

As the FDA became aware of liver problems in patients taking Duract during the year that the drug was available, it took interim steps to notify physicians of emerging safety problems.¹⁷⁷ Despite the labeling informa-

173. See *Liver Injuries Prompt Warning for Diabetes Drug*, FDA CONSUMER, Jan./Feb. 1998 (describing the range of potential liver complications associated with use of the drug).

174. See Stolberg, *supra* note 2, at A1.

175. See Rochelle Sharpe, *How a Drug Approved by the FDA Turned into a Lethal Failure*, WALL ST. J., Sept. 30, 1998, at A1 (commenting, on the Duract pre-approval evaluation, that "despite the lengthy screening process, it still was the public that conducted the final trial that led to the drug's undoing").

176. See *id.* Dr. Rudolph Widmark noted that Duract appeared to cause more liver-cell damage than any other drug of its kind, suggested that the drug be used for no more than 14 days at a time, and expressed concern that, because there were already many other similar analgesics on the market, physicians might not read the new drug's labeling very carefully. See *id.* Dr. Widmark's concerns were well-founded; some patients received prescriptions for several month's worth of the drug. See *id.*

177. The FDA sent a letter to physicians warning that the drug was unsafe when used

tion, some physicians prescribed Duract for longer than ten days, and the agency began receiving reports of liver failure. The FDA responded by requiring prominent boxed warnings in the drug's labeling, and the manufacturer issued a "Dear Doctor" letter emphasizing the drug's dangers and describing the parameters for proper use.¹⁷⁸ These efforts did not completely prevent the inappropriate prescribing of Duract for long-term use. Thus, in June 1998, after the FDA concluded that it could not impose effective restrictions on the duration of use, the manufacturer voluntarily withdrew the drug from the market.¹⁷⁹

Recent adverse drug reaction reports have linked the diabetes drug Rezulin (troglitazone) with forty-three cases of acute liver failure, including twenty-eight deaths.¹⁸⁰ The drug had generated optimism among physicians treating patients with diabetes because clinical trials suggested that it could eliminate the need for insulin treatment in many diabetics.¹⁸¹ The lead FDA reviewer opposed the approval of the drug based on the manufacturer's inadequate safety testing as well as animal and clinical trials that suggested an association between use of the drug and jaundice. Nevertheless, the FDA removed the reviewer from the NDA panel and approved the drug with unusual speed.¹⁸² Because of the drug's uniqueness and potential positive effect on the lives of many patients, the agency may have felt strong pressure to approve the drug despite early evidence of liver toxicity during the clinical trials.

The FDA approved Rezulin in January 1997. By the end of that year, however, an increase in ADRs forced the agency to warn physicians to

longer than the 10-days tested in the clinical trials. It also required the manufacturer to add a large boxed warning to the drug's label describing the potential fatal hepatic complications, including jaundice and fulminant hepatitis, associated with Duract. See Sharpe, *supra* note 175, at A1; *Summaries of "Dear Health Professional" Letters and Other Safety Notifications*, FDA MED. BUL., Summer 1998, available in <<http://www.fda.gov/medbull/summer98/summarie.html>>.

178. See Letter from Wyeth-Ayerst Laboratories to "Dear Health Care Professional" (Feb. 10, 1998), available in <<http://www.fda.gov/medwatch/safety/1998/duract.htm>> (warning about bromfenac).

179. See FDA, *Wyeth-Ayerst Laboratories Announces the Withdrawal of Duract from the Market*, Talk Paper No. T98-36, June 22, 1998, available in <<http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html>>.

180. See John Schwartz, *FDA Panel Backs Diabetes Drug*, WASH. POST, Mar. 27, 1999, at A6; see also Letter from Wyeth-Ayerst Laboratories to "Dear Health Care Professional" (June 22, 1998), available in <<http://www.fda.gov/medwatch/safety/1998/duract3.htm>> (withdrawing the drug).

181. See Natalie Hopkinson, *Advocacy Group Petitions FDA to Ban Diabetes Drug Troglitazone*, WALL ST. J., July 28, 1998, at B6.

182. See Schwartz, *supra* note 49, at A1 (noting that the reviewer on the Rezulin NDA panel was removed after Warner-Lambert officials accused the reviewer of inappropriate language and behavior during panel meetings).

monitor their patients closely for liver damage. The FDA required the sponsor to print more prominent boxed warnings on the drug's label, and it recommended that physicians test patients' liver function regularly, especially during the first six months of drug use.¹⁸³ The drug's manufacturer continues to market Rezulin, asserting that its risks are justified because the drug offers a unique therapy and because the incidence of adverse effects is only one out of 60,000 patients who take the drug.¹⁸⁴ An FDA advisory committee met to review the drug's safety and concurred, by a vote of eleven to one, with the position of the manufacturer; one year later, the agency opted to withdraw marketing approval for Rezulin because of 63 fatalities linked to the drug.¹⁸⁵

Problems associated with liver function in patients taking new drugs continue to appear and demand close monitoring. The FDA recently warned physicians not to prescribe another new drug, the antibiotic Trovan (trovafloxacin), except to treat life-threatening infections because the drug appears to cause liver damage. The agency has recommended strict prescribing and monitoring restrictions for the drug's continued use,¹⁸⁶ and the drug's future remains uncertain. For now, the drug's manufacturer will continue to market Trovan in the United States. In Europe, however, the Committee for Proprietary Medicinal Products has recommended a marketing suspension for one year so that scientists and physicians can more carefully evaluate the drug's risks.¹⁸⁷

183. See FDA Endocrinologic and Metabolic Drugs Advisory Committee Minutes at 13 (Mar. 26, 1999), available in <<http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3499t1.rtf>>.

184. See Schwartz, *supra* note 49, at A1 (noting also that the company believes that better post-approval monitoring for liver problems in patients taking Rezulin will further reduce the future incidence of adverse side effects).

185. See Schwartz, *supra* note 180, at A6 (noting also that the advisory panel voted eight to four to recommend that the drug not be used as a first-line therapy for diabetes, and that it not be used alone but only in combination with insulin); Denise Grady, *F.D.A. Withdraws Drug for Diabetics, Citing Health Risks*, N.Y. TIMES, Mar. 22, 2000, at A1. An FDA spokesperson stated that the agency "had changed its position on Rezulin because data on . . . two newer drugs showed them to be safer" to treat the same condition. *Id.*

186. In order to ensure that physicians comply with the prescribing and monitoring recommendations (short-term use for 14 days or less), the FDA now only permits prescribing in inpatient health care facilities where careful monitoring of liver function is feasible. Adverse drug reaction reports suggest that five patients have died as a result of taking the drug, and another 14 patients have suffered acute liver failure. See *FDA Heeds Urging to Ban Trovan Use, Warns of Reported Liver Toxicity*, MEALEY'S EMERGING DRUGS & DEVICES, June 18, 1999, available in LEXIS, Health Library, MEADMD file.

187. See *id.*

C. Unexpected Drug Interactions

Recent reports have uncovered a serious and unexpected drug interaction problem with a number of prescription drugs. Practically speaking, it is virtually impossible for a manufacturer to test a new chemical entity with every other medication that might create an adverse interaction.¹⁸⁸ During the clinical trials process, a sponsor of an NDA must select, with input from the FDA, likely drugs to test in combination with its new drug in order to uncover potential drug interactions. Those who evaluate drug safety find it particularly difficult to predict drug interactions at the clinical trials phase of the new drug evaluation process because many variables, such as particular patient sensitivities and lifestyle habits, confound the causation assessment.

For example, in pre-approval trials for the blood pressure and angina medication Posicor (mibefradil), the sponsor tested the new drug with drugs selected as likely combinations, including drugs that the sponsor believed would create adverse interactions. The FDA advisory committee voted five to three to approve Posicor, with the dissenters expressing serious concerns about the drug's safety based on the clinical studies.¹⁸⁹ Although at the time of approval the agency was aware that Posicor tended to interact badly with other commonly-prescribed drugs, it took the widespread use of the drug after approval to demonstrate the magnitude of the problem. The reported ADRs suggested that Posicor interacts negatively with as many as two dozen other prescription drugs.¹⁹⁰ Furthermore, the patients for whom doctors prescribe the drug are mainly elderly and often have multiple health problems; thus, these patients tended to take a variety of prescription drugs concurrently, thereby increasing the odds of a negative interaction. Numerous reports of adverse drug interactions, including low heart rates, irregular heartbeats, kidney damage, and twenty-four reported deaths, convinced the FDA to withdraw its approval of the drug.¹⁹¹ After less than one year on the

188. See Langreth, *supra* note 25, at B16 (describing Posicor's interactions with several cholesterol-lowering drugs).

189. See *id.* (noting that one of the dissenters, Dr. Lemuel Moye of the University of Texas Health Science Center, expressed concern about the "stampede for efficiency in getting drugs approved" and believes that the FDA should require drug companies to conduct longer clinical studies before granting marketing approval).

190. See *id.* (noting that Posicor is the latest in a large class of drugs called calcium-channel blockers).

191. See *Roche Laboratories Announces Withdrawal of Posicor from the Market*, Talk Paper No. T98-33, June 8, 1998, available in <<http://www.fda.gov/bbs/topics/ANSWERS/ANS00876.html>> (noting that the drug reduces the activity of certain liver enzymes which metabolize other drugs, causing the other drugs to accumulate in the body at dangerously

market, the manufacturer discontinued the sale of Posicor. At the time of the withdrawal, more than 200,000 patients in the United States and 400,000 patients in other countries had taken the drug.¹⁹²

The FDA recently warned physicians that they should prescribe the heartburn drug Propulsid (cisapride) only as a therapy of last resort because of its tendency to cause serious heart-rhythm problems when combined with a variety of other medications.¹⁹³ Since its approval in 1993, millions of patients have taken Propulsid. The FDA has received reports of at least seventy deaths associated with the use of Propulsid,¹⁹⁴ though doubts remain about the causal connection between the drug and these deaths. Because of these accumulating reports, the manufacturer agreed to add new warnings to the product's labeling. The FDA has not yet requested a recall of the drug, but it has asked the drug's manufacturer to send out 800,000 "Dear Doctor" letters to warn physicians of the drug's potential problems.¹⁹⁵

Accumulating evidence also suggests that other popular drugs may pose unjustifiable interaction hazards. For example, the allergy drug Seldane (terfenadine) was available by prescription for twelve years before mounting evidence of adverse interactions with a variety of other prescription drugs, such as cardiac arrhythmias, began to cause concern.¹⁹⁶ The drug's manufacturer voluntarily agreed to discontinue selling Seldane in February 1998 under strong pressure from the FDA.¹⁹⁷

high levels). Critics of the FDA question why the drug was approved in the first place. Dr. Sidney Wolfe, the director of Public Citizen's Health Research Group, commented that "when you've got a drug that no one remotely thinks is any better than any of the other eight or nine already on the market, why for the purpose of public health or public safety do you approve it?" Stolberg, *supra* note 2, at A1.

192. *See id.*

193. *See* Robert Langreth & Rochelle Sharpe, *Drug May Pose Risks, FDA Warns of Side Effects from Propulsid*, WALL ST. J., June 30, 1998, at B5.

194. *See* Jane E. Henney, *Revised Labeling for Cisapride*, 283 JAMA 1131 (2000).

195. *See* Langreth & Sharpe, *supra* note 193, at B5 (noting that Johnson & Johnson, the manufacturer of Propulsid, issued warnings to physicians at the request of the FDA about potential adverse effects when the drug is taken in combination with certain antidepressants, antibiotics, antifungals, and protease inhibitors, among other medications); *see also* Letter from Janssen Pharmaceutical Research Foundation to Healthcare Professionals (June 26, 1998), available in <<http://www.fda.gov/medwatch/safety/1998/propul.htm>>.

196. *See* Nancy Ann Jeffrey & Robert Langreth, *Viagra's Lesson: New Drugs, Unknown Risks*, WALL ST. J., June 10, 1998, at B1; *see also* Kessler, *supra* note 125, at 2765 (describing Seldane's interaction with antifungal and antibiotic drugs, and noting that individual differences in drug metabolism can cause a wide range of patient responses to the same drug or drug combination).

197. *See* *Summaries of "Dear Health Professional" Letters*, *supra* note 177. Late in 1997, the manufacturers reformulated and released the drug under a new brand name. *See* Denise Grady, *Need Is Seen for a Drug Safety Board*, N.Y. TIMES, Dec. 29, 1998, at D7 (describing reformulation and re-release of terfenadine under the brand name Allegra).

The popular new impotence drug Viagra (sildenafil), which became available in April 1998,¹⁹⁸ was associated with 130 deaths in the first eight months of its marketing.¹⁹⁹ Although its labeling warns physicians against prescribing Viagra to patients who have cardiac problems or who take nitrate medications, the FDA has received numerous reports of cardiac irregularities in patients who take the drug.²⁰⁰ Because male impotence often accompanies serious heart disease, Viagra users predictably will take other prescription medications concurrently. The interaction between the medications, combined with the physical stresses of intercourse, appears to have triggered heart attacks or strokes in some of these patients.²⁰¹ Viagra's sponsor studied the drug's safety when used with ten other drugs, ranging from the antacid Maalox to the antibiotic erythromycin and the blood thinner warfarin. However, because the company knew of the risk of using Viagra in combination with nitrates, it excluded patients who were taking this type of drug from its clinical trials. In addition, a number of the patients who died were taking the drug in combination with other medications that the company had not studied in its trials.²⁰² Eight months after Pfizer began marketing the drug, the FDA required new label warnings about its safety,²⁰³ and it will continue to monitor Viagra closely.

In the last two years, patients have encountered a number of unanticipated drug-related hazards including pulmonary hypertension and heart valve damage from diet drugs, liver toxicity from several different drugs, and a series of dangerous interactions involving prescription medications. This constellation of drug hazards has led some critics to question both the effectiveness of the pre-approval system, and the ability of the post-approval safety surveillance system to detect and respond quickly to previously-unknown drug risks. Conversely, to the extent that the FDA feels insecure about the effectiveness of its post-approval monitoring sys-

198. See Jeffrey & Langreth, *supra* note 196, at B1 (noting that, in the first 10 weeks of its marketing, pharmacists filled approximately 1.7 million new prescriptions for the drug).

199. See Rochelle Sharpe & Robert Langreth, *Pfizer and FDA Agree to New Warnings on Labels for Viagra, Behind 130 Deaths*, WALL ST. J., Nov. 25, 1998, at B7.

200. See *id.* (noting that 70% of the men who died while using Viagra had one or more risk factors for cardiovascular disease).

201. See Jeffrey & Langreth, *supra* note 196, at B1.

202. See *id.*

203. See *New Warning Issued on Use of Viagra*, N.Y. TIMES, Nov. 25, 1998, at A23 (describing five separate points in the warnings: information about sudden cardiac death and hypertension; priapism; temporary low blood pressure; contraindications for men with unstable angina, retinitis pigmentosa, stroke; and other cardiac problems); see also Sharpe & Langreth, *supra* note 199, at B7 (describing new warning requirements).

tem, there is a risk that it may overreact to an apparent crisis.²⁰⁴ Although the agency recently has defended both its pre-approval and post-approval regulatory approach, it has also acknowledged that there is room for improvement.

III. POSSIBLE SOLUTIONS

Currently, the FDA has at its disposal a range of possible responses to the problems associated with ADRs. It has only begun, however, to tackle the problem of how to improve the quality and quantity of the information on which it bases its responses. Moreover, the FDA does not appear to have seriously considered expanded and more formalized roles for the medical profession, or for other federal agencies, which might permit better responses to the negative impact of ADRs on patient care. Congress and the FDA can implement a variety of changes that would improve the ability of physicians, manufacturers, patients, and the FDA itself to gather and use information about side effects associated with new drugs. Many of the proposed approaches discussed below would require the FDA, the CDC, pharmaceutical manufacturers, and health care providers to participate more actively in the collection and analysis of population-based ADR data. This participation is necessary to ensure that the risks accompanying prescription drug therapy, which plays such a significant role in the treatment and prevention of illness, remain justified by the benefits.

A. Changes in Regulatory Emphasis

Increased FDA resources represent one obvious response to the problem of identifying and dealing with adverse drug reactions. Additional regulatory staff are already available at the pre-approval stage to meet the public demand that NDAs be reviewed in a timely fashion. The agency also needs additional staff to implement a more effective post-approval monitoring process in response to the problems arising from the

204. The FDA's approach toward problems associated with breast implants is revealing. See Marcia Angell, *Shattuck Lecture—Evaluating the Health Risks of Breast Implants: The Interplay of Medical Science, the Law, and Public Opinion*, 334 *NEW ENG. J. MED.* 1513, 1514 (1996) (describing how the FDA's initial "relaxed attitude" towards silicone gel-filled breast implants changed in response to public outcry about anecdotal reports of auto-immune disease in women with the implants and large jury verdicts to plaintiffs who complained of injury from the devices). The agency finally banned the devices "not because implants had been found dangerous, but because they had not been proved safe," and one commentator suggested that the FDA's response was unjustifiably drastic and caused a panic in many women who received the implants. See *id.*

increasing stream of newly-approved drugs.²⁰⁵ Congress and the FDA clearly recognize the need for increased funding, and they appear to be taking steps in the right direction.²⁰⁶ In addition to increased appropriations, Congress should consider amending the statutory provisions authorizing user fees and targeting a percentage of fees specifically for adverse drug reaction monitoring, instead of directing all of the user fee proceeds towards increasing personnel to review NDAs.²⁰⁷

Separately, the FDA should continue its effort to improve the clarity of its existing post-approval reporting requirements. The agency might accomplish this goal by amending its existing regulations, or it might issue additional guidelines to aid in the interpretation of the regulations.²⁰⁸ Because current regulations provide manufacturers some leeway to make judgments about whether to forward ADRs to the FDA, commentators have expressed concern that the FDA sees only a fraction of the reports that physicians forward to manufacturers.²⁰⁹ Clarifying reporting requirements may help to diminish the underreporting that arises from a lack of understanding of certain key regulatory terms. Past regulatory amendments and guidance documents, however, have proven somewhat ineffective at increasing the rate of ADR reporting.

The accelerated approval procedures may pose a heightened risk of error in the pre-approval safety assessment process and can create undesirable pressure on the agency's post-approval system by increasing the overall volume of reports. In order to facilitate post-approval surveillance of these new drugs, the FDA could narrow the class of eligible products or establish restrictions on distribution. At the front end, the FDA recently has limited the availability of fast-track review to drugs

205. In 1998, the FDA's Center for Drug Evaluation and Research (CDER) redesignated its Division of Pharmacovigilance and Epidemiology to become the Office of Post-marketing Drug Risk Assessment. See CDER REPORT TO THE NATION, *supra* note 13, at 22.

206. See Charles Marwick, *FDA May Get Welcome New Funds in Its Budget*, 281 JAMA 888, 888 (1999) (describing the FDA's proposed 2000 budget requesting an increase of 16% (\$216 million) over its 1999 budget to enable the agency to focus on improving surveillance of adverse drug events and postmarket quality assurance).

207. Other commentators also have recognized the pressing need for additional resources targeted at postmarket drug safety monitoring, and they have proposed both public and private funding initiatives for this purpose. See, e.g., Gelijns et al., *supra* note 45, at 697 (proposing public funding to investigate potentially beneficial uses of new drugs, and noting that such research presumably also would yield additional safety information).

208. See *supra* notes 96-106 (describing existing guidelines).

209. See Green, *supra* note 114, at 499 n.139 (describing examples of "flagrant manufacturer disregard" for ADR reporting requirements).

that have the potential to respond to "unmet medical needs."²¹⁰ Therapeutic substitutes for already-marketed drugs that provide no significant additional benefit to patients do not warrant accelerated approval.²¹¹

In practice, some physicians refrain from prescribing new drugs when existing drugs (with a more developed safety profile) will accomplish the desired results.²¹² As a final step in the NDA process, the FDA might consider formally classifying certain newly-approved drugs as "high risk" to assist physicians in identifying drugs that should be used with extra caution.²¹³ It already makes such determinations on an ad hoc basis. For example, the FDA recently decided to permit the sale of thalidomide for treatment of Hansen's Disease (leprosy), and it attached unusually stringent prescribing safeguards as a condition of marketing approval for this purpose.²¹⁴ Such a classification system might revolve around three easy-

210. See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 506(a)(1), 111 Stat. 2296, 2309 (codified at 21 U.S.C. § 356 (Supp. III 1997)); see also *id.* § 561(c)(2), 111 Stat. at 2366 (limiting treatment INDs to conditions for which "there is no comparable or satisfactory alternative therapy available"); Salbu, *supra* note 57, at 139 (noting the ambiguity surrounding the question of whether safe and effective drug treatments are available).

211. See *supra* notes 175-80 and accompanying text (discussing the approval and subsequent withdrawal of Duract, a NSAID that joined the market with a large group of already-approved NSAIDs). Although Duract was not approved under accelerated or expedited review, the safety problems that became apparent prior to approval suggest that the agency might have been more cautious and demanded additional safety data before permitting the drug to enter the market. See Stolberg, *supra* note 2, at A1 (discussing a proposal to limit fast-track approval only to breakthrough drugs, not "me too" drugs). As one commentator recently stated: "The more effective and safe the approved treatments, the less urgent the patient's need for alternatives, and hence the weaker the patient's claims of exigency." Salbu, *supra* note 57, at 139.

212. See Rochelle Sharpe, *MedWatch System Comes Under Fire: FDA Defends Drug Monitoring as Physicians, Advocates Are Cautious*, WALL ST. J., June 24, 1998, at B5.

213. See *FDA Gets Advice on Modernization Act Compliance*, 280 JAMA 1214, 1214 (1998) (describing various recommendations concerning prescription drug safety and the reporting of adverse drug reactions, including creating a high-risk drug category to alert physicians that certain drugs require especially close monitoring). Studies have recognized the risks associated with the hasty prescribing of new, and relatively untested, drugs. One British study noted that physicians who prescribed newly-approved drugs most heavily were also least likely to file adverse reaction reports. See William Inman & Gillian Pearce, *Prescriber Profile and Post-Marketing Surveillance*, 342 LANCET 658, 659-60 (1993).

214. See FDA, *FDA Approves Thalidomide for Hansen's Disease Side Effect, Imposes Unprecedented Restrictions on Distribution*, Talk Paper No. T98-44 (July 16, 1998) <<http://www.fda.gov/bbs/topics/ANSWERS/ANS00887.html>> [hereinafter *FDA Talk Paper*]. Thalidomide shows tremendous promise in the treatment of Hansen's Disease, as well as lupus, AIDS, and other auto-immune diseases, but the potential for devastating birth defects remains. Many may question the wisdom of marketing this drug under any circumstances, yet the FDA believes that it has implemented sufficient restrictions and safeguards to prevent the birth of children with Thalidomide injuries. The manufacturer of Thalidomide, Celgene, plans to engage the Sloane Epidemiology Unit of Boston Uni-

to-distinguish categories of newly-approved drugs. "Category I" could refer to drugs approved on an accelerated basis for which the FDA requires post-approval studies as a condition of continued marketing. "Category II" might apply to newly-approved drugs that raise unusual lingering safety concerns, which are elaborated elsewhere in the package insert, but that promise a previously unavailable benefit to patients.²¹⁵ "Category III" could refer to drugs that, while newly-approved, appear to raise no significant safety concerns, either because they are closely related to drugs with an established safety profile or because the agency's pre-approval review left no lingering safety concerns unresolved.²¹⁶

Other changes in the adverse drug event reporting system would help to shift the FDA and corporate mindset away from the traditional approach, which requires manufacturers to send reports of ADRs to the agency, to a more cooperative approach between pharmaceutical manufacturers and health care providers.²¹⁷ For example, although the FDA generally lacks jurisdiction over the practice of medicine,²¹⁸ a require-

versity to monitor prescriptions in order to trace the birth of any Thalidomide babies. See Kolata, *supra* note 12, at F1. The FDA requires as a condition of marketing that Celgene implement the "System for Thalidomide Education and Prescribing Safety (STEPS)" program. See *FDA Talk Paper, supra*. Under the terms of STEPS, only registered physicians may prescribe Thalidomide to patients, who must comply with mandatory contraceptive requirements and mandatory pregnancy testing. See *id.* Thalidomide's dangers are well-documented, permitting the FDA to monitor its use with due care. The problem of appropriate post-approval monitoring remains, however, for other, newer drugs whose dangerous side-effects are yet undiscovered.

215. Rezulin represents an example of such a drug because, although the reviewing panel expressed concern about its liver toxicity, see *supra* note 186, it provides a new mechanism of action to manage diabetes.

216. Cf. Margaret Gilhooley, *Innovative Drugs, Products Liability, Regulatory Compliance, and Patient Choice*, 24 SETON HALL L. REV. 1481, 1496-98 (1994) (advocating that a digest of current scientific studies about drug safety issues that the FDA is considering, but has not yet acted upon, be made available to physicians). The FDA has used similar classification systems in reviewing the effectiveness of drugs first approved before 1962, active ingredients in OTC drugs, and medical devices. See *id.*

217. One group of commentators has explored methods of ADR data collection for physicians in the hospital setting and has recommended a computer monitoring strategy as one method for identifying drug problems while minimizing the shortcomings of other, more labor-intensive approaches such as chart review. See Jha et al., *supra* note 20, at 311-12.

218. See 21 U.S.C. § 396 (Supp. III 1997) (medical devices); 37 Fed. Reg. 16,503, 16,504 (1972) (concluding that "it is clear that Congress did not intend the [FDA] to regulate or interfere with the practice of medicine"). Required physician participation in a health-related safety reporting system is not unprecedented. Nearly all states mandate physician reporting of suspected cases of child abuse. See, e.g., N.Y. SOC. SERV. LAW § 413(1) (McKinney 1999). Physicians must also report patient threats to individual intended victims, certain types of communicable diseases, and gunshot and knife wounds. See CODE OF MEDICAL ETHICS, *supra* note 121, Op. 5.05.

ment that physicians send reports of suspected drug reactions directly to the agency, rather than to manufacturers, would increase the rate of reporting serious adverse events, to which safety reviewers at the FDA would give special attention.²¹⁹ After all, physicians can best detect possible connections between prescription drugs and patient problems. Although the FDA can work to clarify and strengthen post-approval reporting procedures, health care professionals have an equally important ethical duty to report ADRs,²²⁰ which serves the interests of their current and future patients.

B. Generating Better Data

Additional resources and clearer regulatory requirements alone will not, however, provide an adequate response to the problem of identifying unexpected adverse drug events. Several approaches might help to improve the quality and quantity of data on which health care professionals base their prescribing decisions.

Congress should consider authorizing explicit Phase IV study requirements for all newly-approved drugs, not just for those approved under an accelerated review process.²²¹ In contrast to the current approach of passively waiting for additional information about new drugs from manufacturers and health care providers, required Phase IV post-approval studies or other special post-market surveillance conditions could more readily generate additional information early in the marketing process and in a more systematic fashion.²²² The FDA and the industry should make better use of the opportunities that Phase IV studies present in order to uncover serious or rare adverse drug reactions and interactions more

219. See *supra* notes 122–24 and accompanying text.

220. See *supra* Part I.B.2.

221. The FDA long ago issued regulations to govern postmarketing research. See *Approved New Drugs that Require Continuation of Long Term Studies, Records, and Reports*, 35 Fed. Reg. 14,784 (1970) (codified as amended at 21 C.F.R. § 310.303 (1999)). Except for fast-track drug approvals, the FDA does not appear to have the power to require Phase IV trials. A few courts have, however, held that manufacturers of prescription drugs have an obligation to conduct post approval studies to clarify risks. See, e.g., *Kociemba v. G.D. Searle & Co.*, 707 F. Supp. 1517, 1528-29 (D. Minn. 1989).

222. The FDA has conditioned NDA approval on a requirement of specific post-approval research or other special monitoring and safety controls many times in the past. In addition to the controls described above for the marketing of Thalidomide, the agency has required large postmarketing surveillance studies and smaller post-approval research studies for a variety of other drugs. See Nancy Mattison & Barbara W. Richard, *Postapproval Research Requested by the FDA at the Time of NCE Approval, 1970-1984*, 21 DRUG INFO. J. 309, 309 (1987). One study found that the FDA had conditioned its approval of one-third to one-half of new drugs on the NDA sponsor's conducting additional post-approval safety studies. See *id.* at 323.

quickly.²²³ Simple post-approval safety trials will detect rarer adverse reactions by studying a large, diverse group of patients.²²⁴ In the past, the FDA has required special surveillance protections as a condition for marketing of some new drugs and also for some medical devices.²²⁵ If the agency implemented the categorization system for newly-approved drugs as described above, it could require large, simple post-approval trials for Categories I and II to generate high quality safety data in the early phases of the drugs' marketing. Such an approach would quickly provide the FDA with a greater amount of controlled data from which to draw conclusions about possible serious side effects associated with recently approved new drugs.²²⁶ This would also shift the additional financial burden of gathering such information to the private sector.

Likewise, the clinical research community plays a vital role in detecting adverse reactions associated with investigational and newly approved drugs. In addition to requiring physician reporting of ADRs via the MedWatch system, the FDA should consider permitting clinical researchers and physicians access to information concerning ADRs directly from a centralized database so that these health care providers can use the information in making prescription decisions.²²⁷ Physicians may embrace a required reporting scheme more readily if they are allowed easy access to the data that results from their efforts. Clinical researchers and

223. See Woosley, *supra* note 39, at 187-88.

224. See Marwick, *supra* note 10, at 316.

225. For example, the acne drug Accutane, manufactured by Hoffman-La Roche, is marketed under a program that requires doctors to register all women for whom they prescribe the drug. The drug causes severe birth defects in the children of women who take the drug during pregnancy. Boston University's Sloane Epidemiology Unit monitors the registry, which enrolled 24,503 women during its first seven years. See Kolata, *supra* note 12, at F8. During that period, 402 of the enrolled women became pregnant while taking the drug; although most of these women had abortions, 32 babies were born, one with serious birth defects. See *id.* Critics point out that the problem with such registry surveillance programs is that they rely on physicians to encourage their patients to participate. See *id.* When a physician fails to be conscientious about prescribing the drug and monitoring the patient, the system breaks down, with potentially disastrous consequences.

226. See Salbu, *supra* note 57, at 146 (arguing that FDA conservatism should decrease with the increasing utility of post-approval drug monitoring procedures that can mitigate potential harm attributable to new drug treatments).

227. Providing access to ADR databases potentially raises problems under the Freedom of Information Act (FOIA). See Pub. L. No. 89-487, 80 Stat. 250 (1966) (codified as amended at 5 U.S.C. § 552 (1994); see also 45 C.F.R. pt. 5 (1998) (Health and Human Services FOIA regulations). Courts have limited adverse reaction data report disclosure in the past. See *Public Citizen Health Research Group v. FDA*, 704 F.2d 1280 (D.C. Cir. 1983) (holding, on remand, that company-specific adverse reaction rates for intraocular lenses could be withheld under FOIA but that averaged adverse reaction data had to be disclosed).

epidemiologists also may be able to use preliminary data to improve the design of future research into the safety and efficacy of pharmaceutical products.²²⁸

Finally, greater coordination of information-gathering efforts at the national and international level would clearly enhance the FDA's ability to respond quickly to a pattern of suspected adverse drug reactions. The FDA should compile information about ADRs from clinical trials, medical records, and computerized databases, including the FDA's MedWatch database, in one centralized database and evaluate this information to detect patterns of adverse reactions.²²⁹ The FDA has taken an important step in this direction recently by implementing the Adverse Event Reporting System (AERS), a computerized database that combines the ADR reports from MedWatch with the required reports from manufacturers.²³⁰ Continued improvement of data coordination should prove useful without adding significantly to the financial burdens associated with the drug safety system.

Ideally, improved efforts at coordinating information would take place at an international level, and the FDA has already begun to expand its cooperation with foreign governments in recognition of the global marketplace,²³¹ through participation in the International Conference on Harmonization (ICH).²³² It appears, however, that the FDA has directed

228. See Cheryl L. Vogt, Letter to the Editor, *Adverse Drug Reactions: Getting Information Back from MEDWatch*, 272 JAMA 590, 591 (1994) (eliciting a reply from Stuart L. Nightingale of FDA noting the agency's planned efforts to provide direct access to the MedWatch database for health professionals).

229. See Timothy Brewer & Graham A. Colditz, *Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, 281 JAMA 824, 826 (1999) (advocating the collection and evaluation of data from multiple sources to complement the information gathered from spontaneous reporting systems).

230. See CDER REPORT TO THE NATION, *supra* note 13, at 23 (explaining that compilations of reports can generate "signals" indicating a potential for serious, previously-unknown ADRs, which may be analyzed further using epidemiological and analytic databases); FDA Plan for Statutory Compliance, 63 Fed. Reg. 65,000, 65,030 (1998) (describing the AERS system and the FDA's goal of "revitalized pharmacovigilance"); Center for Drug Evaluation and Research, *Pharmacovigilance Screening* (visited Nov. 10, 1999) <<http://www.fda.gov/cder/aers/features.htm>> (describing the AERS system's five levels of analysis for ADR screening).

231. See Sharon Smith Holston, *An Overview of International Cooperation*, 52 FOOD & DRUG L.J. 197, 197 (1997) (describing the divisions charged with various international tasks, including "[s]haring some of the regulatory functions with FDA's counterparts abroad").

232. The ICH is a joint international program designed to discuss which testing procedures should be required to evaluate the safety, quality, and efficacy of new drugs. See Eric M. Katz, *Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace?*, 48 FOOD & DRUG L.J. 301 (1994); Joseph G. Contrera, Comment, *The Food*

most of its efforts so far at facilitating the exchange of pre-market evaluation information. The FDA has started the process of implementing an international exchange of adverse events information, but the system is not yet fully functional.²³³ The European Community's European Agency for the Evaluation of Medicinal Products oversees a centralized procedure for reporting adverse drug reactions and other new drug-related safety data, and all EC member states share the data.²³⁴ Better coordination between the FDA and its foreign counterparts at the post-approval stage may help to fill this foreign marketing data gap.²³⁵

C. New Models for Post-Approval Safety Surveillance

Some commentators have suggested that one way to compensate for the scarce agency resources devoted to post-approval monitoring of drugs is to create a separate and independent drug safety board.²³⁶ Such a board might be industry-funded or independent of both industry and the FDA.²³⁷ An industry-funded board seems appealing, because it would place the financial burden associated with post-approval surveillance on those entities that benefit financially from the marketing of new drugs. Such a system would not, however, resolve the inherent conflict of interest that would exist in requiring the industry to fund and administer a system to collect adverse data about the products that it relies on for revenue.²³⁸ Even in a cooperative industry venture, the potential for an

and Drug Administration and the International Conference on Harmonization: How Harmonious Will International Pharmaceutical Regulations Become?, 8 ADMIN. L.J. AM. U. 927 (1995).

233. See CDER REPORT TO THE NATION, *supra* note 13, at 28 (describing the FDA's collaboration with ICH to minimize duplication in approving and monitoring new drugs internationally); see also Holston, *supra* note 231, at 199-200.

234. See Richard F. Kingham et al., *The New European Medicines Agency*, 49 FOOD & DRUG L.J. 301, 313 (1994).

235. Recently, patient advocacy groups and others have pressured the FDA to approve certain new drugs that are already available in Europe, and better international coordination of safety and efficacy information will help the agency to respond to these demands, while doing its best to ensure safety. Cf. Merrill, *supra* note 29, at 1862-63 (describing a proposal to require that the FDA formally accept or justify rejecting approval decisions for drugs approved in the European Community).

236. See Wood et al., *supra* note 36, at 1852.

237. See Elizabeth M. Rutherford, *The FDA and "Privatization"—The Drug Approval Process*, 50 FOOD & DRUG L.J. 203, 210-11, 225 (1995) (describing the advantages and disadvantages of privatization of the pre-approval process, and concluding that limited privatization of discrete agency functions may be feasible).

238. See Wood et al., *supra* note 36, at 1852-53 (comparing the investigation process for airplane crashes, and noting that "[w]e do not leave the investigation of such tragedies solely to the aircraft manufacturer, the airline, or the agency responsible for the regulation of the industry").

over-emphasis on positive data about safety and efficacy and an under-emphasis on the corresponding negative data remains.

Other areas of safety regulation divide responsibility among different agencies in order to avoid the potential conflicts of interest inherent in the FDA model. The FDA plays a dual role in monitoring prescription drug safety. At the front end, the agency sets and applies regulatory standards that determine whether an NDA sponsor will be permitted to market a new drug. At the back end, once a new drug enters the market, the FDA sets and applies a different set of regulatory requirements designed to monitor the safety of the drugs it has approved. The agency may be loathe to second-guess its pre-approval decisions when it becomes apparent that a newly-marketed drug poses unanticipated safety risks.

In some ways, the ADR manufacturer reporting requirements create a conflict of interest akin to that of designating an airplane manufacturer as the sole investigator into a crash of one of its aircraft.²³⁹ To avoid such a conflict, the Federal Aviation Administration (FAA) regulates airplane safety by creating and enforcing safety standards for aircraft, while the National Transportation Safety Board (NTSB) is charged with directing the investigation of aviation disasters.²⁴⁰ The two regulatory entities play separate but complementary roles in the safety assurance process.²⁴¹ In tandem with investigating particular accidents, the NTSB often forwards recommendations for modifying standards to the FAA. In this model, the agency that sets design, operator, and safety standards is not entrusted to direct the investigation into situations in which those standards appear to have failed.²⁴² Instead, the independent NTSB directs the re-

239. See *id.* at 1852 (noting that, although only 511 fatalities occurred in airline accidents from 1995 to 1997, each accident was investigated thoroughly by the National Transportation Safety Board (NTSB), and demanding the "same level of scrutiny" for ADRs).

240. See 49 U.S.C. § 1131 (1994) (authorizing the NTSB to investigate various types of transportation accidents under the jurisdiction of other units of the Department of Transportation); Matthew L. Wald, *Two Positions on Safety*, N.Y. TIMES, Aug. 30, 1998, at A16 (describing the relationship between the FAA and the NTSB, and discussing recent accidents which led the NTSB to recommend more aggressive safety regulations to the FAA).

241. See *The FAA Should Inspect Itself*, WASH. POST, May 23, 1996, at A20 (noting the NTSB's long-running criticism of the FAA); see also Wood et al., *supra* note 36, at 1851 ("Such independence is essential to ensure objectivity"). For an overview and critique of the FAA's operations by an outspoken former Inspector General of the Department of Transportation, see MARY SCHIAVO, *FLYING BLIND* (1996).

242. Even in the aviation disaster model, critics complain that airplane manufacturers play an important role in the investigation process, although such entities assist primarily with information-gathering and less with analysis and recommendations for the future. See Matthew L. Wald, *Rand to Assess How Federal Safety Board Runs Crash Inquiries*,

quired investigation, drawing on the expertise of the FAA and private industry as necessary.²⁴³ The regulatory model used for aviation accidents may offer some useful lessons for the FDA.

To avoid the apparent conflict, commentators have recommended the creation of a completely independent drug safety board to compile and review drug product safety and efficacy data.²⁴⁴ Such a board would bypass manufacturer tendencies to discount negative safety information and would counteract the FDA's natural hesitancy to confess error when a drug it just approved generates unusual and unexpected rates of adverse reactions. The independent board might oversee a requirement for mandatory postmarket data collection among a representative population of patients with typical conditions and duration of treatment for the particular drug.²⁴⁵ In addition, the independent board could investigate specific instances or patterns of ADRs, and it could make regulatory reform or policy recommendations to the FDA so that the agency could reduce the risk of similar events in the future.²⁴⁶

Finally, CDC, which like the FDA, is a unit of the Public Health Service in the Department of Health and Human Services, might undertake the role of a disinterested "drug safety board."²⁴⁷ Because the FDA

N.Y. TIMES, July 17, 1998, at A16.

243. See *id.* (describing how the NTSB directs investigations into transportation accidents "using the people, expertise and equipment of other Government agencies, the pilots' unions and the companies involved in the accident").

244. See Wood et al., *supra* note 36, at 1852-53. For example, the board would assume responsibility for compiling safety data, investigating reports of drug toxicity, and recommending to pharmaceutical manufacturers or to the FDA actions to reduce the risks associated with new drug therapy. See *id.*; see also Grady, *supra* note 197, at D7; Rochelle Sharpe, *Academics Call for Independent Board to Review Problems of Approved Drugs*, WALL ST. J., Dec. 17, 1998, at B7 (noting that experts have been calling for an independent board since the 1970s).

245. See Wood et al., *supra* note 36, at 1852. These commentators have also proposed that the independent drug safety board collect and analyze comparative data on the safety of different drugs used to treat the same condition. Surprisingly, such data is not routinely gathered or analyzed by the FDA currently. See *id.* at 1853. The authors added that such data can also be used to confirm the validity of surrogate end points sometimes used for marketing approval of a new drug. Once sufficient data on a new drug becomes available, the drug safety board might be able to confirm that, for example, a drug which is proven to reduce high blood pressure also has a long term positive benefit for morbidity or mortality associated with high blood pressure, while maintaining an acceptable safety profile. See *id.*; see also Lars Noah, *Pigeonholing Illness: Medical Diagnosis as a Legal Construct*, 50 HASTINGS L.J. 241, 262 (1999) (discussing the regulatory relevance of denominating hypertension as a free-standing disease entity).

246. See Wood et al., *supra* note 36, at 1852.

247. The FDA and the CDC already work cooperatively to run the Vaccine Adverse Event Reporting System (VAERS). The VAERS system receives spontaneous reports from the public, health care professionals, and vaccine manufacturers. Interestingly, the CDC also recently implemented an active vaccine adverse event system using data from

would remain responsible for the initial pre-approval safety evaluation for all new drugs, the CDC, in the role of safety monitor, could provide an independent analysis of safety data as it becomes available. Moreover, the CDC has the requisite biostatistical and epidemiological expertise to perform the task effectively, and the capability to conduct quick follow-up investigations in the field. Commentators have called for greater epidemiological expertise at the FDA, noting that the number of trained epidemiologists at the agency has declined in recent years and suggesting that the FDA utilize outside resources.²⁴⁸ The FDA and CDC are ideally situated to play the independent and complementary roles necessary to improve prescription drug safety and the overall quality of patient care.

IV. CONCLUSION

The FDA, together with physicians and clinical researchers, should rethink the existing approach to the monitoring of unexpected side effects associated with prescription drugs. The increased pace of new drug approval demands a concomitant retooling of the post-approval monitoring process, with an emphasis on directing significant additional resources to the task. In addition, pharmaceutical manufacturers must be encouraged, or even required, to commit more resources to drug safety tracking and testing. The FDA has rightly decided that it is important to increase the speed with which new drugs are approved for marketing. Now it must respond to the volume of safety data that this more efficient approval process creates. Once the FDA has designed improved safety monitoring systems, Congress must respond with budgetary support and amended statutory authority, as needed. Ultimately, however, the agency can improve the ADR monitoring system only to a limited extent. Physicians and other health professionals remain responsible for making individualized prescribing decisions, and the FDA must do its part to ensure that physicians have the best possible information on which to base medication choices for their patients.

four health maintenance organizations. See Timothy Brewer & Graham A. Colditz, *Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, 281 JAMA 824, 826 (1999).

248. See Gerald A. Faich, Letter to the Editor, *Postmarketing Surveillance: Beyond MedWatch*, 270 JAMA 2180 (1993). Dr. Faich opined:

Stimulating reporting without providing resources to ensure adequate follow-up and epidemiologic assessments is only a partial solution. . . . While the agency has increased preapproval resources and activities, the proportion of manpower and funding allocated for postapproval work has actually declined [The FDA should] provide for expanding internal and external epidemiologic expertise.

Id.