Drug Safety and Effectiveness: Issues and Action Options After FDA Approval

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Summary

COX-2 inhibitors and SSRIs—the U.S. public has become more familiar with these technical abbreviations for biochemical processes than one might expect from our general level of science knowledge. Safety concerns about these drugs—used primarily to treat pain and depression—have turned a spotlight on the Food and Drug Administration (FDA) and its approach to protecting the public from drug risks that had not been identified before FDA-approval allowed the drugs on the market.

Two regulatory frameworks exist for the review of prescription drugs. First, in the *premarket approval* process, FDA reviews the safety and effectiveness of new drugs that manufacturers wish to market in the United States. A large part of this review is FDA's examining the manufacturer-provided data from clinical testing—studies in which humans take the *investigational new drug* in carefully controlled, and usually randomized, trials—from progressively larger *Phase I*, *II*, and *III* trials.

Second, after a manufacturer has sufficiently demonstrated a drug's safety and effectiveness for a defined population and specified conditions, and the drug is *FDA-approved*, FDA acts through its *postmarket* regulatory procedures. Manufacturers must report all serious and unexpected adverse reactions to FDA and clinicians and patients may do so.

The law gives FDA authority to take limited action if it finds a drug's post-approval use presents an increased risk of an adverse event. However, many suggest that not only does FDA need a broader range of enforcement tools, but that FDA also is not taking full advantage of the authority it does have.

While critics of FDA differ in their assessment of what is wrong with FDA's approach to postmarket safety activities, there is broad agreement that it needs significant change. Discussion of the problems and possible solutions revolves around six areas: FDA organization, FDA budget, role of industry, opportunities to use the drug approval process to enhance postmarket activities, insufficient postmarket information, and lack of public access to available data. Some of the proposed changes lie within the power of FDA to implement. Others would require congressional action.

This report examines various options for strengthening FDA's ability to protect the public. It will be updated from time to time to reflect legislative action by Congress.

Contents

Tables

Contacts

Introduction

A little over two years ago, the Senate Finance Committee convened to hear testimony sparked by concern over the popular Merck anti-inflammatory drug Vioxx. A few weeks before, Merck had notified the Food and Drug Administration (FDA) that it was withdrawing Vioxx from the market in response to recent study results indicating an increased risk of heart attacks and sudden cardiac deaths among the millions of patients who had been using Vioxx since its introduction in 1999. Senators wanted to find out what had gone wrong and what could be done to prevent it from happening again.

This was not the first time that this Congress had reacted to news about dangers posed by drugs that had already reached the market. Earlier that year, the House Committee on Energy and Commerce's Subcommittee on Oversight and Investigations had held hearings because of controversy over the safety of antidepressants when prescribed to children. In both cases, Members were worried that neither the public nor FDA were sufficiently informed by manufacturers—or, in the case of FDA, sufficiently forthcoming—about risks occurring after the drugs had been first approved.

At the Finance Committee hearing, David Graham, Associate Director for Science and Medicine in FDA's Office of Drug Safety, was asked whether these concerns were warranted in the case of Vioxx. He stated, "I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless."[1] Pressed to name other marketed drugs he thought troublesome, Graham named five.[2]

The February 2005 meeting of two FDA advisory committees—coming three months after Dr. Graham's testimony to the Senate Finance Committee and five months after Merck withdrew Vioxx from the market—also drew intense public attention.[3] After weighing the evidence on the safety and risk-to-benefit of Vioxx and similar drugs, the committees unanimously asserted that the three COX-2 inhibitors then holding FDA approval for sale in the United States—Vioxx, Celebrex, and Bextra—do increase the risk of heart attack and stroke. Illustrating the complexity of decisions that FDA faces, a majority of the committee members, noting that the benefits of the drugs outweigh the risks for certain groups of people, therefore, recommended to FDA that the agency permit the sale of these drugs—with, however, several severe limitations on advertising

[1] Testimony of David J. Graham, M.D., M.P.H., Associate Director for Science, Office of Drug Safety, Center for Drug Evaluation and Research, U.S. Department of Health and Human Services, Food and Drug Administration, Washington, D.C., before the U.S. Senate Committee on Finance hearing, "FDA, Merck and Vioxx: Putting Patient Safety First?" Nov. 18, 2004, at http://finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf. (Hereafter "Graham, Nov. 18, 2004.")

[2] Marc Kaufman, "FDA Officer Suggests Strict Curbs on Five Drugs; Makers Dispute Claims About Health Risks," *Washington Post*, Nov. 19, 2004, p. A1. The five drugs named were Accutane (to treat acne), Bextra (a COX-2 inhibitor used to treat pain), Crestor (a statin used to lower cholesterol), Meridia (for weight loss), and Serevent (to treat asthma).

[3] Concerns about postmarket safety involve many drugs. The Vioxx situation, however, has uniquely sparked congressional and public attention because of the sheer numbers of prescriptions filled—93 million by some estimates. Dr. Graham's analysis led him to see a "7-fold increase in heart attack risk" resulting in, he calculated, between 88,000 and 139,000 Americans who suffered heart attack or stroke from the drug. In addition, there have been a wide variety of recent books, editorials, and polls on industry and FDA responsibilities for action that , offering criticisms similar to those Graham made in November.

and strong warnings in consumer and clinician labeling about cardiovascular risk that is likely associated with dose and duration of use.[4]

The furor surrounding Dr. Graham's testimony reawakened interest in a variety of regulatory issues that have surfaced periodically ever since the storm of protest over "filthy, decomposed or putrid" food and "worthless" medicines resulted in FDA's creation during Theodore Roosevelt's presidency.[5]

Concerns about regulatory agencies' abilities to protect the public are not unique to FDA or public health.[6] The life-and-death issues of medicine, however, strike most closely to home for many Americans. There has not been a decade since FDA's creation without a highly publicized incident involving drug safety that has led to legislation expanding and strengthening FDA's authority to protect the public. Examples include the scores of children killed by an untested antibiotic (elixir of sulfanilamide) marketed by a company in Tennessee in 1937; the mistakes at a plant manufacturing polio vaccine in 1954 that actually caused 260 cases of polio and 11 deaths; and, in 1962, thalidomide, the sleeping pill that eventually resulted in the birth of at least 8,000 severely deformed babies and thousands of prenatal deaths, mostly in Europe.[7]

Today, as the 110th Congress prepares to consider a variety of health issues, Members still share concerns over drug safety and efficacy. The agency most responsible for such issues is the Food and Drug Administration (FDA). In FY2006, FDA operated on a budget of $1.88 billion ($1.49 billion in appropriated funds and $382 million from user fees),[8] more than $6 per U.S. citizen. With that money, FDA was expected to oversee about $1 trillion of goods, which make up about one-quarter of all U.S. consumer spending.[9]

Congressional funding for FDA has increased at about half the rate as that of industry user fees, established by Congress as a way to defray the costs of hiring additional agency personnel so that drug approval review could be quicker. Even though the user fees account for somewhat less than 20% of the FDA total, they made up 59% of FDA's Center for Drug Evaluation and Research (CDER) FY2006 budget.

Two regulatory frameworks exist for the review of prescription drugs. First, FDA reviews the safety and effectiveness of new drugs that manufacturers wish to market in the United States; this process is called *premarket approval* or *preapproval review*. Once a drug has passed that

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[4] FDA, Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, Gaithersburg, Md., Feb. 16-18, 2005, Agenda, at http://www.fda.gov/oc/advisory/accalendar/2005/cder12532ddd0216171805.html, and Discussion Points, at http://www.fda.gov/ohrms/dockets/ac/05/questions/2005-4090Q1_Final.pdf; and Marc Kaufman, "FDA Panel Opens Door for Return of Vioxx," *Washington Post*, Feb. 19, 2005, p. A1.

[5] Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2003), pp. xi and 54. (Hereafter "Hilts, 2003.")

[6] Robert B. Reich, "A Suitable Remedy: When the FDA Is Weak," *Washington Post*, Jan. 9, 2005, p. B5. (Hereafter "Reich, Jan. 9, 2005.")

[7] Hilts, 2003, p. 158; and FDA, "Milestones in U.S. Food and Drug Law History," *FDA Backgrounder*, May 3, 1999, updated Aug. 5, 2002, at http://www.fda.gov/opacom/backgrounders/miles.html, visited Feb. 7, 2005.

[8] FDA, *Budget in Brief, Fiscal Year 2007*, All Purpose Table, Total Program Level, p. 81, at http://www.fda.gov/oc/oms/ofm/budget/2007/pdf/2consolidatedBIB.pdf.

[9] FDA, "Protecting Consumers, Promoting Public Health," Office of Public Affairs, Aug. 2004, at http://www.fda.gov/oc/opacom/fda101/fda101text.html, visited Feb. 11, 2006.

threshold and is *FDA-approved*, FDA acts through its *postmarket* or *post-approval* regulatory procedures.

This report examines issues related to drug safety, specifically in the context of the regulatory process that Congress and the FDA have established for ensuring that drugs are safe and effective. It includes a primer on drug approval: how drugs are approved and come to market, including FDA's role in that process. It also describes FDA and industry roles once drugs are on the pharmacy shelves, the *postmarket* (also called the *post-approval*) period. The report then moves on to a discussion of the problems in identifying and resolving the postmarketing safety and effectiveness issues that are raised most frequently in the debate. Finally, it outlines actions that a variety of analysts have suggested to improve the situation, both ones that FDA could adopt on its own and others for which legislation would be necessary.

FDA Approval of New Drugs

Legislative History

Derived from the Dutch word meaning *to boast (quacken)*, "quack" was the word Americans commonly used to describe charlatans in medicine. Quacks peddled adulterated and mislabeled medicines throughout the United States without penalty, until 1906, when Congress passed the Food and Drugs Act, outlawing the practice. It was the first in a series of laws intended to assure Americans that the medicines they used did no harm and actually worked—that they are, in other words, *safe and effective*.

Over the next half-century, Congress passed two major pieces of legislation expanding FDA authority in pursuit of those goals. It passed the Federal Food, Drug, and Cosmetic Act (FFDCA)[10] in 1938, requiring that drugs be proven safe before they could be sold in interstate commerce. Then, in 1962, in the wake of the thalidomide tragedy, Congress amended the law to require that drugmakers prove the effectiveness of their products as well.[11]

The process has not remained the same since 1962. The 1983 Orphan Drug Act began a series of additional laws passed by Congress in recent decades to boost pharmaceutical research and development, speed the approval of new medicines, or, in some cases, both. The Orphan Drug Act provided incentives for pharmaceutical manufacturers to develop drugs, biotechnology products, and medical devices for the treatment of rare diseases and conditions. Other laws include the 1984 Hatch-Waxman Act, the landmark compromise balancing greater patent protection of manufacturers with quicker public access to lower-priced generic drugs; the 1992 Prescription Drug User Fee Act (PDUFA), which ushered in user fees and performance goals for faster drug approvals; and the 1997 FDA Modernization Act (FDAMA), which relaxed clinical testing requirements, eased access to experimental therapies, and awarded drugmakers six more months of marketing protection for testing drugs in pediatric patients. The 107th Congress reauthorized the FDAMA pediatric testing provision within the 2002 Best Pharmaceuticals for Children Act,

[10] The Federal Food, Drug, and Cosmetic Act, P.L. 75-717, 1938.

[11] Kefauver-Harris Drug Amendments to the FFDCA, P.L. 87-781, 1962.

and extended the drug user fee law for five more years under the Public Health Security and Bioterrorism Preparedness and Response Act.[12]

All six pieces of legislation inform the U.S. drug approval process, which is supervised by FDA in accordance with the laws from 1938 and 1962. In the following section, we describe the drug approval process as it functions now.

The Current System

A drug cannot be marketed in the United States without FDA approval, for which the manufacturer must demonstrate the drug's safety and effectiveness to FDA's satisfaction, see its manufacturing plant pass FDA inspection, and obtain FDA approval for the drug's labeling—a term that includes all written and electronic material about the drug, including packaging, prescribing information for physicians, and patient brochures.[13] There are four steps leading to FDA approval of a drug for marketing in the United States:

Investigational New Drug (IND) Application

Before testing in humans—referred to as *clinical* testing—the drug's sponsor (usually its manufacturer) must file an IND application with FDA. It includes information about the proposed study protocol, completed animal test data, the lead investigator's qualifications, and the written approval of an Institutional Review Board based on its determination that the study participants will be made aware of the drug's investigative status and that any risk of harm will be necessary, explained, and minimized. The manufacturer will meet with FDA to discuss whether the clinical study design has sufficient statistical power to enable the manufacturer to draw valid estimates of the safety and effectiveness of the drug.[14] The application must include an *Indication for Use* section that describes what the drug does and the clinical condition and population for which drug use is intended. Trial subjects should be representative of those who would receive the drug if it is approved. The FDA has 30 days to review an IND. If there is no objection, a manufacturer may begin clinical testing after that time.

[12] The Orphan Drug Act (P.L. 97-414), the Hatch-Waxman Act (the Drug Price Competition and Patent Term Restoration Act of 1984, P.L. 98-417), PDUFA (P.L. 102-571), FDAMA (P.L. 105-115), the Best Pharmaceuticals for Children Act (107-109), and the Public Health Security and Bioterrorism Preparedness Act (P.L. 107-188).

[13] Labeling has become the focal point for much of the controversy involving safety and effectiveness. Some contend that changes in prescribing information are not enough to protect the public's health because, as recent questions from consumers and Members of Congress demonstrate, the labeling language, clear to those in the drug approval business, can confuse lay readers. For example, "Effectiveness in children has not been demonstrated" represents a different state of knowledge than "Studies in children have not demonstrated effectiveness." In the second sentence, we learn that researchers have looked to see whether it was effective and were unable to find that evidence—although, the drug still could be effective in children but the study design or analysis did not see that. The first sentence, however, does not make clear whether any study had been done. In January 2006, FDA issued a final rule, final guidance, and supporting documents to overhaul the labeling requirements for prescription drugs; see the *FDA News* release for links to various documents, at http://www.fda.gov/bbs/topics/NEWS/2005/NEW01272.html.

[14] A trial result may be considered *positive* if it demonstrates that the new drug has a statistically significant benefit over a placebo or comparative drug. Accordingly, a result could be called *negative* if, despite sufficient statistical power to demonstrate that the new drug offers a benefit over placebo or comparative drug, the trial does not show a benefit. A trial with insufficient statistical power to draw a conclusion regarding effectiveness, most often due to inadequate sample size, that does not find an association is considered *inconclusive*.

Clinical Trials

With IND status, researchers proceed to test in a small number of human volunteers the safety they had demonstrated in animals. These trials, called ***Phase I clinical trials***, "try to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects." If the product still seems viable, the sponsor continues with ***Phase II and Phase III trials*** to gather evidence of the drug's efficacy and effectiveness in larger groups of individuals with the particular characteristic, condition, or disease of interest, while continuing to monitor safety.[15]

New Drug Application (NDA)

Once the clinical trials are completed, the sponsor submits an NDA to FDA's Center for Drug Evaluation and Research (CDER), containing not only the clinical trial results, but also information about the manufacturing process and facilities, including quality control and assurance procedures. During the review, CDER officials evaluate the drug's safety and effectiveness data, analyze samples, inspect the facilities where the finished product will be made, and check the proposed labeling for accuracy.

FDA Review

The Federal Food, Drug, and Cosmetic Act requires "substantial evidence" of drug safety and effectiveness.[16] FDA has interpreted this to mean that the manufacturer must provide at least two adequate and well-controlled Phase 3 clinical studies, each providing convincing evidence of effectiveness. The agency, however, exercises flexibility.[17] As its regulations describe in detail, FDA can assess safety and effectiveness in a variety of ways, relying on combinations of studies by the manufacturer and reports of other studies in the medical literature.[18]

FDA has 180 days to review an NDA. If it finds deficiencies, such as missing information, the clock stops until the manufacturer submits the additional information. If the manufacturer cannot respond to FDA's request (i.e., if a required study had not been done, making it impossible to evaluate safety or effectiveness), the manufacturer may voluntarily withdraw the application. If and when the manufacturer is able to provide the information, the clock resumes and FDA continues the review.

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[15] *Safety* tests, often referred to as toxicity testing, seek to determine the highest tolerable dose or the optimal dose of the drug needed to achieve the desired benefit. Studies that look at safety also seek to identify any potential adverse effects that may result from exposure to the drug. *Efficacy* refers to whether a drug demonstrates a health benefit over a placebo or other intervention when tested in an ideal situation, such as a tightly controlled clinical trial. *Effectiveness* describes how the drug works in a real-world situation. Effectiveness is often lower than efficacy because of interactions with other medications or health conditions of the patient, sufficient dose or duration of use not prescribed by the physician or followed by the patient, or use for a off-label condition that had not been tested. Also, see Carol Rados, "Inside Clinical Trials: Testing Medical Products in People," *FDA Consumer*, Sept.-Oct. 2003, at http://www.fda.gov/fdac/features/2003/503_trial.html; and CRS Report RL32478, *Genetic Testing: Scientific Background and Nondiscrimination Legislation*, by Michele Schoonmaker and Erin Williams.

[16] FFDCA (P.L. 75-717, 1938), Section 505(d).

[17] See FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, CDER and CBER, May 1998, at http://www.fda.gov/cder/guidance/1397fnl.pdf.

[18] The requirements for adequate and well-controlled studies are given in 21 C.F.R. § 314.126.

For many NDAs, FDA convenes advisory panels of experts to review the clinical data. While not bound by an advisory panel's recommendation regarding approval, FDA usually accepts it. FDA makes the final determination: "approved," "approvable" (if certain changes, such as more testing, are made), or "unapprovable." FDA can reject an NDA on two grounds: if the manufacturer failed to perform adequate tests to demonstrate safety and effectiveness for its proposed use, or if the clinical data were not sufficient to show a favorable benefit-to-risk profile. A manufacturer may appeal FDA's decision by filing a complaint with CDER's Ombudsman.

Finally, once a drug is marketed, its manufacturer and FDA monitor its overall safety using MedWatch, the agency's postmarketing surveillance system (described later in this report); any ***Phase IV clinical trials*** that FDA required as a condition of approval or for which the sponsor otherwise agreed with FDA and committed to undertake; and any other valid information that FDA has learned.

Funding of the Approval Process

FDA funds its new drug approval reviews with appropriations provided by Congress and fees paid by industry. The current funding arrangement grew out of the long-standing tensions between FDA and both industry and consumer groups over how long the FDA reviews took.

In 1993, median review time for priority drugs was 16.3 months,[19] a figure FDA acknowledged could be lower with more FDA staff. The pressure for quicker approvals came from two directions. First, manufacturers wanted it. Because the 20-year patent protection begins with NDA submission, manufacturers see the time from NDA submission to FDA approval decision as lost income. The Pharmaceutical Research and Manufacturers of America (PhRMA) argues that because of the long approval process and the Hatch-Waxman Act, encouraging generics, "the average effective patent life for prescription medicines ... is 11-12 years, compared to an average of 18.5 years for other products."[20] Meanwhile, consumer groups also wanted quicker approvals to speed their access to promising drugs.

Congress reacted by looking for legislative ways to speed up the drug review process without lowering approval standards, especially those whose weakening might compromise patient safety. In 1992, it passed the Prescription Drug User Fee Act (PDUFA) and five years later, in 1997, the Food and Drug Administration Modernization Act (FDAMA). These laws created a system in which congressional appropriations only partially fund new drug review; those monies are supplemented with "user fees" paid by pharmaceutical companies.[21] A third of the user fee money comes from an application fee; the remaining two-thirds is unlinked to the application process, based instead on the type of manufacturing facility and product submitted for review. User fees are paid at the start of the fiscal year. Following the introduction of user fees, FDA quickly reduced its median approval time for priority new drugs from the 16.3 months of 1993. By 1995,

[19] FDA, "Approval Times for Priority and Standard NDAs and BLAs; Calendar Years 1993-2004," at http://www.fda.gov/cder/rdmt/NDAapps93-04.htm, visited Feb. 12, 2006.

[20] PhRMA, "Fact Sheet: Pharmaceutical Patent Incentives," at http://www.phrma.org/publications/publications/17.06.2003.746.cfm, visited Feb. 12, 2006. Also, CRS Report RL30756, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act")*, by (name redacted) and (name redacted).

[21] See CRS Report RL31453, *The Prescription Drug User Fee Act: Structure and Reauthorization Issues*, by (name red acted) and (name redacted).

it had fallen by half, where it generally remained until 2002 when it jumped to 13.8 months, coming down to 7.7 months in 2003. Beginning with its data for 2004, FDA includes Biologics License Application (BLA) approvals along with New Drug Applications (NDAs); for 2004, the median approval time was six months.[22] FDA has established, and maintains, detailed records tracking its use of PDUFA fees.

FDA Postmarket Regulation of Approved Drugs

We now turn to a discussion of FDA's role after a drug appears on the market. First, we describe the current system. Then we present what critics have identified as problems—and the solutions they propose.

Legislative History

The Federal Food, Drug, and Cosmetic Act gives the Secretary of Health and Human Services (HHS) the authority to withdraw marketing approval of a drug.[23] FDA-issued regulations regarding new drug approval require postmarketing reports of adverse drug experiences and of other information produced or acquired by the sponsor.[24]

The Current System

Offices throughout FDA, mostly in the Center for Drug Evaluation and Research, address the safety of the drug supply. These include the Office of Surveillance and Epidemiology (OSE, formerly the Office of Drug Safety); as well as the Office of Regulatory Affairs; the Division of Drug Marketing, Advertising and Communications; the Division of Drug Information; and the Division of Compliance Risk Management and Surveillance.

Office of Drug Safety (Office of Surveillance and Epidemiology)

The webpage of FDA's Office of Drug Safety (ODS)[25] describes its duties to include using reports of adverse events that consumers, clinicians, or manufacturers believe might be drug-related to "identify drug safety concerns and recommend actions to improve product safety and protect the public health. Activities include updating drug labeling, providing more information to the community, implementing or revising a risk management program, and, on rare occasions, reevaluating approval or marketing decisions."[26]

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[22] FDA, "Approval Times for Priority and Standard NDAs and BLAs; Calendar Years 1993-2004," at http://www.fda.gov/cder/rdmt/NDAapps93-04.htm, visited Feb. 12, 2006.

[23] Section 505 of the FFDCA (21 U.S.C. § 355: New drugs.). In particular, 21 U.S.C. § 355(e): Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health.

[24] At 21 C.F.R. § 314. Applications for FDA approval to market a new drug. See, in particular: Section 314.80. Postmarketing reporting of adverse drug experiences; Section 314.81. Other postmarketing reports; Section 314.150. Withdrawal of approval of an application or abbreviated application; Section 314.200. Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing; and Section 314.126. Adequate and well-controlled studies.

[25] Despite the office's name change, the FDA website continues to post pages referring to the "Office of Drug Safety."

[26] FDA, "Organizational Components: Office of Drug Safety," CDER, at http://www.fda.gov/cder/Offices/ODS/ (continued...)

OSE has three divisions. The staff in the Division of Drug Risk Evaluation works to detect and evaluate safety data and published literature, and assesses manufacturer-provided plans for epidemiologic studies and surveillance tools. The Division of Medication Errors and Technical Support assesses specific drug labeling questions. The Division of Surveillance, Research, and Communication Support manages risk communication activities that include research and patient materials, and MedWatch and other epidemiologic data resources.[27]

Safety Functions Outside the Office of Drug Safety

Other significant drug safety functions reside outside the Office of Drug Safety. These include risk management plans, routine inspection of manufacturing facilities, regulation of imported prescription drugs, and product recalls and withdrawals. A Drug Safety and Risk Management Advisory Committee was established in 2002.

In November 2004, in a move widely considered to be in response to the heightened criticism of the agency's handling of possible dangers of COX-2 inhibitors and antidepressants, FDA announced actions "to strengthen the safety program for marketed drugs."[28] These included plans to sponsor an Institute of Medicine (IOM) study of the drug safety system; implement a program for adjudicating differences of professional opinion; appoint a Director of the Office of Drug Safety; conduct drug safety/risk management consultations; and publish risk management guidances. These were followed by FDA's May 2005 announcement of a new "Drug Safety Initiative."[29] New activities were to include more drug-specific information for healthcare professionals, patients, and other consumers; "Drug Watch," a new program to publicly share emerging drug safety information;[30] and a Drug Safety Oversight Board.

FDA's *Manual of Policies and Procedures* states, "The DSB [Drug Safety Oversight Board] has been established to provide independent oversight and advice to the Center Director on the management of important drug safety issues and to manage the dissemination of certain safety information through FDA's Web site to health care professionals and patients."[31] While generally supporting the FDA safety initiative goal of increasing safety decision oversight, including extending membership beyond FDA officials, critics noted that by limiting membership to federal government employees, FDA could exclude the public from board proceedings. Some members of FDA's similarly named Drug Safety and Risk Management Advisory Committee also publicly criticized FDA's approach to the DSB, saying its "name is misleading ..." and that FDA is "setting [itself] up for failure ... in this age of transparency."[32]

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default.htm, visited Feb. 9, 2005.

[27] FDA, "Organizational Components: Office of Drug Safety," CDER, June 22, 2004, at http://www.fda.gov/cder/Offices/ODS/default.htm, visited Feb. 12, 2006.

[28] FDA, "FDA Acts to Strengthen the Safety Program for Marketed Drugs," *FDA Statement*, Nov. 5, 2004, at http://www.fda.gov/bbs/topics/news/2004/NEW01131.html.

[29] FDA, "FDA's New Drug Safety Initiative," May 10, 2005, updated Dec. 20, 2005, at http://www.fda.gov/cder/drugSafety.htm, visited Feb. 12, 2006.

[30] Note: "FDA Goes 'Back to the Drawing Board' on Drug Watch Web Site," *FDA Week*, Inside Washington Publishers, Dec. 2, 2005.

[31] FDA,"Drug Safety Oversight Board," *Manual of Policies and Procedures*, MAPP 4151-3, CDER, effective May 4, 2005, at http://www.fda.gov/cder/mapp/4151-3.pdf.

[32] Lisa Richwine, "US advisers criticize FDA drug safety board," Reuters, Feb. 14, 2006, at http://www.nlm.nih.gov/(continued...)

Studies

For certain categories of new drug approvals (those applications approved under rules for accelerated approval, the animal efficacy rule, or the Pediatric Research Equity Act), the manufacturer and FDA negotiate timeframes and postmarket study requirements at the time of drug approval. Although not required for an application that falls outside of those categories, other postmarket study agreements between manufacturer and FDA can be set at the time of approval.[33]

Reporting

Once FDA approves a drug, it monitors safety. Manufacturers *must* report all serious and unexpected adverse reactions within 15 days of becoming aware of them (21 C.F.R. § 310.305) to FDA's Adverse Events Reporting System (AERS). Health professionals and patients *may* report adverse reactions to FDA's MedWatch reporting system at any time.

FDA can approve a drug even when it still has questions about the drug's longer-term effects; in such cases, FDA can require formal postmarket studies and summary reports as conditions of approval. These mechanisms of postmarket study are particularly important when it comes to identifying rare adverse events. Often, these become clear only after many people have taken the drug.

Labeling

Some adverse events warrant regulatory actions such as labeling changes, letters to health professionals, or, once in a great while, a drug's withdrawal from the market. The regulations require the company to make the label change as soon as there is reasonable evidence—not proof—of an *association* with serious hazard.[34] The art and science of these judgments result, at times, in different decisions by different reviewers. A current example appeared on FDA's website February 9, 2005, regarding Adderall, a stimulant medication used to treat attention deficit disorder. On the basis of data from U.S. reporting systems, Canadian authorities chose to stop sales, whereas U.S. authorities chose to alert the public yet not restrict sales at this time.[35] One year later, however, the FDA Drug Safety and Risk Management Advisory Committee reviewed data that "suggested stimulants might increase the risks of strokes and serious arrhythmias in children and adults" and recommended that FDA "require manufacturers to provide written guides to patients and place prominent warnings on drug labels describing these risks...."[36]

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medlineplus.

[33] FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), March 2005, at http://www.fda.gov/cder/guidance/6359OCC.pdf; and FDA, *Guidance for Industry: Reports on the Status of Postmarketing Studies—Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997*, CDER and CBER, Feb. 2006, at http://www.fda.gov/cder/guidance/5569fnl.htm.

[34] 21 C.F.R. § 201.57(e).

[35] FDA, "Statement on Adderall," *FDA Statement*, Feb. 9, 2005, at http://www.fda.gov/bbs/topics/news/2005/NEW01156.html, and FDA, Public Health Advisory for Adderall and Adderall XR, Feb. 9, 2005, at http://www.fda.gov/cder/drug/advisory/adderall.htm, visited Feb. 12, 2006.

[36] Gardiner Harris, "Warning Urged on Stimulants Like Ritalin," *New York Times*, Feb. 10, 2006; and FDA, CDER, (continued...)

The effectiveness of labeling—and black-box warnings in particular—is a topic of debate. A recent study of physician compliance with the warnings found that when prescribing drugs with black-box warnings, doctors violated those warnings in 7% of prescriptions.[37]

FDA can institute label changes on the basis of information it gathers from mandatory industry reports to AERS and committed postmarket studies and from voluntary adverse event reports from clinicians and patients. When it believes data from original or published studies support a new use for a drug, a manufacturer itself can initiate a label change to support a new marketing claim. It submits to FDA the new data in a supplement to the original NDA, and requests that FDA allow it to modify the labeling.

Risk Management

FDA describes its approach to risk management as "an iterative process" that includes both risk assessment and risk minimization.[38] Actions available to FDA include education and outreach (e.g., new professional labeling, patient-oriented labeling, public notices); guides to prescribing, dispensing, or use (e.g., informed consent, program enrollment, practitioner certification, special packaging or limited refills); restricted access (e.g., registration of physicians, pharmacists, or patients, and documentation of laboratory tests before dispensing); and suspension or termination of product marketing.[39]

The FDA *Manual of Policies and Procedures* notes that risk management includes the attempt to "minimize [a drug's] risks while preserving its benefits." The balance is not always clear. For example, FDA put in place a rigorous risk minimization plan for Accutane, a drug that treats a severe type of acne and carries with it a risk of birth defects and possible suicidal actions. Some clinicians object to what they feel are onerous prescribing requirements, saying that those requirements serve to deny the drug to individuals who need it.[40] FDA allowed an exception, for example, for oncologists prescribing Accutane for cancer treatment.[41]

(...continued)

Draft Agenda, Drug Safety and Risk Management Advisory Committee, Gaithersburg, Md., Feb. 9-10, 2006, at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4202B1_03_FDA-Tab03.pdf.

[37] Karen E. Lasser, Diane L. Seger, D. Tony Yu, et al., "Adherence to Black Box Warnings for Prescription Medications in Outpatients," *Archives of Internal Medicine*, vol. 166, Feb. 13, 2006, pp. 338-344.

[38] FDA, "Review Management: Risk Management Plan Activities in OND and ODS," *Manual of Policies and Procedures*, MAPP 6700.1, CDER (Originator: Office of New Drugs), effective Sept. 8, 2005, at http://www.fda.gov/cder/mapp/6700.1.pdf.

[39] Toni Piazza-Hepp, FDA presentation: "Risk Management Programs," at the Risk Management Public Workshop, CDER, Washington, D.C., April 10, 2003, at http://www.fda.gov/cder/meeting/RMtranscript2.doc; and FDA, *Center for Drug Evaluation and Research 2004 Report to the Nation: Improving Public Health Through Human Drugs*, Aug. 2005, at http://www.fda.gov/cder/reports/rtn/2004/rtn2004.pdf.

[40] Gardiner Harris, "System Said to Fail to Steer Women From Acne Drug," *New York Times*, Feb. 11, 2006.

[41] "FDA Announcement Re: iPledge Program for Isotretinoin," memorandum from Richard Pazdur, Div. of Oncology Drug Products, CDER, at http://www.ons.org/fda/documents/fda050306.pdf; and FDA, "FDA and Manufacturers of Accutane and its Generics to Implement iPLEDGE Program on March 1, 2006," *FDA Statement*, Feb. 23, 2006, at http://www.fda.gov/bbs/topics/NEWS/2006/NEW01324.html.

Enforcement Authority

At many recent congressional hearings, Members have asked FDA officials about the agency's enforcement authority. The responses have not included the specificity for which the questioners were looking; this seems to be unclear territory, and FDA's authority is limited. The law authorizes FDA to withdraw a drug's approval. To get label changes and most other actions, FDA must couch its concerns as requests to the manufacturer. Another FDA webpage, *The Enforcement Story: Fiscal Year 2003*, presents the range of FDA-wide legal and other enforcement activities.[42]

Off-Label Use

The law prohibits a manufacturer from promoting or advertising a drug for any use not listed on the FDA-approved label: those claims for which FDA has reviewed safety and effectiveness evidence. However, the FFDCA does not give FDA authority to regulate the practice of medicine; that responsibility rests with the states and medical professional associations. Once a drug is approved, a licensed physician may—except in highly regulated circumstances—prescribe it without restriction. A prescription to an individual whose demographic or medical characteristics differ from those indicated in a drug's FDA-approved labeling is called *off-label use* and is accepted medical practice.

Examples of off-label use: a drug that was tested in an eight-week trial may be prescribed for long-term use; if it was tested at one dose it may be used at higher or lower doses; one tested in adults may be prescribed to children; and a drug tested for the treatment of one disease may be prescribed in an attempt to prevent another. Using drugs in these new ways (for which researchers have not yet demonstrated safety and effectiveness) can create problems that premarket studies did not address. Off-label use also presents an evaluation problem to FDA safety reviewers. Manufacturers rarely design studies to establish the safety and effectiveness of their drugs in off-label uses, and individuals and groups wanting to conduct such studies face difficulties finding funding.

Funding of Post-Approval Activities

The FY2006 program level budget for drug safety was $32.5 million, up from $15.4 million in FY2002.[43] The growth came primarily from the addition of PDUFA user fees beginning in FY2003. The 2002 amendments known as PDUFA III were the first to authorize the use of user fees for postmarket activities.[44] The FY2007 request is $39.2 million. Staff full-time equivalent

[42] In *The Enforcement Story: Fiscal Year 2005*, FDA describes agency actions including civil money penalties, disqualification of clinical investigators, prosecutions, seizures, injunctions, recalls, and warning letters, not all relating to postmarketed drugs (at http://www.fda.gov/ora/about/enf_story/intro.htm#_top, visited Nov. 30, 2006).

[43] FDA, "Improving Drug Safety," FY2007 Budget, Budget Formulation and Presentation, at http://www.fda.gov/oc/oms/ofm/budget/2007/HTML/5DrugSafetyPOM.htm.

[44] PDUFA III is the popular name for Subtitle A of Title V of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, P.L. 107-188. According to the FDA Budget and Evaluation Office, the Office of Drug Safety funding has been as follows: FY2002, $15.4 million (BA only); FY2003, $20.2 million total ($13.4 million BA, $6.6 million user fees); FY2004, $23.8 million total ($15.8 million BA, $8.0 million user fees); FY2005 estimate, $26.9 million total ($17.9 million BA, $9.0 million user fees); and FY2006 estimate, $33.4 million total ($22.9 million BA, $10.5 million user fees) (FPC Spreadsheets/ODS figures FY1996 to FY2005, dated Jan. 31, 2004). See FDA, "Prescription Drug User Fee Act: Adding Resources and Improving Performance in FDA Review of New Drug Applications," (undated white paper, sometime after September 2004), at http://www.fda.gov/oc/pdufa/
(continued...)

(FTE) levels went from 77 in FY2002 to 109 in FY2005. The FY2006 budget request included an additional 20 FTEs,[45] and the FY2007 would add another eight.[46]

Safety and Effectiveness Issues and Options Once a Drug Is FDA-Approved

In the last few years, several authors—historians, clinicians, and editors—have published books about what they see as problems with government and industry's handling of drug safety issues. These include Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What to Do About It* (New York: Random House, 2004); Jerry Avorn, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs* (New York: Alfred A. Knopf, 2004); and Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2003). Also, an FDA task force proposed sweeping changes in its 1999 report, *Creating A Risk Management Framework: Report to the FDA Commissioner from the Task Force on Risk Management*, May 1999, available at http://www.fda.gov/oc/tfrm/riskmanagement.pdf.

While these analysts are in broad agreement that FDA's approach should be changed, they differ about what should be changed. The rest of this report is organized around the six areas where most analysts view the problems in postmarketing surveillance, study, and regulatory action. Options listed in one section, however, might not be possible without those from other sections—especially ""FDA Budget."

Most difficult to categorize is the influence of industry. To make the discussion manageable, this report limits the options listed under Industry Role to those that would *diminish* what some analysts consider inappropriate industry behavior. The options aimed at increasing postmarket information, many of which involve *expanding* industry role, appear in the other procedure-defined sections.

That said, the six areas around which most recommendations revolve are:

- FDA organization
- FDA budget
- Role of industry
- Opportunities to use the drug approval process to enhance postmarket activities
- Insufficient postmarket information
- Lack of public access to available data

(...continued)

PDUFAWhitePaper.pdf, visited Feb. 22, 2006.

[45] FDA, *FY 2006 Budget Summary and Budget in Brief*, at http://www.fda.gov/oc/oms/ofm/budget/2006/PDFs/Summary/Pages28thru31.pdf.

[46] FDA, *Budget in Brief, Fiscal Year 2007*, Table 5: Overview of FY2007 Initiatives and Offsets, p. 12, at http://www.fda.gov/oc/oms/ofm/budget/2007/pdf/2consolidatedBIB.pdf.

Some of the proposed changes lie within FDA's legislative authority to implement. Others would require congressional action. In **Table 1**, we provide a list of concerns, FDA options, and congressional options.

FDA Organization

Some critics have argued that FDA's Office of Drug Safety (ODS) cannot be effective because it has so much less influence within CDER than the Office of New Drugs (OND) in regard to safety and effectiveness decisions.

In his November 2004 testimony,[47] Dr. Graham put it this way:

> The organizational structure within CDER is entirely geared towards the review and approval of new drugs. The same group that approved the drug is also responsible for taking regulatory action against it postmarketing. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything ... can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public ... A close second in my opinion is an ODS management that sees its mission as pleasing the Office of New Drugs.

At the time of Dr. Graham's testimony, the FDA organization chart for CDER showed ODS as one administrative level lower than OND. ODS was part of the Office of Pharmacoepidemiology and Statistical Science, which was parallel to OND, both reporting directly to the CDER director.[48]

Dr. Graham has not been alone in his belief. A 2002 HHS Inspector General-conducted survey of FDA scientists found that almost one-fifth of them sometimes felt pressured to ignore their safety reservations.[49] A 2004 commentary in the British medical journal *The Lancet* raises a more general point. It asks whether bureaucratic or other constraints inhibit ODS from finding fault with a drug that its sibling office, OND, had approved for marketing as safe and effective.[50]

Critics have recommended actions to address ODS scientists' feeling political pressure or being inhibited by a bureaucratic reluctance to restrict a drug that OND had earlier approved. Although some have suggested legislation to compel FDA to reorganize the agency, others suggest organizational solutions that FDA already has the authority to implement. They have also recommended other ways to increase ODS power relative OND, more staff, for example. While

[47] Graham, Nov. 18, 2004.

[48] FDA, "CDER Organization Charts and Directories," Jan. 26, 2006, at http://www.fda.gov/cder/cderorg.htm, visited Feb. 12, 2006. However, in a statement that FDA issued regarding the Nov. 18, 2004 hearing, the acting CDER director stated, "Both the Office of New Drugs and the Office of Drug Safety report directly to me as the Director of the Center" (Statement by Dr. Steven Galson, Acting Director, CDER), regarding November 18, 2004, Committee on Finance of the U.S. Senate Hearing on Drug Safety and the Worldwide Withdrawal by Merck & Co., Inc., of Vioxx, *FDA Statement*, Nov. 18, 2004, at http://www.fda.gov/bbs/topics/news/2004/NEW01138.html).

[49] Marc Kaufman, "Many FDA Scientists Had Drug Concerns, 2002 Survey Shows," *Washington Post*, Dec. 16, 2004, p. A1. HHS had not released those survey findings; they were obtained from FOIA material that public interest groups requested.

[50] Richard Horton, "Vioxx, the Implosion of Merck, and Aftershocks at the FDA," *The Lancet*, vol. 364, no. 9450 (Dec. 4-10, 2004), p. 1995.

this certainly would be an organizational change, proponents point out that more staff would require a bigger budget. This option is discussed in the section titled ""FDA Budget."

Over the past two years, CDER has reorganized its drug safety activities. Two positions now report directly to the CDER Director: the new Director of the Office of Surveillance and Epidemiology (OSE) and the Associate Center Director for Safety Policy and Communication. Although a September 2006 FDA *Fact Sheet* states that OSE is the former ODS, responsibility for MedWatch moved to the office of the new Associate Center Director.[51]

FDA Options

Put the Office of Drug Safety (now the Office of Surveillance and Epidemiology) and the Office of New Drugs under different supervisors

Now, the Director of CDER is responsible for both. Some believe that FDA should continue with that structure because a drug's risks cannot be assessed independently from its benefits. Others maintain that having the offices together may create pressure to keep CDER-approved drugs on the market. In November 2004, FDA asked the Institute of Medicine (IOM) of the National Academies to examine its post-approval safety program.[52] The IOM Committee on the Assessment of the U. S. Drug Safety System issued its report in September 2006. Although the committee discussed separating ODS and OND, it did not include that action in its recommendations, which included others on the agency's organization and culture.[53]

Institute scientific dispute-resolution mechanisms

Right now, when a scientist at FDA disagrees with the decisions of a supervisor, there is no mechanism for resolving that disagreement except by discussion between the two of them. This may silence reviewers who want to raise drug safety concerns. In November 2004, FDA announced a one-year pilot[54] program for "Documenting Differing Professional Opinions and Dispute Resolution,"[55] saying that this internal dispute-resolution process, under consideration during the preceding year, would use ad hoc panels outside the direct supervisory chain to adjudicate cases involving scientific disagreement among agency reviewers. According to the then acting director of the drug center, the intent is to formalize standard agency practices for resolving scientific disagreements.[56] Critics, though, argue that keeping a dispute within FDA, no

[51] FDA, "FDA Drug Safety Initiative," *Fact Sheet*, at http://www.fda.gov/oc/factsheets/initiative.html, posted Sept. 22, 2006; and FDA, "FDA Names First Associate Center Director for Safety Policy and Communication in the Center for Drug Evaluation and Research: FDA Centralizes Drug Safety Policy and Communication," *FDA News*, April 18, 2006, at http://www.fda.gov/bbs/topics/NEWS/2006/NEW01359.html, both visited Nov. 30, 2006.

[52] FDA, "FDA Acts to Strengthen the Safety Program for Marketed Drugs," *FDA Statement*, Nov. 5, 2004, at http://www.fda.gov/bbs/topics/news/2004/NEW01131.html.

[53] Institute of Medicine, Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, Alina Baciu, Kathleen Stratton, Sheila P. Burke, Editors, (Washington, DC: National Academies Press, 2006) at http://www.nap.edu/catalog/11750.html.

[54] A Feb. 2006 search of the FDA website did not reveal any 2005 activity of this pilot.

[55] FDA, "Documenting Differing Professional Opinions and Dispute Resolution—Pilot Program," *Manual of Policies and Procedures*, MAPP 4151.2, Office of the Center Director, CDER, Nov. 4, 2004.

[56] "CDER Dispute Resolution Policy Will Test 'Ad Hoc' Arbitration," *The Pink Sheet*, Nov. 15, 2004, p. 10.

matter how the resolution is structured, makes scientific objectivity impossible because the judge is an interested party. For example, after someone requests a review through the CDER ombudsman, the decision to proceed still involves the CDER director.

Congressional Options

Move safety oversight to another federal agency

Supporters of this option compare such a move to the National Transportation Safety Board's placement outside of the Department of Transportation, which separates it from the Federal Aviation Administration. Harvard Medical School professor Jerry Avorn suggests that assigning drug safety tasks to the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, the National Institutes of Health, or a new unit in HHS could give safety reviewers the independence that he believes they need.[57]

Provide whistleblower protection

Dr. Graham's testimony and subsequent reported agency actions to him have drawn attention to the fact that the protection given corporate whistleblowers does not extend to those in government. Congress may consider doing that in order to give scientists recourse when they feel improper pressure to disregard safety concerns.

FDA Budget

Two aspects of FDA's budget for post-approval activities attract criticism. One is the overall program level designated for safety issues after drugs are on the market. The other is the presence of industry user fees, which can be perceived—by both FDA reviewers and industry—as an influence on safety judgments and FDA action.[58] Total user fee contributions to FDA spending have increased at a quicker rate than the contributions from congressional appropriations, provoking further concern among those critics worried about undue industry influence.[59]

Congressional Options

Those who see budgetary solutions to postmarketing problems have offered solutions that are primarily legislative.

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[57] Jerry Avorn, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs* (New York: Alfred A. Knopf, 2004), p. 213. (Hereafter "Avorn, 2004.")

[58] A similar consideration occurred around Medicare inspection funding. Proposals to require Medicare and Medicaid nursing homes to pay user fees for the inspections that would determine their compliance with law and regulations have never been enacted, in part, because of concern that inspectors might become too influenced by nursing home owners.

[59] From FY1997 to FY2005, FDA's congressional appropriation just about doubled. During the same period, PDUFA fees—FDA's other source of income—almost quadrupled. The change from FY2004 to FY2005 is especially dramatic: a 0.02% decrease in congressional dollars, but a 12.5% increase in user fees (FDA, *Justification of Estimates for Appropriations Committees, Fiscal Years 1998-2005*). FDA, Office of Management, Budget Formulation and Presentation, Table of Estimates and Appropriations, S&E, at http://www.fda.gov/oc/oms/ofm/budget/2007/HTML/8AppHistorytables.htm.

Revise (or repeal) PDUFA

Some critics maintain that FDA could keep the current structure intact, but, by reducing the industry contribution proportion, proportionally decrease industry influence. Others recommend using more of the user fees to support post-marketing safety activities. Still others, such as Marcia Angell, a former editor-in-chief of the *New England Journal of Medicine*, believe that no amount of industry support is acceptable, and that the public would be best served only when reviewers' independence is rigorously maintained. They propose that Congress repeal PDUFA and increase FDA appropriations to cover (or exceed) current user fee levels.

Even *with* user fees, the FDA program level has decreased in buying power, FDA advocates explain, because routine inflation adjustments do not adequately cover increases in employee benefits or FDA's costs of recruiting and retaining highly educated and skilled scientists.[60] That, coupled with the additional tasks and responsibilities the Congress has required that FDA take on, presents problems that go beyond drug safety, affecting FDA's food, biologics, and animal drug programs.

Increase FDA appropriations

Independent of any action regarding PDUFA, some analysts urge increases in congressional budget authority to FDA in general and the Office of Drug Safety in particular.

Develop alternative funding

Dr. Avorn points out that there actually are a wide variety of ways to conduct postmarket reviews other than by government. Some alternatives, all of which would require legislation to implement, include research by organizations such as HMOs, universities, or insurers. He suggests as possible ways to fund such reviews: a 10-cent fee per filled prescription; a user fee by payers on a per person-covered basis; or fees paid by manufacturers—although those studies would need to be managed independently.

Industry Role

In some ways, criticism of the pharmaceutical industry is the most complicated issue in this list. While the immensely profitable and widely resented industry has drawn sharp criticism, many of the specific criticisms of its role are passionately rebutted, not just by industry spokespeople but by academics, and with substantive arguments.

Many observers believe that FDA's dependency on industry user fees has gradually worn away at the agency's willingness to confront drug makers. They say that, more than a funding issue, the problems indicate what they have called a cultural issue. They contend that FDA, rather than exercising the respected scientific authority it has earned over the decades to combat corporations interested only in the bottom line, instead sees as its role to accommodate industry.

[60] The FDA Alliance, presentation to the Congressional Research Service, Dec. 18, 2006.

Again, Dr. Graham's testimony[61] articulated this point, and, because he argues from within FDA, his remarks attracted wide attention.

> The corporate culture within CDER is also a barrier to effectively protecting the American people. The culture is dominated by a world-view that believes only randomized clinical trials provide useful and actionable information and that postmarketing safety is an afterthought. This culture also views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety.

The criticism of industry traditionally coalesces around one argument: that in its zeal to market drugs, companies could overlook dangers that might be more evident to unbiased researchers. Thus, Hilts writes that in the case of thalidomide, the "marketing department, not the medical department, ran the 'trial.'"[62] Accounts of the Vioxx controversy, four decades later, indicate that some Merck scientists did argue for further study of the drug but were met with objections from marketing divisions.[63]

Certainly, industry makes its influence felt in many ways. For example:

Data. Information on which FDA approval is based comes from studies funded by the manufacturer. While industry argues that its sense of social responsibility and concerns about litigation keep reporting honest, critics have found that difficult to square with cases such as the one involving Vioxx, in which data indicating increased risk were available to the manufacturer four or five years before it withdrew the drug.

Funding. User fees have been mentioned elsewhere in this report because they influence issues such as FDA organization and, of course, budget. But there are those who are primarily interested in it as an example of inappropriate industry role. User fees support new drug reviews. In 2005, industry paid FDA more than $269 million in PDUFA fees, almost all of it directed to new drug reviews by law. This influx of money also allows FDA to pay for staff conferences, travel, and training—but is limited primarily, some say, to new-drug reviewers.

Independent research. Although this is changing, journals, conferences, and researchers themselves do not always clearly identify their funding sources. Researchers presumed to be independent often receive grants, vacations, status, patients, or fees from industry; this could give the appearance of compromised objectivity. At universities, traditionally perceived to be the bastion of unbiased research, industry funding has become so pervasive that former Harvard University president Derek Bok, pointing to research showing clinical trials supported by industry are "more ... favorable to sponsors" than independent research, has warned, "the dependence on corporate support has reached such a point that it will be difficult for medical schools to free themselves of industry influence."[64] Whether researchers are influenced by industry funding consciously, unconsciously, or not at all, the perception of influence on both premarket and post-approval research contributes to some people's lack of trust in findings.

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[61] Graham, Nov. 18, 2004.

[62] Hilts, 2003, p. 151.

[63] Anna Wilde Mathews and Barbara Martinez, "Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage," *Wall Street Journal*, Nov. 1, 2004, p. A1. (Hereafter "Mathews and Martinez, Nov. 1, 2004.")

[64] Derek Bok, *Universities in the Marketplace: The Commercialization of Higher Education*, Princeton, N.J.: Princeton University Press, 2003, as quoted in Avorn, 2004, p. 213.

Direct-to-consumer (DTC) advertising. The United States is one of only two countries in the world that allow pharmaceutical companies to advertise directly to consumers—the other is New Zealand.[65] Industry argues this is a powerful tool for informing consumers about diseases and the treatments available for them. Industry critics agree that it is powerful tool—for *mis*informing consumers about the same issues.

These concerns regarding industry influence are listed elsewhere in this paper. The reason is that not everyone sees these problems in the same way. For example, is it the fault of industry for supporting a solution, such as user fees, that could compromise objectivity? Or does the fault lie with Congress for not appropriating enough money for safety—forcing, as one writer put it, "a marriage between the agency and industry years ago for the rich dowry that industry offered"?[66]

Despite debate over detail, there seems to be widespread consensus that FDA needs to be objective about the industry it regulates. Suggestions for revamping the industry role to reduce postmarketing problems lie almost entirely within the legislative arena.

FDA and Administration Options

Maintain stable FDA leadership

During the hearings and activities in 2004 and 2005, FDA had an acting commissioner and acting directors of the Center for Drug Development and Evaluation and its Office of Drug Safety. Acting officials throughout government tend to act with caution, in part because they are not perceived (even by themselves) as having the political backing to stand up to industry, researcher, and consumer pressure.[67] Over the following few months, the President nominated—and the Senate confirmed—then Acting Commissioner Lester Crawford as commissioner. FDA also made permanent appointments to the CDER and ODS director positions. However, when the new commissioner abruptly resigned in September 2005, Andrew von Eschenbach, who then headed the National Cancer Institute at NIH, stepped in as the new acting commissioner.[68]

[65] Presentation by Dean G. Smith, Lynne Eagle, Kerry Chamberlain, and Lawrence C. Rose, "The Views of Healthcare Professionals and Consumers on Direct-to-Consumer Promotion of Prescription Drugs in New Zealand," FDA Public Meeting, Washington, D.C., Sept. 23, 2003, at http://www.fda.gov/cder/ddmac/p6smith/tsld001.htm; and New Zealand Ministry of Health, Medicines and Medical Devices Safety Authority, Advertising: Guidelines for Advertising Prescription Medicines Direct to the Consumer, Jan. 2001, at http://www.medsafe.govt.nz/reg.htm. See also CRS Report RL32853, *Direct-to-Consumer Advertising of Prescription Drugs*, by (name redacted).

[66] Harris, Dec. 6, 2004.

[67] Marc Kaufman, "FDA's Reliance on Unconfirmed Chiefs Is Faulted," *Washington Post*, Dec. 19, 2004, p. A1; and Jonathan D. Rockoff, "Series of fill-in leaders is seen hampering FDA effectiveness," *Baltimore Sun*, Feb. 4, 2006. Many observers urged the President to move quickly to appoint a commissioner so that the agency could act to fill its vacant science management slots. For example, see a letter, dated Feb. 1, 2005, from Senators Enzi, Kennedy, and 15 other members of the Senate Committee on Health, Education, Labor and Pensions to the Hon. George W. Bush.

[68] Marc Kaufman, "FDA Commissioner Steps Down After Rocky Two-Month Tenure," *Washington Post*, Sept. 24, 2005, p. A7.

Congressional Options

Reassign conduct of premarket studies away from manufacturer to government

Dr. Angell believes that marketing considerations unduly influence even premarket studies. She argues that government—whether FDA or NIH—should control the clinical trials designed to test safety and effectiveness. One potential drawback of this proposal is the cost. According to PhRMA, its member companies spent $38.8 billion in research and development in 2005,[69] an expense Congress might find difficult to fund. Some observers have proposed assessing industry for those costs but legislating ways to eliminate industry influence in how the funds are spent.

Diminish marketing role in study design

As the Vioxx story makes clear, marketing is where pharmaceutical employees have the sharpest conflict of interest when it comes to scientific decisions.[70] With 93 million Vioxx prescriptions having been written since its approval in 1999, with worldwide sales in 2003 of about $2.5 billion, it is not surprising that, in the gray area where research is not crystal-clear, marketers will clamor for more proof of safety or effectiveness concerns. More available funding for independent research could mitigate the pressure that marketing considerations place on research decisions.

Create transparency in funding of academic research

Congress could mandate full and open disclosure of industry contributions to premarket and post-approval research in the same way it has mandated the disclosure of campaign contributions.

Reduce conflicts of interest in consumer and physician education

An essential ingredient in industry marketing efforts is its use of sales representatives, conferences, and direct advertising. Pharmaceutical companies argue that such efforts play a constructive role in educating consumers and doctors.

Suggestions for limiting direct-to-consumer (DTC) advertising range from the minor to an outright ban of it. Industry promotion to physicians, too, is the focus of critics. Some, such as Dr. Angell, say that these provide little health benefit and those could be accomplished in other ways. She argues that the majority of Phase IV clinical trials are manufacturers' marketing opportunities to introduce products to clinicians and the public. Some have proposed banning or limiting such practices as industry sponsoring of conferences, gifts, and other practices that many see as compromising objectivity; alternatively, sponsors could announce their support publicly and physicians could declare receipt of the benefit. In particular, some recommend that members of the advisory committees that review data and make recommendations to FDA should not receive financial or other benefit from pharmaceutical companies.

[69] PhRMA, *2005 Industry Profile*, at http://www.phrma.org/2005_industry_profile/5/, visited Feb. 13, 2006.

[70] Mathews and Martinez, Nov. 1. 2004.

The members of the FDA advisory committees that met in February 2005 regarding Vioxx, Celebrex, and Bextra addressed consumer and physician advertising. They discussed a range of approaches, including a complete ban on DTC advertising, something FDA officials said was beyond their authority. The committees also suggested various ways to restrict DTC ads, some of them severe. One proposal, for example, would require government-produced alternative ads focused on a drug's risks.[71]

Maintain tort claim option

Former Secretary of Labor Reich readily acknowledges that both regulation and torts "can function far better than they do now." However, he went on to point out that when FDA is weak, "the tort liability system is our only real defense against corporate negligence."[72] At a time when Congress is exploring tort reform, it may consider what such action could do to influence industry behavior when it comes to keeping drugs safe and effective.

Opportunities to Use the Drug Approval Process to Enhance Postmarket Activities

Aside from whether FDA is wholly independent, there is broad agreement among those who have looked closely at FDA's process for drug approval that a number of specific changes in the evaluation process could make FDA more likely to anticipate, identify, and handle problems in ensuring the safety and effectiveness of drugs. FDA has the power now to implement many of these changes. Congress may choose to act, however, if it appears that FDA is declining to act.

Is it possible to identify more problems during Phase III trials before a drug goes to market? Not without slowing the process down. Premarket trials assess the safety and effectiveness of a drug when it is used for a specific purpose in a specifically defined group of people. But some problems may occur in one user out of a hundred thousand. Only when millions of people are using that drug can such an effect become apparent. But that is not to say there can be no changes in process for approving new drugs. Some problems, pointed to by a wide range of critics, include the following:

Inability to attach strings to new drug approval. Some critics think that FDA assesses safety disproportionately at the approval stage by providing close to a one-time, *all-or-nothing*, approval. This severely restricts FDA's ability to act once a drug is on the market. Companies are under no obligation to continue research for safety and effectiveness—even though some kinds of dangers take years to spot.

Inability to enforce postmarket research deadlines. Critics note that manufacturers do not always complete the postmarket studies the law requires in certain approval categories or to which a manufacturer has otherwise agreed. FDA reports industry-committed study status annually in the *Federal Register*,[73] but many feel that not only does FDA not have adequate authority to compel

[71] Gardiner Harris, "FDA Is Advised to Let Pain Pills Stay on Market," *New York Times*, Feb. 19, 2005.

[72] Reich, Jan. 9, 2005.

[73] See, for example, FDA, "Federal Register Report and FDA Web Site on Postmarketing Studies," *FDA Talk Paper*, May 22, 2003, at http://www.fda.gov/bbs/topics/answers/2003/ans01223.html; and HHS, FDA, "Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies; Availability," *Federal* (continued...)

compliance, it does not sufficiently follow through with the tools it does have to enforce those commitments.

Inability to stimulate comparative effectiveness analysis. For premarket approval, current law requires evidence of effectiveness and safety only in comparison to a placebo treatment. Because most new drugs offer only incremental changes to older products, a comparison to placebo is not particularly relevant. Observers argue that consumers and physicians need to know—from unbiased sources—whether the new drug is better than others on the market. The Vioxx controversy brought into sharp relief the potential value of comparing one drug against other drugs used to treat the same illness. Even if Vioxx had proven to be perfectly safe, consumers and physicians would have wanted to know whether it was safer or more effective than ibuprofen. And was it safer for everyone or just the tiny number of people for whom nonsteriodal anti-inflammatory drugs (NSAIDs) produce gastric distress?

Inability to approximate anticipated circumstances of use. FDA accepts as evidence of safety and effectiveness data from trials that do not include what some critics see as a reasonable range of patient, disease, and care characteristics. That is, clinical trials often limit study to people without problems other than the one being studied. The initial trials of COX-2 inhibitors, such as Vioxx, therefore, excluded patients likely to have heart attacks or strokes. Yet, once the drugs went on the market, such patients became COX-2 users—as one might expect of a drug prescribed for arthritis because both arthritis and increased cardiovascular risk are associated with getting older. Excluding groups from clinical trials is a well-established approach to drug research. If it is reasonable to expect that those groups not represented in the trials will buy the drug, however, it is argued that there must be alternative ways to make sure the drug is safe for them.

Reluctance to set limits on the use of approved drugs. Right now, except in a very few circumstances outlined in FDA regulations,[74] physicians can use any approved drug for any illness they deem appropriate. Such off-label use has been particularly controversial recently in the issue of antidepressants and children. An FDA Task Force noted that "[o]nce medical products are on the market, however, ensuring safety is principally the responsibility of healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis."[75] No one recommends banning off-label use because it can offer relief not otherwise available, and can identify a use that can later be tested. Some urge that mechanisms be set up to monitor it.

Congressional Options

Drug approval requirements are set in law. So most options to change the process would require legislation.

(...continued)

Register, vol. 70, no. 33, Feb. 18, 2005, at http://www.fda.gov/cber/pstmrkt/pstmrkperf0205.pdf.

[74] FDA currently restricts the prescribing of 11 drugs to physicians registered or enrolled in a drug's risk management plan (Claudia B. Karwoski, Pharm.D., Scientific Coordinator for Risk Management, FDA Office of Surveillance and Epidemiology, "Practical Experience with Risk Management Plans in the US," presentation at the Drug Information Association (DIA) annual meeting, Philadelphia, 2006, at http://www.fda.gov/cder/present/DIA2006/Karwoski.pdf, visited Dec. 1, 2006).

[75] FDA, "Managing the Risks From Medical Product Use: Creating a Risk Management Framework," Executive Summary of the Report to the FDA Commissioner from the Task Force on Risk Management, May 1999, at http://www.fda.gov/oc/tfrm/1999report.html.

Institute a two-phase approval process that includes mandatory reevaluation

Abandoning the all-or-nothing approach means that FDA could re-evaluate safety using postmarket data concerning prescribing patterns, use patterns, adverse events, and effectiveness, for example. One approach could be to routinely set license-renewal dates. Ongoing review authority would be consistent with FDA's broader mission, supported by the FFDCA and related regulations, to protect the public from unsafe and ineffective drugs.

Require specific postmarket surveillance and study commitments for initial approval

FDA has the authority now. With increased resources, FDA could gather data and analyses to justify additional requests, set due dates, and strengthen its enforcement. Congress could also give FDA the authority to assess and enforce penalties for noncompliance. As a condition of approval, FDA could require the postmarket continuation of preapproval clinical trials to assess, for example, the ramifications of long-term use or latent safety risks that may become evident years after use. FDA could require rigorous postmarket trials of whatever off-label uses become evident.

Require comparative effectiveness trial commitments for initial approval

These trials would assess the comparative safety and effectiveness of a new drug relative to other available drugs and treatments for the condition.

Require commitment to study likely users not considered in preapproval trials

FDA approval could require future studies that would be designed to test safety and effectiveness across the range of people to whom and conditions for which physicians will prescribe the drug.

Restrict use of newly approved drugs when first on the market

There are a few critics who argue for banning all off-label prescribing. More common are those who recommend limiting it and rigorously monitoring it.

So far, this report has looked at problems that become apparent in the postmarket period that may have been avoided by actions in the preapproval process. But whatever the limitations of the premarket review and approval procedure, it produces useful and peer-scrutinized data and analysis. The focus of *postmarket* data collection and analysis dramatically shifts, with changed incentives and statutory and regulatory requirements for both the manufacturer and the FDA. Critics and even some supporters of the system find that postmarket information on the safety and effectiveness of FDA-approved drugs is insufficient to support the kinds of decisions clinicians and patients need to make.

The following discussion divides these problems into two groups:

- insufficient postmarket information, and
- lack of access to existing information.

Insufficient Postmarket Information

Analysts of the current FDA system point out that it is one of *passive surveillance.* Rather than reaching out to identify problems, FDA waits for consumers and physicians to voluntarily report concerns with drugs; manufacturers are required to pass on to FDA the reports they receive. Such reports are valuable aids to researchers looking for potential risks. FDA's Adverse Events Reporting System (AERS) received 464,068 reports in 2005, about 25,000 as MedWatch reports from individuals and the rest from manufacturers.[76]

What are the limitations of a passive approach? A 2000 study by the General Accounting Office (GAO, renamed the Government Accountability Office in 2004) estimated that FDA receives reports on no more than 10% of all adverse drug events. The picture painted by the data, therefore, is "fragmentary and inconsistent."[77] First, in relying on anecdotal evidence, it provides an incomplete and distorted picture of actual problems. Second, the system relies on a physician or consumer making the connection between an adverse event with a drug. Physicians are much more likely to report rare conditions that follow drug use than more common conditions that could be expected in an older user even without the drug. So, liver failure and anaphylactic shock get reported, but fatigue and heart attacks do not.

There are other reasons that voluntary reports do not present a balanced picture. A 63-year-old, weekend tennis player taking a COX-2 inhibitor for knee pain may not even consider reporting a heart attack as a drug reaction. Meanwhile, consumers and physicians report many events that occur immediately after a drug's use that may have nothing to do with that drug. Furthermore, the system relies on physicians or consumers actually following through and reporting their concerns that adverse events are related to the drug.

Finally, data from surveillance reports do not include sufficient information about the medical, behavioral, and sociodemographic characteristics of the patient. Scientists analyzing the data need that information to clarify what appear to be associations between drugs and events. MedWatch provides a count of events but does not provide the total number of people taking the drug. MedWatch may get 100 reports of adverse events. But, are 1000 people taking the drug or a million? Without the denominator, a cluster of events reported to a system such as MedWatch serves only as a red flag to prompt further investigation.

There is a second, more aggressive way to find drug effects after a drug is on the market. Researchers can design studies to address a suspected association of a drug and an adverse event by trying to hold constant other characteristics of the illness and the patient. Researchers also can design studies to test hypotheses suggested by a drug's mechanism of action, or based on findings concerning other drugs in its class. They may also measure a drug's safety and effectiveness for known off-label uses; and can comply with commitments made as part of the drug approval process.

Postmarket effort to identify safety and effectiveness problems requires a two-pronged approach: first, an accurate assessment of what is happening to patients—the warning signs that something

[76] FDA, *CDER 2005 Report to the Nation*, at http://www.fda.gov/cder/reports/rtn/2005-3.htm.

[77] GAO, *Adverse Drug Events: The Magnitude of Health Risk Is Uncertain Because of Limited Incidence Data*, GAO/HEHS-00-21, Jan. 18, 2000.

may be wrong; and, second, carefully designed, rigorously impartial research to see what *is* wrong.

FDA Options

Reassess criteria qualifying as a "signal"

Whatever the surveillance mechanism, FDA could reassess the criteria it uses to decide that the surveillance data indicate a problem—called a *signal*—and then could clarify what steps it could take.

The next two postmarket activities also appear among preapproval options. There, the issue is commitment to do the studies. Here, in the postmarket options section, the issue is actually doing them.

Periodically assess the range of off-label use

FDA could actively collect prescribing or pharmacy data, by characteristics of patient and medical reason for prescribing.

Design and conduct rigorous studies, including clinical trials, to test the safety and effectiveness of drugs as used off-label

FDA and the manufacturer could design studies based on anticipation of likely off-label use and postmarket data on actual off-label use.

Use administrative, financial, and clinical databases

FDA could develop data collection and analysis procedures that validly capture necessary information. In doing so, FDA would need to establish privacy and confidentiality mechanisms that allow patient-level linkages among diagnostic, sociodemographic, treatment, coverage, and outcome data. Other approaches might include the use of automated databases and targeted medical record reviews or patient interviews when necessary.

The President's budget submission for FY2007 describes database activities in its justification of drug safety spending. Planned projects include enhancing data integration with the Centers for Medicare and Medicaid Services (CMS) to allow FDA access, for example, to CMS-population drug safety information. Other data-access goals, including linked analyses, involve other federal agencies, insurers, hospital systems, and pharmacy benefit managers.[78]

[78] FDA, FY2007 Budget, Consolidated Budget In Brief, *Performance Budget Overview*, at http://www.fda.gov/oc/oms/ofm/budget/2007/PDF/2ConsolidatedBIB.pdf.

Congressional Options

Mandate more active surveillance

Some critics urge a drug surveillance system similar to FoodNet, which aggressively seeks food poisoning reports from doctors and laboratories in nine states across the country. Others urge what GAO calls a "proactive examination of a random sample of patient records."

Who would fund this system, and how? It is a question that applies to many of the solutions presented in this paper. There are not an infinite series of choices: increased federal appropriations and industry-generated funds—with restrictions on industry influence—are those mentioned most often by public health analysts.

Authorize FDA to require postmarket studies of situations that had not been anticipated at the time of approval

Right now, FDA can only request studies, using an implied or stated threat to withdraw a drug from the market. Congress could authorize FDA to require studies, avoiding the current gamesmanship and asserting FDA's role. There is another approach: Congress could give FDA authority to take specific enforcement steps other than the current all-or-nothing threat of revoking approval and, therefore, halting U.S. sales.

Require comparative effectiveness studies

The clinical trials that manufacturers field to support applications to FDA usually compare outcomes in two groups: people with the disease who are given the new drug and people with the disease who are given a placebo. What this approach does not provide, though, is any comparison of the new drug with other available treatments. A clinician who is deciding whether to prescribe drug A wants to know more than whether drug A is better than nothing; the clinician also wants to know whether drug A is better—more effective or safer—than drug B.[79]

In part because FDA does not require comparative effectiveness studies, manufacturers rarely mount them. And in part because comparative effectiveness studies are expensive, neither do other researchers.

Congress has included some comparative effectiveness study provisions in bills that recently have become law. The 2003 Medicare Modernization Act directed the HHS Agency for Healthcare Research and Quality (AHRQ) to "conduct and support research" dealing with "the outcomes, comparative clinical effectiveness, and appropriateness of health care items and services (including prescription drugs)...." and authorized the appropriations to do so.[80] AHRQ's FY2007 budget request refers to "the $15 million in continued support related to Section 1013 ... [that] has

[79] In comparing the effectiveness of two or more treatments in reaching a desired outcome, these studies generally do not consider financial cost. Other studies may examine the cost of the treatments as faced by, for example, the patient, the insurer, or the provider; and still others may attempt to weigh the financial and health values of alternative treatments.

[80] Section 1013, P.L. 108-173, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. In this section, Congress authorized $50 million in appropriations for FY2004 and necessary amounts for subsequent years.

evolved into the Effective Health Care Program."[81] Other bills in the 109th Congress addressed comparative effectiveness: the Fair Access to Clinical Trials Act of 2005 (the FACT Act, S. 470 and H.R. 3196), the National Innovation Act of 2006 (S. 2109 and H.R. 4654), the Medical Advertising Reform Act (H.R. 3696), the Traumatic Brain Injury Act of 2006 (H.R. 5738 and S. 3668), and the Prescription Drug Comparative Effectiveness Act of 2006 (H.R. 5975). The Senate-passed language on comparative effectiveness in S.Con.Res. 18 did not appear in the final concurrent resolution on the budget FY2006 (H.Con.Res. 95).

Increase funds to FDA

A larger budget would enable intramural scientists to analyze data and design and carry out follow-up studies based on data-suggested hypotheses. Alternatively, or in addition, Congress could increase funds that FDA can provide to extramural researchers for this work, as well as supporting training programs.

Explore alternative systems

Congress may choose to examine some of the systems adopted in other countries—the "pharmaco-vigilance centers" used by doctors in France, or Great Britain's "green card" requests that researchers send to doctors asking for more information when they spot a possible problem.[82]

Existing Information Unavailable to All Groups

Lack of research into the kinds of safety and effectiveness questions that clinicians and patients could use in treatment decisions is one problem. But there is also significant research information that exists—but is not available. The reasons are more complicated than what some critics assert: that drug companies keep unfavorable results secret. Among other reasons:

Publication bias. Medical journal editors have traditionally paid more attention to positive findings—that a treatment works, for example—than to reports of no differences or statistically insignificant differences between new treatments and old or no treatments. As a result, many researchers, whether industry-affiliated or not, often decide not to submit negative studies for publication. A clinician, patient, or insurer, therefore, could seek information on a drug and, finding only positive reports, assume that the drug is good.

Insufficient FDA resources. A description of FDA's system for collecting possible adverse drug event information appears earlier in this report. Whether because of budget constraints or the unlikely prospect of identifying valid associations within haphazardly collected and incomplete reports, FDA leaves much of these surveillance data unanalyzed. In addition, the agency lacks enough trained pharmacologists, epidemiologists, pharmacoeconomists, and other researchers

[81] HHS, Fiscal Year 2007, Justification of Estimates for Appropriations Committees, Agency for Healthcare Research and Quality, at http://www.ahrq.gov/about/cj2007/cj2007.pdf. The Effective Health Care Program released its first report in December 2005; see AHRQ reports *Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities* released Feb. 9, 2006, and *Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease* released Dec. 13, 2005, at http://effectivehealthcare.ahrq.gov/synthesize/reports/final.cfm.

[82] Anna Wilde Mathews, "As Drug-Safety Worries Grow, Looking Overseas for Solutions," *Wall Street Journal*, Dec. 31, 2004, p. A1.

with the specialized skills necessary for analysis. FDA's budget justification of the FY2006 request appears to recognize this by referring to "the wealth of data in its Adverse Event Reporting System (AERS) to assist medical officers involved in the review process by providing a data mining tool to identify trends in adverse event data."[83]

Industry use of information as marketing. Drug manufacturers do not release all their findings to the public.[84] Critics note that when manufacturers do publicize their findings, in DTC advertisements[85] and marketing materials aimed at physicians, they may provide an incomplete and distorted view of a drug's indications, safety, and effectiveness. Physicians—relying on information packaged by the manufacturer or provided by its detailers—therefore may not have full safety and effectiveness information.

Industry suppression of bad news. Researchers report that the companies sometimes move to suppress the publication or presentation of findings when they could harm a product's sales. This raises complicated matters of policy and scientific procedure. What should FDA do when researchers uncover a risk? What is FDA's duty to disclose industry data? Incorrect decisions can result from action taken too quickly or action delayed from an excess of caution. The problem is that in scientific research, chance, poor study design or analysis, or an unrelated event can imply that a drug is risky when it is safe or safe when it is risky. Limiting or withdrawing a drug, in that case (based on erroneous conclusions), protects no one—and hurts those who would have been helped by it.

Labeling requirements. Labeling does not refer to the little sticker on a pharmacy-issued vial of a prescription drug. It is the detailed package insert, which the manufacturer ships to the drugstore with the medication, that provides prescribing information to the clinician and the patient. The law requires that pharmacists include them for patients, but that does not always occur.

We have mentioned that once FDA approves a drug and the manufacturer puts it on the market, physicians are mostly free to prescribe it as they wish. A doctor may prescribe a drug approved for adults to a child; prescribe a lipid-lowering or anti-inflammatory drug as a possible preventive measure against dementia; or prescribe a drug that the manufacturer tested for six-week use at one dose to someone at a higher or lower dose or for months, years, or a lifetime.[86] Neither the clinician nor the patient—nor FDA—can look up possible side effects of off-label use, either because these uses have not been tested or results not been revealed.

Why? The FDA's passive system for picking up such problems certainly limits it usefulness. In addition, industry is not likely to ask questions that might hurt the drug's financial prospects. The result: even when off-label uses are widely known and suspected of being unsafe or ineffective, the labeling often does not change.

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[83] FDA, Human Drugs, CDER, budget documents, at http://www.fda.gov/oc/oms/ofm/budget/2006/PDFs/Summary/Pages156thru193.pdf, visited Feb. 10, 2005.

[84] Manufacturers must report all studies to FDA.

[85] For a discussion of issues involved in the DTC advertising of prescription drugs, see CRS Report RL32853, *Direct-to-Consumer Advertising of Prescription Drugs*, by (name redacted).

[86] For examples, see Shankar Vedantam, "FDA Links Antidepressants, Youth Suicide Risk," *Washington Post*, Feb. 3, 2004, p. A1; and David Tuller, "Seeking A Fuller Picture Of Statins," *New York Times*, July 20, 2004, p. F5.

FDA Options

Enhance drug-information dissemination options

Especially with use of the Internet, opportunities exist beyond traditional peer-reviewed professional journals, while maintaining standards of scientific quality. For example, the not-for-profit Public Library of Science (PLoS) established a Web-based public forum for published research results.[87] Since May 2005, the National Library of Medicine has strongly encouraged NIH-funded researchers to voluntarily submit their reports (after peer review and acceptance by a research journal) to its PubMed Central database, which will be publicly accessible.[88] Many applaud these types of actions. Others worry that, while these two activities involve only published material, other websites' posting unpublished reports, thereby circumventing the current system of anonymous peer review and editorial oversight, would weaken the protection and integrity the traditional system of research publication provides.

Transfer current information to prescribers

FDA might explore developing an education outreach program to physicians. Such a system might use computer software; round-the-clock opportunities for telephone and e-mail consultations; and visits to physician offices, a practice called "academic detailing" in reference to the promotional visits, called "detailing," made by drug company representatives.

Extend collaborative data collection and analysis activities

Comparative effectiveness studies and safety monitoring need not await government's taking them on. Diverse groups have begun sharing data and results and making them available to others. Examples of such work are the Cochrane Collaboration,[89] the *British Medical Journal*'s Clinical Evidence website,[90] the Oregon Drug Effectiveness Review Project,[91] and the Centers for Education and Research on Therapeutics (CERTs) program funded by the Agency for Healthcare Research and Quality.[92] Many urge that, with funding contributed by government, as well as by foundations, healthcare payers, and industry, the information could—and should—be made public and free.

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[87] According to its website, the Public Library of Science is a "nonprofit organization of scientists and physicians committed to making the world's scientific and medical literature a public resource" (http://www.plos.org/about/index.html, visited Feb. 4, 2005).

[88] National Institutes of Health, "NIH Calls on Scientists to Speed Public Release of Research Publications: Online Archive Will Make Articles Accessible to the Public," *NIH News*, Feb. 3, 2005, at http://www.nih.gov/news/pr/feb2005/od-03.htm; and Sheldon Kotzin, Chief, Bibliographic Services and Executive Editor, MEDLINE, National Library of Medicine, National Institutes of Health, "NIH Public Access Policy," presentation at the Council of Science Editors Meeting, May 24, 2005, at http://www.nlm.nih.gov/bsd/ppt/CSE2005.ppt#258,2,Background.

[89] The Cochrane Collaboration, "an international non-profit and independent organisation, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide," produces the Cochrane Database of Systematic Reviews; see website at http://www.cochrane.org/docs/descrip.htm, visited Feb. 11, 2005.

[90] *Clinical Evidence* is a website owned by BMJ Publishing Group Limited, at http://www.clinicalevidence.com/ceweb/about/index.jsp, visited Jan. 10, 2005.

[91] The Oregon Evidence-based Practice Center, Oregon Health and Science University, webpage describes the collaborative program, at http://www.ohsu.edu/drugeffectiveness/description/.

[92] The CERTs fact sheet, at http://www.ahrq.gov/clinic/certsovr.pdf.

Congressional Options

Require that labeling address off-label uses

Right now, labeling addresses the indications for which the manufacturer requested and received approval. When it is apparent that clinicians are prescribing a drug for other purposes or to populations other than those addressed in the approval application with its supporting safety and effectiveness data, FDA could require that the label include known information and an assessment of hypothesized safety and likely effectiveness in the off-label use. A less ambitious approach would be to require that the label clearly acknowledge that the safety and effectiveness of the common off-label uses have not been studied with the rigor (or at all) required by FDA for new drug approval. This information could be updated regularly. After a drug has been used long enough or by enough people, FDA could require formal assessment (with controlled clinical trials and well-designed observational studies) of safety and effectiveness for those off-label uses.

Remove postmarket study responsibility from both manufacturers and FDA

Avorn suggests that HMOs, academics, insurers, contract research organizations, and other private groups could carry out postmarket studies under government or industry contracts. He gives as examples a 10-cent fee for every filled prescription, or user fees from payers on a per person-covered basis. If the funding came from a line-item in the federal budget or from industry contributions, a mechanism could be imposed to guarantee that the studies were managed independently, without input from the government or industry. That way, the data would not be owned by entities potentially reluctant to release them to the public.[93]

Require clinical trial registration

Congress acted in 1997 to require sponsors to publicly list any clinical trial at its outset to enable individuals to participate.[94] This public notice had a collateral effect: the public could follow-up, years later, what the sponsor had found. Discussion in Congress has focused on registration as a way to compel this openness. Incentives suggested to increase compliance included linking registration either to permission to begin clinical studies in humans[95] or to publication of studies' results.[96]

Make data public

This would avoid the potentially dangerous withholding of data. It would present the opportunity to others to validate findings and conclusions or to analyze the data differently. Making data

[93] Avorn, pp. 384-386.

[94] The Food and Drug Administration Modernization Act. See, also, CRS Report RL32832, *Clinical Trials Reporting and Publication*, by (name redacted).

[95] See the Fair Access to Clinical Trials Act (S. 470 and H.R. 3196), the American Center for Cures Act of 2005 (S. 2104), the Vaccine Safety and Public Confidence Assurance Act of 2006 (H.R. 5887), and the Enhancing Drug Safety and Innovation Act of 2006 (S. 3807).

[96] Catherine De Angelis, Jeffrey M. Drazen, Frank A. Frizelle, et al., "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors," *New England Journal of Medicine*, vol. 351, no. 12, Sept. 16, 2004, p. 1250, at http://content.nejm.org/cgi/content/full/351/12/1250.

public could cause problems, too. If a proposed study *might* yield findings that would hurt a drug's sales, the manufacturer might choose not to pursue the research. If data were widely disseminated before they were replicated, understood, or rejected, they could prematurely form the basis of ill-informed treatment decisions. The enormity of data collected would be unwieldy and difficult to analyze (or analyze within a useful timeframe) without sophisticated statistical knowledge and computer software.

Give FDA enhanced authority to regulate DTC advertisements

Much of the information about drugs available to physicians and the public comes directly from the pharmaceutical industry. Although the law and regulations require that material include description of risks as well as benefits, DTC advertisements are designed to sell a product, and some think that the balance of information is distorted in favor of the product. Currently FDA reviews a DTC advertisement if it becomes aware of a problem. Some would prefer a total ban on DTC advertising; others urge stronger controls. One would require that FDA review and approve advertising copy before it is published. This may require budget action; according to Angell, in 2001 FDA had 30 reviewers for 34,000 DTC advertisements submitted.[97] Other proposals would prohibit DTC advertising in the few years immediately following a new drug's approval.[98]

Give FDA ability to institute penalties for misleading ads

This may require coordination with Federal Trade Commission regulations.

Conclusion

No drug is completely safe. In fact, the Federal Food, Drug, and Cosmetic Act even defines a *prescription* drug as one with "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 drug."[99]

Physicians have a responsibility to weigh benefits against risks when prescribing drugs. To do so requires, in addition to their training and experience, available information. Many ethicists say that the public, too, must have enough information about risks to make up their own minds. However, in-depth analysis is often required to assess a drug's full effects. Some question whether individuals or even their physicians can meaningfully interpret all relevant information.

The FDA's task involves providing that in-depth analysis as it weighs benefits against risks. For example, codeine provides pain relief but is addictive; Tamoxifen keeps breast cancer at bay for those who have had a single mastectomy, but can cause uterine cancer and blood clots; ibuprofen relieves inflammation but can cause gastrointestinal distress; and statins lower cholesterol but

[97] Angell, 2004, p. 124.

[98] For example, the Medical Advertising Reform Act (H.R. 3696, introduced by Rep. S. Brown); the Responsibility in Drug Advertising Act of 2005 (H.R. 3950, introduced by Reps. DeLauro and Emerson); the Food and Drug Administration Safety Act of 2005 (S. 930, introduced by Sens. Grassley and Dodd); and the Enhancing Drug Safety and Innovation Act of 2006 (S. 3807, introduced by Sens. Enzi and Kennedy).

[99] FFDCA Section 503(b)(1).

may weaken muscle fibers. Manufacturers and researchers should find new ways to diminish or mitigate risk. Furthermore, if a drug is not effective, there is no potential benefit to counterbalance even the smallest risk.

FDA's advisory committees routinely tackle these tasks.[100] But the February 2005 joint advisory committee meeting made clear how hard it is to assess the unique and intertwined qualities of *safety*, *benefit*, and *risk*. The committees heard patients testify that they would rather die than live without the COX-2 inhibitor that allows them to function. They heard highly trained researchers present analyses of a drug's risk and come up with different conclusions. Finally, they sat for three days surrounded by conversation and press releases carrying often sharply divergent views from drug companies, consumers, academic researchers, the media, Members of Congress, and the FDA itself.

While few question that FDA applies the necessary statutory, regulatory, and procedural requirements for premarket approval, there is broad criticism of its postmarket enforcement activities. Many observers maintain that the law does not provide sufficiently strong authority for FDA to act.

In this 100th year of the Food and Drug Administration, Congress is clearly poised to examine whether FDA needs more legal authority to regulate the safety and effectiveness of drugs. It could also examine how FDA can better use the legal—and moral—authority it already has (1) to encourage and participate in developing, gathering, analyzing, and disseminating information; (2) to act on that information when necessary; and (3) by its powers to both offer incentives and enforce penalties—and by its own example—to encourage industry cooperation.

There is broad agreement about what problems hamper postmarket activity. This paper has summarized what observers point to as possible solutions. Congress now has a much tougher job—picking the approaches that work best.

[100] FDA, "Human Drug Advisory Committees," at http://www.fda.gov/cder/audiences/acspage/index.htm#Introduction.

Table 1. Concerns and Options Raised by Observers

	Concerns	FDA Options	Congressional Options
FDA organization	—Political pressure —Bureaucratic reluctance to restrict an already approved drug	—Put Office of Drug Safety and Office of New Drugs under different supervisors —Institute scientific dispute resolution mechanisms	—Move task of overseeing safety to another federal agency —Provide whistleblower protection
FDA budget	—Imbalance in funding		—Revise (or repeal) PDUFA —Increase FDA appropriations —Develop alternative funding
Industry role	—FDA dependency on industry —Cultural issue —Influence over data —Influence over funding —Influence over research —Direct-to-consumer advertising	—Fill vacant positions in FDA	—Reassign premarket study responsibility from manufacturer to government —Diminish marketing role in study design —Create transparency in the funding of academic research —Reduce conflicts of interest in consumer and physician education —Maintain tort claim option
Opportunities to use the drug approval process to enhance postmarket activities	—Inability to attach strings to new drug approval —Inability to enforce postmarket research deadlines —Inability to stimulate comparative effectiveness analysis —Inability to approximate anticipated circumstances of use —Reluctance to set limits on the use of approved drugs		—Institute two-phase approval process that includes mandatory reevaluation —Require commitments to specific postmarket surveillance and studies for initial approval —Require commitments to comparative effectiveness trials for initial approval —Require commitments to study likely users not considered in preapproval trials —Restrict use of newly approved drugs when first on the market
Insufficient postmarket information	—Passive surveillance provides fragmentary and inconsistent picture —Relies on physician or consumer to make event–drug connection and then report it —Surveillance reports do not include sufficient information about medical, behavioral, and sociodemographic characteristics of the patient —Without denominators, reported clusters of events serve only as red flags —Researchers also can design studies to test hypotheses	—Reassess criteria qualifying as a "signal" —Periodically assess the range of off-label use —Design and conduct rigorous studies, including clinical trials, to test the safety and effectiveness of drugs used off-label —Use administrative, financial, and clinical databases	—Mandate more activist surveillance —Authorize FDA to require postmarket studies of situations that had not been anticipated at the time of approval —Require comparative effectiveness studies —Increase funds to FDA —Explore alternative systems

	Concerns	FDA Options	Congressional Options
Existing information unavailable	—Publication bias —Insufficient FDA resources —Industry use of information as marketing —Industry suppression of bad news —Labeling requirements	—Enhance drug-information dissemination options —Transfer current information to the prescriber —Extend collaborative data collection and analysis activities	—Require that labeling address off-label uses —Remove the responsibilities for postmarket studies from both the manufacturers and FDA —Require clinical trial registration —Make data public —Give FDA enhanced authority to regulate DTC advertising —Authorize FDA to institute penalties for misleading ads

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