

Monitoring Adverse Reactions to Drugs

July 2005

Executive Summary

In late September of 2004 the drug manufacturer Merck voluntarily withdrew its arthritis pain reliever, Vioxx, from the world market. Annual global Vioxx sales had reached \$2.5 billion in the previous year, and the company was filling 90 million prescriptions annually in the United States. However, post-marketing clinical trials found that Vioxx may have contributed to between 28,000 and 55,000 heart attacks and sudden cardiac deaths between 1999 and 2003. The Vioxx debate elevated public concern over the safety of pharmaceutical products and focused regulatory attention on the post-market surveillance of drugs.

Adverse drug reactions (ADRs) are defined as unintended responses to approved pharmaceuticals given in appropriate dosages. Although the exact number of ADRs is unknown, research indicates that ADRs represent a significant public health problem.

The Food and Drug Administration (FDA) and drug manufacturers share responsibility for oversight of ADRs. The current U.S. approval process for drugs relies on a pre-market drug testing system in which laboratory based studies precede three phases of clinical trials. Collectively, these studies usually include exposure to no more than 3,000 to 4,000 patients and two or more confirmatory clinical trials intended to demonstrate, before release, that a drug is effective and reasonably safe for a recommended use.

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To provide information on longer term or broader exposure, the United States maintains a post-marketing surveillance system of mandatory and voluntary reporting of adverse events. Drug manufacturers are required to report all ADRs, and physicians are encouraged to voluntarily report reactions among their patients. The process of collection of ADRs from the industry and doctors is intended to generate signals of possible adverse events, which are analyzed by the FDA to calculate potential risks to patients. This system produced 321,000 ADR reports in 2002. Over 90 percent of these reports were generated by drug manufacturers.

Most modern nations maintain post-marketing surveillance of drugs, and an active international organization operates to coordinate and track drug events. There are wide variations between countries regarding who reports and what is reported. The most critical differences relate to the role of drug manufacturers in the oversight of ADRs and whether or not reporting of ADRs by physicians is mandatory or voluntary. Among the seventy-five nations participating in the international system, one of the most effective regulatory systems is operated by New Zealand, which generates nearly double the number of reports per million persons recorded in the United States.

The intense scrutiny brought about by Vioxx highlighted public concern of the safety of pharmaceutical products. As a result, there has been interest by Congress, the Institute of Medicine, the Government Accountability Office, the Securities and Exchange Commission, and the federal Department of Justice in investigating the oversight of post-marketing surveillance.

Exploring Adverse Drug Reactions

An adverse drug reaction is defined as an unintended response to an approved product given in an appropriate dosage. An adverse drug reaction is considered serious if it results in admission to a hospital, prolonged hospitalization, increased treatment costs, birth defects, danger to life, or death.

Prevalence and Incidence

Research indicates that ADRs represent a significant public health problem. However, the exact number of ADRs is unknown due to lack of data, unreliable reporting, and lack of a common reporting methodology.

The Institute of Medicine reported in January 2000 that an estimated 7,000 deaths occur annually due to ADRs.¹ However, one study estimated over 350,000 ADRs occur in U.S. nursing homes each year.²

¹ Committee on Quality of Health Care in America: Institute of Medicine, *To Err Is Human: Building A Safer Health System* (Washington, DC: National Academy Press, 2000), 2. The Institute of Medicine is an organization that was established under the charter authority of the National Academy of Sciences.

² J.H. Gurwitz et al., "Incidence and Preventability of Adverse Drug Events in Nursing Homes," *American Journal of Medicine* 109, No. 2 (2000): 87-94. This study, however, used a broader definition of ADR than is otherwise used in this report, including, in

Another study estimated a high incidence of serious ADRs among hospitalized patients. In 1998 a study that appeared in the *Journal of the American Medical Association* (JAMA), analyzing thirty years of data, found that 6.7 percent of patients hospitalized in the United States had a serious adverse drug reaction.³ Based on the number of hospital admissions, the study estimated that in 1994 there were 2.2 million serious ADRs among hospitalized patients, causing 106,000 deaths. The study also suggested that this incidence of fatal ADRs would have ranked ADR-related deaths between the fourth and sixth leading cause of death in the United States in 1994.⁴

Dr. David W. Bates of Partners HealthCare Systems and Brigham and Women's Hospital cautioned that there were several concerns about the way the above-mentioned study was done.⁵ Dr. Bates noted that there are limitations to small, heterogeneous studies and suggested that the studies may have been conducted in hospitals with sicker patients and more ADRs. Nonetheless, Dr. Bates acknowledged the study was important, and the incidence of ADRs is much higher than generally recognized.

Data is also limited on the health care costs associated with adverse drug reactions. One estimate of the cost of drug-related morbidity and mortality, based on the costs in 1992 of hospitalization, long-term care facilities, and doctor visits, ranged from \$30.1 billion to \$136.8 billion annually.⁶ To the extent such costs have risen since that study, the estimate would not reflect the current costs.

Regulation of Adverse Drug Reactions

The FDA and drug manufacturers share responsibility for oversight of adverse drug reactions, although the standards and requirements for reporting vary widely. For example, the FDA, through regulation, requires manufacturers to report known ADRs, but, as in most industrialized nations, reporting of ADRs by physicians and hospitals is voluntary. As to manufacturers, reports of serious events must be made within fifteen days of a manufacturer's receipt of

addition to ADRs in which no error was involved, medication errors such as administering the wrong drug or the wrong dose of a drug. Subtracting out the medication errors, the number of ADRs estimated by this study would be roughly halved. It should also be noted that the results of the study include all ADRs classified as either significant, serious, or fatal.

³ J. Lazarou, B. Pomeranz, and P. Corey, "Incidence of Adverse Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies," *Journal of the American Medical Association* 279, No. 15 (1998): 1200-1205.

⁴ Ibid. 1202.

⁵ D. Bates, "Drugs and Adverse Drug Reactions, How Worried Should We Be?" *Journal of the American Medical Association* 279, No. 15 (1998): 1216-1217.

⁶ J.A. Johnson and J.L. Bootman, "Drug-Related Morbidity and Mortality: A Cost-of-Illness Model," *Archives of Internal Medicine* 155, No. 18 (1995): 1952-1953. These costs are attributable not just to ADRs as defined in this report, but also to noncompliance by the patient or inappropriate prescribing and/or monitoring by health care professionals. Costs attributable to noncompliance comprise anywhere from \$8.5 billion to \$50 billion of the estimated costs of ADRs.

information of an adverse event; reports of nonserious incidents are submitted quarterly. Additionally, manufacturers and distributors of FDA-approved pharmaceuticals (drugs and biologics) and medical devices, as well as pharmaceutical packers and device users, are required to report to the FDA all adverse events and to provide case information that is as complete as possible. Hospitals, in order to be accredited, must also monitor adverse events involving pharmaceuticals and medical devices “per applicable law or regulation.” However, federal law requires hospitals to report adverse events with devices, but only encourages voluntary reporting of pharmaceutical events. Another way adverse events get reported is by individual patients who may, but are not required to, report. However, adverse reactions to over-the-counter medicines are not reportable unless the medicine is marketed under a new drug status, and adverse reactions to dietary supplements are also not reportable.

The FDA maintains the Adverse Event Reporting System to track adverse drug reactions. The reporting system is a computerized information database designed to support post-marketing safety surveillance of all approved therapeutic products. Manufacturers send reports of ADRs directly to this system, while voluntary individual and professional reports, known as “spontaneous reports,” are transmitted through the Medwatch program, a separate and parallel reporting mechanism. Medwatch serves as a two-way communication between the FDA and the treating community by accepting information on adverse events and extending warnings or information on drug restrictions.

Spontaneous reports from individuals and physicians are intended to act as signals to the FDA of potential serious and otherwise unrecognized events. When such a signal is identified, further testing of the indicated pattern is pursued through epidemiological and analytic databases, studies, and other instruments and resources. The Adverse Event Reporting System and Medwatch accept either paper or electronic submissions and maintain international compatibility and pharmacovigilance screening.⁷

In 2002 the FDA received nearly 321,000 adverse drug reaction reports, composed of 20,455 reports received directly from individuals and health professionals and 300,415 from manufacturers.⁸ It is noteworthy that between 1995 and 2002, the number of reported post-market adverse events doubled. This increase was attributable to increased manufacturer fifteen-day serious reports, periodic reports, and nonserious reports. The number of individual and professional reports transmitted through Medwatch remained constant.⁹

⁷ Pharmacovigilance refers to all observational post-approval scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events with the goals of identifying and preventing these events to the extent possible. Food and Drug Administration, *FDA News: FDA Issues Final Risk Minimization Guidances* (2005), available at <http://www.fda.gov/bbs/topics/news/2005/NEW01169.html>.

⁸ Food and Drug Administration, *Center for Drug Evaluation and Research 2002 Report to the Nation: Improving Public Health Through Human Drugs* (Rockville, MD: 2002), 25, 27.

⁹ Ibid.

In addition to the direct voluntary reports from consumers and physicians, and the mandatory reporting of adverse drug experiences required of pharmaceutical companies, the FDA's post-marketing surveillance program includes:

- ♦ Review of drug utilization information by outpatients, inpatients, and physicians via contracted sources;
- ♦ Access through cooperative agreements to large population databases of drug products and special populations;
- ♦ Background incidence rates;
- ♦ Information from studies in humans and animals;
- ♦ Searches of real-time data from several federal agencies, including the Veterans Administration; and
- ♦ Information on adverse events from electronic medical records.

In 2001 the FDA contracted with AdvancePCS, Premier Inc., and Child Health Corporation of America for access to commercial databases that contain information, unidentifiable by patient, on the actual use of marketed prescription drugs in adults and children. The FDA is now developing an online reporting system on the Medwatch Web site to share information on harmful products. To populate this system, the FDA electronically scans patient and coroner records received by mail and transmits the documents to medical personnel investigating a product's effects. In the future this system will provide case- and product-specific information to the public online.

The FDA's review of drug products consists primarily of pre-market testing rather than post-market surveillance. Post-marketing oversight operates with but a small fraction of the resources committed to pre-market drug testing. Within the FDA, approximately 2,300 analysts work on pre-market approvals, while less than 300 analysts track post-market reporting.¹⁰ Because of this imbalance, compliance and enforcement of post-market monitoring has been a source of much criticism for the FDA.

The increased resources devoted to pre-market testing dates back to Congress' enactment of the Prescription Drug User Fee Act (PDUFA) of 1992. The goal of PDUFA was to speed up the review of applications for new drugs and biological products. To accomplish this goal, PDUFA requires drug manufacturers to pay user fees to the FDA to supplement the FDA's budget and support the FDA's review process. To balance the imposition of user fees on the industry, PDUFA also established performance goals for the FDA, specifically with the intent of

¹⁰ S. Prakash, National Public Radio, Weekend All Things Considered, *Challenges Facing the FDA in Its Monitoring of Drug Safety After a Drug Reaches the Market*, November 7, 2004.

reducing the amount of time required to review a new drug.¹¹ The advent of user fees has served to allow the FDA to increase the number of staff reviewing drug applications and, consistent with the intent of PDUFA's performance goals, reduce the length of the review process. In fact, between 1993 and 2001, median approval times for standard drugs decreased from about twenty-seven months to about fourteen months.¹² Rapid reviews are very much in the interest of drug manufacturers, as any time saved in the FDA review process increases the time a product may be sold under a profitable exclusive patent. This makes user fees palatable.

Until 2002 user fees were restricted to pre-market reviews. And the disparity between resources put into this area and other areas was apparent. In fact, the FDA notes that while the budget and personnel assigned to pre-market reviews has increased markedly since 1992, the staff and resources for most programs other than drug approvals, including post-market surveillance, have been reduced.¹³

The FDA's more limited attention to post-marketing surveillance can be further evidenced by an FDA publication which notes that "once medical products are on the market, however, ensuring safety is principally the responsibility of health care providers and patients, who make risk decisions on an individual, rather than a population, basis."¹⁴ In the view of the FDA, doctors and consumers are expected to use the labeling information generated by pre-market research to appropriately select products and minimize adverse events.

However, with the PDUFA amendments of 2002, for the first time some money was earmarked for post-market surveillance. Effective 2003, PDUFA allowed user fees to be used for risk management plans for the first two years after a product is approved, and for post-market surveillance for three years after the drug's approval. "FDA anticipates that user fees for risk management will total approximately \$71 million over five years, and will permit the agency to add 100 new employees to monitor drug safety and track adverse effects from drugs already on the market."¹⁵

Adverse Drug Reactions in the United States and Other Nations

The majority of modern nations maintain systems for reporting adverse drug reactions. But the organization and relative effectiveness of international ADR monitoring varies significantly. The greatest variation between systems is how

¹¹ General Accounting Office, *FDA: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, Pub. GAO-02-958 (Washington, DC: 2002), 1, 6, 7.

¹² Ibid. 3, 8, 9.

¹³ Ibid. 14-15.

¹⁴ Food and Drug Administration, *Managing the Risks from Medical Product Use: Creating a Risk Management Framework* (Rockville, MD: 1999), ES-4.

¹⁵ General Accounting Office, *FDA: Effect of User Fees*, 28.

aggressively enforcement is carried out, whether reporting is voluntary or mandated, who may submit reports, and what products are monitored.

A number of nations have supported reporting operations for more than thirty years, while others have been established only recently. Most operations rely on voluntary reports, though two major European nations, France and Spain, mandate reporting of ADRs by health professionals. Reports are accepted from doctors, dentists, and pharmacists in all of the major economies. However, the role of other health professionals and the general public varies among nations. Differences in the reactions and products reported differ widely among national systems. In some countries (e.g., Denmark and New Zealand), reports of all reactions are sought, while other countries focus exclusively on serious reactions to newly marketed products. In Australia a separate reporting system for drug-induced congenital malformations is maintained, and Canada, South Africa, and the United States run separate operations for tracking vaccines. The numbers of spontaneous reports received also varies considerably – from a few hundred each year in South Africa to over 20,000 in the United States. Formal operations for tracking spontaneous reports now operate in fifty-four nations.¹⁶

The World Health Organization maintains an international program to follow and communicate adverse drug reactions. Known as the Programme for International Drug Monitoring, the World Health Organization's effort includes seventy-five member nations and eleven associate nations. Member countries are required to meet certain monitoring and reporting standards, maintain compatible records, and agree to share reports of critical outcomes. The Programme for International Drug Monitoring is administered from the World Health Organization's headquarters in Geneva, while program operations are carried out through the Uppsala Monitoring Center in Uppsala, Sweden. The Programme collaborates with three international organizations¹⁷ and maintains a network of 3,000 European experts. The center has recorded more than 1.9 million reports of adverse drug reactions.

Voluntary and Mandated Reporting

As noted, most international ADR reporting programs depend on voluntary reports from health professionals. However, France and Spain mandate reporting by physicians. The mandatory nature of reporting in France and Spain do not result in higher numbers of reports in these countries, however. For example, although France's population is similar to that of the United Kingdom, the number of reports in France is less than one-half of the reports made in the United Kingdom, where reporting is voluntary.¹⁸

¹⁶ The World Health Organization Adverse Reaction Database, World Health Organization Collaborating Centre (Uppsala, Sweden). Available at <http://Hwww.who-umc.orgH>.

¹⁷ They are the European Medicines Agency within the European Union, the Medicines and Healthcare Regulatory Agency, and the Drug Safety Research Unit in the United Kingdom.

¹⁸ M. Hughes, C. Whittlesea, and D. Luscombe, "Review of National Spontaneous Reporting Schemes," *Adverse Drug Reaction Toxicology Review* 21, No. 4 (2002): 231-241. France annually reports 163.8 adverse drug reactions for each of its 1 million

Researchers believe that one reason for the low reporting under mandates is the difficulty in enforcing such a law.¹⁹ As medical information is confidential, failure to report an ADR is likely to go unnoticed. Mandated reporting could increase the number of ADR reports, but only if an effective enforcement mechanism can be designed.

Expanding the Number of Adverse Drug Reaction Reporters

In addition to reports from physicians, adverse drug reaction reporting systems take reports from a variety of different individuals. Virtually all ADR systems accept reports from physicians and pharmacists, but the involvement of dentists, nurses, midwives, coroners, and patients is less common. In most nations surveyed, the majority of reports come from either the drug manufacturers (as in Germany, South Africa, and the United States) or from doctors (such as in Australia and the United Kingdom).²⁰

Increasing the number of reporters could increase reporting, but there are concerns regarding the quality of reports from nonphysicians. Community pharmacists in Australia provide reports on over-the-counter medications and, in Ireland, nurses have made a significant contribution to ADR reporting. The role of the patient in reporting is controversial, and only a handful of nations surveyed permit reporting by individuals. The concern has been that patient participation results in spurious reporting, which complicates ADR assessments.²¹

Nevertheless, patient reporting has been increasing, and several observers believe the impact has been generally positive.²² In the United States, patient reports are accepted and have been incorporated into post-marketing systems. In Canada, patients have reported more reactions than have nurses. Observers believe the role of the patient is likely to increase in the near future.²³

Content of Adverse Drug Reaction Reports

Nations differ on drug events to be reported. For example, several countries, including the United States, have systems for reporting vaccines and medical devices.

Major differences also exist regarding the types of reactions that are reported. All nations request reports of serious reactions. Most nations request reports of

people. The United Kingdom reports 310.8, the United States reports 416, Australia 479.7, and New Zealand 740.7. See World Health Organization Adverse Reaction Database.

¹⁹ M. Hughes, "Review of National Spontaneous Reporting Schemes," 238.

²⁰ Ibid. 234 at Table III, 238.

²¹ Ibid. Eighteen nations were surveyed. Of the twelve that responded, only six permit reporting by individuals.

²² Ibid. 238.

²³ Ibid.

reactions to newly marketed products and unexpected reactions to more established drugs. One unique feature in New Zealand is that all reactions, regardless of severity or cause, are reported. This feature may partly explain why New Zealand has the highest ADR reporting rate in the world.²⁴

Causes of Adverse Drug Reactions

One source of increasing numbers of adverse drug reactions may be the growing prevalence of pharmaceutical products in our country. Hundreds of new pharmaceutical products enter the marketplace every year. There are approximately 10,000 prescription drugs now available in this country and more than 3 billion prescriptions written each year. An increasing percentage of the public uses prescription drugs, the duration of prescriptions is lengthening, and the number of prescriptions per consumer has steadily risen. Pharmaceutical products are now delivered through an increasingly complex health care environment and emerging global drug market.

ADRs may also result from the inherent limitations of pre-market testing done by the FDA. The short duration, narrow population base, limited analytical indicators, and small sample size of pre-market testing suggest that post-market surveillance may be necessary to identify drug reactions with a rare toxicity or extended latency.

Another possible explanation for the high number of ADRs in the United States is that approval by the FDA is based on pre-market tests on a few thousand people over a relatively short time period. In order to reach a 95 percent chance of detecting an adverse event, with an incidence of 1 per 1,000, exposure of 3,000 patients at risk is required. Adverse reactions which occur less commonly than that are unlikely to be detected in these studies. Current testing typically exposes as few as 500 and no more than 3,000 or 4,000 individuals prior to marketing.²⁵

Criticism of the Federal Drug Administration

During early 2004 the FDA expanded its database for reporting adverse drug reactions to improve its post-marketing surveillance of drugs. While observers generally welcome the expanded database, some have raised concerns regarding the FDA's role in ensuring drug safety.

Watchdog consumer groups argue that despite known dangers of particular drugs in the scientific and international communities, the FDA has neglected to use this information to protect consumers. Critics also point out that the FDA lacks a clear scientific risk standard for drug safety, resulting in ineffectual drug oversight. A risk standard is a predetermined, measurable, and fixed level of harm that is accepted by the agency. Some argue that the absence of a risk

²⁴ Ibid. 236.

²⁵ B.L. Strom, ed., *Pharmacoepidemiology*, 3d ed. (Chichester, England: John Wiley and Sons, 2000): 9; C. Rados, "Inside Clinical Trials: Testing Medical Products in People, *FDA Consumer Magazine*, September-October 2003.

standard permits greater discretion on the part of the FDA than if there were a recognized risk standard.

In one case, congressional inquiries began to investigate whether the FDA inappropriately suppressed crucial findings on a possible link between antidepressants and suicidal behavior in children. Press accounts indicate that a medical researcher for the FDA, Dr. Andrew Mosholder, planned to present a preliminary report to the FDA advisory committee that found that antidepressants doubled, and in some brands tripled, the risk of suicidal behavior in adolescents.²⁶ However, Dr. Mosholder's supervisors reportedly prevented release of the information, explaining that they believed the data was not reliable and that Dr. Mosholder's conclusions were premature.²⁷ The FDA went so far as to state publicly, four months after Dr. Mosholder's analysis was completed, that "no conclusive scientific evidence existed on the link between antidepressants and potentially suicidal behavior by children."²⁸ The FDA commissioned a subsequent study which eventually reached the same conclusions as Dr. Mosholder's original analysis – children on antidepressants are at twice the risk of serious suicide-related events.²⁹

Congressional inquiries were also made into the suppression of research linking antidepressants and suicidal behavior in children in the pre-marketing phase. The inquiries examined alleged selective reporting of clinical trial data. This issue is broader than clinical trials of antidepressants. Despite compelling ethical and scientific reasons, very few clinical trials are reported, and trials with negative indications very rarely have entered the public domain. A Brown University researcher reported that only one of every thirty-seven clinical trials of nonsteroidal anti-inflammatory drugs has been published. Finnish researchers reported that only 10 percent of trials concerning cardiovascular risk from hormone replacement therapy were published.³⁰

In another case, critics argue that the FDA failed to take Rezulin, a drug used for diabetes treatment, off the market despite reported cases of liver damage. According to consumer advocates, Rezulin was first marketed in 1997 and taken off the market in the United Kingdom by December of that year due to reported cases of liver damage. By July 1998 there were 560 reported cases of liver damage, including twenty-six deaths. Rezulin was withdrawn from the U.S. market in January 2000, by which time there were hundreds of additional cases of liver damage and sixty-three deaths.³¹

²⁶ G. Harris, "Expert Kept from Speaking at Antidepressant Hearing," *New York Times*, April 16, 2004.

²⁷ S. Vedantam, "FDA Study Confirms Antidepressant Risks," *Washington Post*, August 10, 2004.

²⁸ E. Shogren, "FDA Sat on Report Linking Suicide, Drugs," *Los Angeles Times*, April 6, 2004.

²⁹ S. Vedantam, "FDA Study Confirms Antidepressant Risks."

³⁰ S. Hensley and L. Abboud, "Medical Research Has Black Hole," *Wall Street Journal*, June 4, 2004. These same Brown University researchers reported that only 30 percent to 50 percent of all studies are eventually published.

³¹ S. Wolfe, "Take Drugs Off the Market," *USA Today*, December 27, 2004.

Another case arose involving a young man who died in April 2004 from liver failure after using Serzone. This product had been pulled from the European and Canadian markets, and the FDA's Adverse Event Reporting System reported more than twenty similar deaths. The FDA had issued warnings on the use of Serzone in 2001, but allowed the product to remain available in the United States.³²

Storm Over Vioxx

On September 30, 2004, the drug manufacturer Merck voluntarily pulled its arthritis pain reliever, Vioxx, from the world market. Vioxx had recorded global sales of more than \$2.5 billion in 2003 and had been taken by 20 million Americans. Post-marketing studies had found that Vioxx, and quite possibly similar medications, may have contributed to as many as 55,000 heart attacks and sudden cardiac deaths between 1999 and 2003.³³ The controversy, and subsequent claims of a coverup by Merck, triggered a cascade of civil actions, criminal complaints, financial losses, and political reactions for the drug manufacturer. Within these events, accusations of the actions and inactions of the FDA figured very prominently.

The *Wall Street Journal* reported that internal e-mails, marketing documents, and interviews with outside scientists who questioned the safety of Vioxx indicated that Merck was aware of safety concerns related to the medication and sought to hide potential injuries to protect sales. As early as 2000, internal Merck e-mails recognized the dangers of Vioxx and, even in the face of clinical trials to the contrary, issued public statements that Merck had affirmed the favorable safety profile of Vioxx.³⁴ Merck also sought to silence outside critics of Vioxx and to prevent publication of any negative research, the newspaper reported.³⁵

Merck's actions prior to the withdrawal of Vioxx initiated formal investigations by Congress, the Securities and Exchange Commission, the Government Accountability Office, the federal Department of Justice, and the Institute of Medicine. Merck reported on October 31, 2004, that 375 lawsuits representing 1,000 plaintiff groups have been filed against it, as well as several class action suits and state consumer fraud and fair business practice actions.³⁶

In September 2004, after the withdrawal of Vioxx, the FDA convened a panel of thirty-two experts to sift through studies and weigh the risks and benefits of

³² B. Martinez, "Teen Death Stirs Fresh Debate About Depression Medication," *Wall Street Journal*, April 20, 2004.

³³ D. Graham, associate director of the Office of Drug Safety, FDA, in testimony before Congress, as reported in, M. Kaufman, "FDA Offices Suggests Strict Curbs on Five Drugs," *Washington Post*, November 19, 2004; K. Dooley, "FDA Analysts Put a Number on Heart Attacks from Vioxx," *Philadelphia Inquirer*, November 30, 2004.

³⁴ A. Mathews and B. Martinez, "E-mails Suggest Merck Knew Vioxx's Danger at Early Stage," *Wall Street Journal*, November 1, 2004.

³⁵ Ibid.

³⁶ L. Loyd, "Merck Reveals Federal Criminal Probe of Vioxx," *Philadelphia Inquirer*, November 9, 2004.

Vioxx and two drugs made by Pfizer, Celebrex and Bextra. On February 18, 2005, the panel unanimously agreed that the painkillers cause worrisome heart problems, but recommended nonetheless that all three be available to patients, accompanied by strong warnings of the risks. The panel agreed that the potential benefits of the pain-killing drugs outweighed the dangers they posed for cardiovascular problems.³⁷ In April 2005 the FDA decided to remove Bextra from the market and require Celebrex, along with other prescription drugs, to include stronger warning labels.³⁸

Vioxx was the first prescription drug since 2001 to be taken off the market for safety reasons. The withdrawal came just weeks after the company defended the safety of the drug and the FDA approved the use of Vioxx in children as young as two-years-old. While the FDA pressed Merck for a stronger safety component in the three-year study that ultimately established Vioxx's risk, the FDA took no action to regulate or control the product. At the time of its approval, the FDA had clinical trials for Vioxx that had lasted twelve months. The increased cardiac risks that prompted Merck to withdraw Vioxx did not appear in the research until older patients had taken the drug for eighteen months.

This inaction on the part of the FDA is, according to the *Washington Post*, part of a noticeably less aggressive policing of harmful drugs in the last four years.³⁹ The *Post* notes that fewer medications have been taken off the market, and fewer warning letters have been sent to challenge misleading or dishonest advertising. Between 1996 and 2001, ten medications were taken off the market, while between 2001 and 2004 only three medications were removed, even as the number of adverse events reported doubled between 1996 and 2004. Similarly, the FDA sent 130 "cease and desist" letters on medication marketing practices in the immediate past four years, as compared with nearly 500 between 1996 and 2001.⁴⁰

In general, more than half of all drugs introduced are found to have unanticipated side effects long after clinical trials are completed and marketing approvals are granted. Drug manufacturers, the marketplace, and consumers benefit from quick pre-market approval of drugs and, logically, an extended post-marketing review could permit early distribution of important medicines

³⁷ G. Harris, "Merck May Resume Sales of Painkiller, Official Says," *New York Times*, February 18, 2005; A. Berenson and B. Feder, "A Reminder That No Drug Is Risk-Free," *New York Times*, February 19, 2005; G. Harris, "F.D.A. Is Advised To Let Pain Pills Stay on Market," *New York Times*, February 19, 2005; and Editorial, "The Experts' Verdict on Painkillers," *New York Times*, February 19, 2005. According to the *Times*, most panelists recommended that the FDA place stern warnings on the drugs' labels, ban consumer advertising for the drugs unless they are balanced by FDA or independent group ads, and require each prescription to include a guide outlining the risks.

³⁸ R. Alonso-Zaldivar and D. Gellene, "FDA Warns on Painkillers; Drug Pulled; Bextra Is Withdrawn from the Market. Some Anti-inflammatory Medicines Can Cause Heart Trouble, the Agency Says," *Los Angeles Times*, April 8, 2005, Home Edition.

³⁹ M. Kaufman and B. Masters, "FDA is Flexing Less Muscle; Some Question Its Relationship with Drugmakers," *The Washington Post*, November 18, 2004.

⁴⁰ Ibid.

while providing additional safety. Several observers have suggested that a greater degree of safety could be attained by simply requiring drug companies to conduct longer clinical trials on drugs already in wide use.⁴¹ However, academic researchers note that in the current system there is no provision for systematic assessment of safety for the thousands of medicines in use in the United States.⁴²

The New Zealand Model

Based on the number of annual reports per million inhabitants, New Zealand has the highest adverse drug reaction reporting in the world. On average, New Zealand health professionals have contributed 741 reports per million inhabitants each year. (Australia was second with 479.7 and the United States was third with 416 reports per million.⁴³) The high reporting of New Zealand's adverse reactions is due, in part, to a drug reaction tracking system which focuses intently on a defined cross section of consumers. New Zealand's national post-marketing surveillance approach is distinguished from other spontaneous ADR reporting systems by targeting cohort studies of roughly 10,000 patients taking selected drugs and monitoring them for an average of fifty-eight months.

In New Zealand an independent medical panel makes recommendations on which drugs should be monitored. Presently, the first three medicines of any new class are recommended for monitoring. This program is based on the premise that clinical trials may not provide the complete picture when it comes to safety, and intensive monitoring is necessary in the early post-marketing period. The medical panel gives priority to monitoring those drugs where:

- ♦ Use is expected to be widespread and/or long term;
- ♦ Safety issues have been raised from clinical trials and further evaluation is indicated;
- ♦ Related drugs have significant problems; and
- ♦ Safe treatment options are already available and any increase in risk would be unacceptable⁴⁴.

Whenever a pharmacist fills a patient's prescription for any one of the designated drugs, a printout is transmitted to the national monitoring program, creating a prescribing history for the patient for as long as treatment continues. Throughout the monitoring period, the national office sends questionnaires on each patient to prescribers of the studied drugs for as long as the prescriptions are in force. The prescribers are asked to report any adverse events, which are

⁴¹ D. Henderson, Associated Press, "Vioxx Woes Raise New Questions about Drug Agency Oversight," October 2, 2004.

⁴² Ibid.

⁴³ World Health Organization Adverse Reaction Database.

⁴⁴ D.M. Coulter, "PEM in New Zealand," in *Pharmacovigilance*, eds. R.D. Mann and E.B. Andrews (Chichester, England: John Wiley & Sons, 2002), 346-347.

defined as any untoward experience; whether or not the event is thought to be drug related, including any adverse changes in a pre-existing condition; abnormally changed laboratory values; pregnancy; unexpected failure of therapeutic effect; any possible interactions; accidents; and all deaths.⁴⁵ Participation by pharmacists and doctors is voluntary and unpaid. Physician compliance rates for returning the questionnaires is seldom less than 80 percent, and pharmacist compliance with returning the prescription printouts is 86 percent.⁴⁶

The basic methodology of reporting in New Zealand is, in effect, an extended clinical trial under real-world conditions. Its system, unlike the FDA's, records both who is taking the targeted drugs and any adverse effects those drugs have on the specified population. The largest source of reported adverse events is from the physicians involved in these monitored studies. The information is gained in the world of normal clinical practice where the use of drugs is subject to many influences not present in the artificial world of controlled clinical trials. Trends in prescribing can be followed, and there is a greater chance of identifying longer-term outcomes or events such as death. Reasons for cessation of therapy are recorded, as is information on deaths, compliance, and efficacy.⁴⁷

Observations

The Vioxx example highlights an intrinsic conflict in our current system for post-marketing surveillance: drug manufacturers are largely responsible for collecting, evaluating, and reporting data on the safety of their own products. A second conflict occurs within the FDA itself. The agency charged with determining pre-market safety is also responsible for double-checking itself through post-marketing surveillance. In effect, the agency responsible for drug licensing is also asked to monitor its own record and prove itself wrong.

In its analysis of U.S. pharmaceutical safety, the *Journal of the American Medical Association*⁴⁸ identified fundamental problems with the current surveillance system. First, many adverse drug events are very uncommon, and detecting the events accurately and using them to determine incidence rates can be very difficult within the existing voluntary system of reporting. Second, because of inherent conflicts of interest or competing priorities, drug manufacturers may fail to actively pursue post-marketing research or to report evidence contrary to their pre-market findings.

⁴⁵ D.M. Coulter, "The New Zealand Intensive Medicines Monitoring Programme in Pro-active Safety Surveillance," *Pharmacoepidemiology and Drug Safety* 9 (2000), 274. In part of the nation, they use special duplicate prescription forms which include information about any adverse event since the previous prescription. This approach minimizes the need for the follow-up questionnaires, but is only utilized in 25 percent of the country.

⁴⁶ Ibid. 276.

⁴⁷ Ibid.

⁴⁸ P. Fontanarosa, R. Drummond and C. DeAngelis, "Post-Marketing Surveillance—Lack of Vigilance, Lack of Trust," *Journal of the American Medical Association* 292, No. 21 (2004), 2647-2648.

To genuinely improve the monitoring and safety of marketed drugs, notes *JAMA*, the drug approval process should be decoupled from the post-marketing safety and surveillance system. The American Medical Association and numerous newspaper editorial boards have recommended establishing an independent drug safety board to oversee post-marketing surveillance. *JAMA* argues that it has become evident that the post-marketing surveillance system is long overdue for a major restructuring, citing recent evidence of serious harm resulting from widely used and heavily promoted medications and the influence of the industry over post-marketing data.

Critics have argued that a conflict exists among the FDA's multiple responsibilities. On one hand, the FDA serves an important public interest when it acts quickly to bring to market beneficial products to serve critical human needs. And, in accomplishing that public benefit, the agency diminishes the functioning of another – that of protecting patients from potentially harmful medicines.⁴⁹ One solution to the dilemma would be to continue meeting the public's interest in reasonable access to promising medicines, but to couple this function with an efficient and independent post-marketing system.⁵⁰

Congress has the principal authority to regulate pharmaceutical products and to oversee the Food and Drug Administration. The decisions regarding an independent drug safety program, establishing fixed safety standards, complying with post-marketing clinical trials, and publishing clinical trial data will all be made at the federal level. States have only very limited ability to intervene in the regulation of drugs. However, state governments, particularly state governments as large as California's, do have some policy options.

California could, for example, adopt policies aimed at strengthening the current system for reporting ADRs to the FDA. The state could leverage its negotiating power as a large purchaser of prescription drugs to require contracts with drug manufacturers to include demonstrated compliance with FDA guidelines and regulations. The state could also increase physician reporting to the FDA by targeting outreach or mandating physician reporting. It would be important to have effective enforcement mechanisms in place to help ensure successful implementation of these options.

California could also implement its own adverse drug reaction reporting mechanism to complement the federal reporting system. Such a system could identify a central medical review body, implement a duplicate prescription system for targeted drugs, identify the pool of users and prescription practices, and create a simple ADR reporting system for physicians. Any proposal would also have to address California privacy and confidentiality issues related to reporting prescription usage. California could report findings from the state system directly to the FDA. Implementation of this option could, however, require significant additional state resources.

⁴⁹ Editorial, "Evaluating Vioxx," *Washington Post*, October 14, 2004.

⁵⁰ P. Fontanarosa, "Post-Marketing Surveillance," 2649-2650.

Related Legislation

The California Legislature is evaluating several proposals during the current legislative session related to the reporting and monitoring of adverse drug reactions. Those measures are described briefly below.

SB 329 (Cedillo), as introduced February 16, 2005, would establish the California Prescription Drug Safety and Effectiveness Commission to provide Californians with information on the safety and effectiveness of prescription drugs.

SB 380 (Alquist), as amended June 21, 2005, would require licensed health professionals and health facilities to report all suspected serious adverse drug events that are spontaneously discovered or observed in medical practice to MedWatch.

AB 71 (Chan/Frommer), as amended May 26, 2005, would establish the Office of California Drug Safety Watch to provide Californians with information on the safety and effectiveness of prescription drugs that are frequently advertised on television.

AB 72 (Frommer/Chan), as amended May 26, 2005, would establish the Patient Safety and Drug Review Transparency Act for purposes of making information regarding clinical trials of prescription drugs available to the public, physicians, and researchers.