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Postmarketing Surveillance— Lack of Vigilance, Lack of Trust

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PHYSICIANS AND PATIENTS EXPECT THAT WHEN MEDICATIONS are prescribed correctly for labeled indications and are used as directed, these medications generally will have beneficial effects and will not cause significant harm. This confidence in pharmaceutical products reflects trust in the effectiveness and integrity of the drug approval and monitoring process.

However, the current approval process for drugs and biological agents in the United States has come under intense scrutiny, most notably because of concerns about influence from industry. For instance, since adoption of the 1992 Prescription Drug User Fee Act, which augmented the budget of the Food and Drug Administration (FDA) by charging “user fees” to pharmaceutical firms,¹ the FDA has received approximately \$825 million in fees from drug and biologic manufacturers from fiscal years 1993 through 2001.^{2,3} During that time, median approval times for standard (ie, “nonpriority”) drugs decreased from 27 months in 1993 to 14 months in 2001, but as an inevitable consequence of faster approvals, drug recalls following approval increased from 1.56% for 1993-1996 to 5.35% for 1997-2001.² In addition, an investigation of 18 FDA expert advisory panels revealed that more than half of the members of these panels had direct financial interests in the drug or topic they were evaluating and for which they were making recommendations.⁴

The drug review process has been described as structurally similar to many decisions made by other regulatory agencies, such that it is characterized by high uncertainty, avoidance of observable error, and low (reputational) reversibility, with drug recalls harming the reputation of the FDA for a faulty approval decision,⁵ and often severely affecting the manufacturer. Given that new products are the financial lifeblood of pharmaceutical companies, the stakes are raised higher due to intense lobbying by interested parties such as health professionals and patient advocacy groups, as well as pharmaceutical and technology companies,⁵ so it is no

wonder that, in 2003, the pharmaceutical industry earmarked \$4.9 million to lobby the FDA.⁶

While these concerns are noteworthy, they pale in comparison to the shortcomings and failures of the current imperfect system for postmarketing surveillance. This system is intended to detect adverse drug events and reactions once new products are in widespread use, and thereby limit exposure of the public to hazards of new medications. The inadequacies of the postmarketing surveillance system (ie, FDA’s MedWatch program with passive collection of spontaneous reports of adverse drug reactions) for ensuring safety are well known and include: reliance on voluntary reporting of adverse events by physicians and other health care professionals; poor quality of submitted reports, often with inadequate documentation and detail; underreporting of adverse outcomes with capture of only a small fraction of adverse events that actually occur; difficulty in calculating rates of adverse events because of incomplete numerator data on events, together with unreliable denominator data on exposure; limited ability for spontaneous reports to establish causal relationships; and difficulty in determining whether the adverse event resulted from the drug or the disease it was intended to treat.⁷⁻⁹

Yet the major problem with the current system for ensuring the safety of medications is that drug manufacturers are largely responsible for collecting, evaluating, and reporting data from postmarketing studies of their own products. This approach has many inherent problems. For instance, it appears that fewer than half of the postmarketing studies that manufacturers have made commitments to undertake as a condition of approval have been completed and many have not even been initiated.¹⁰ Moreover, despite the mandatory adverse event reporting system for companies subject to the FDA’s postmarketing safety reporting regulations, drug manufacturers may be tempted to conceal available data that may signal the possibility of major risks. In some cases, the FDA and drug manufacturers may fail to act on that information and fail to conduct appropriate studies to examine a potential risk rigorously and promptly.

The well known saga of the link between the selective serotonin reuptake inhibitors and teenage suicide was notable

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See also pp 2585, 2622, 2643, 2655, and 2658.

in that it took legal action by the New York attorney general to reveal the extent to which the manufacturer withheld from the public information from clinical trials demonstrating harm or lack of efficacy.¹¹ Likewise, the 2 pivotal trials designed to demonstrate lower rates of gastrointestinal problems of cyclooxygenase 2 inhibitors compared with nonsteroidal anti-inflammatory drugs reported results that, because of withheld data, appeared much more favorable about the drug's safety than the facts warranted. With celecoxib, crucial trial data were not revealed; for example, the authors submitted 6-month trial data when, in fact, 12-month data from the trial were available at the time of submission and publication.^{12,13} With rofecoxib, the published data showed that gastrointestinal toxicity with rofecoxib was significantly less than that of the comparison drug (naprosyn), but the increased cardiovascular toxicity was relegated to a brief paragraph in the discussion and erroneously dismissed as being due to the coronary protective effect of naprosyn.^{14,15}

The recent withdrawal of rofecoxib from the market because of adverse cardiovascular events identified in the unpublished Adenomatous Polyp Prevention on Vioxx (APPROVE) study has raised major concerns about the undue control of industry over postmarketing safety data. Topol¹⁶ pointed out that although he and his colleagues published a clear warning about the cardiovascular toxicity of rofecoxib in 2001,¹⁷ the FDA never insisted on a trial to determine the extent of the problem and the manufacturer countered with a "relentless series of publications . . . complemented by numerous papers in peer-reviewed medical literature by Merck employees and their consultants."¹⁶ Moreover, a recent investigation suggests that Merck was well aware of the dangers of rofecoxib but made concerted efforts to conceal those findings.¹⁸ Juni et al¹⁹ show, using cumulative meta-analysis of randomized trials of rofecoxib against control groups, that by the end of the year 2000, the relative risk for cardiovascular events among those taking rofecoxib was 2.30 (95% confidence interval, 1.22-4.33; $P = .01$). Yet, more than 3 years later, when the cardiovascular risks of rofecoxib were documented by FDA researchers several months before the data that ultimately led to removal of the drug from the market became publicly available, FDA officials allegedly attempted to "suppress" the conclusions of the report.^{20,21}

In this issue of *JAMA*, 5 articles²²⁻²⁶ on cerivastatin provide further compelling insights into additional problems that interfere with effective postmarketing surveillance. Cerivastatin was withdrawn from the US market in August 2001 because of high rates of rhabdomyolysis. Psaty and colleagues²² reviewed information from the published literature and unpublished data from internal company documents from the manufacturer of cerivastatin, which became available to the authors while serving as experts for plaintiffs in litigation related to cerivastatin and rhabdomyolysis, and use this information to describe events leading up to the withdrawal of cerivastatin.

Based on their review of the published data, the authors confirm the increased risk of rhabdomyolysis associated with cerivastatin, with the highest risk in patients with concurrent use of gemfibrozil. Furthermore, based on information and unpublished data obtained from company documents made publicly available as part of the court proceedings, the authors suggest that the company was well aware of the risks of rhabdomyolysis and the interaction of cerivastatin with gemfibrozil even as early as 4 months after the launch of cerivastatin. However, that contraindication was not added to the package insert for more than 18 months. The authors question whether pharmaceutical companies' appraisal of such serious adverse drug reactions may be influenced by economic considerations.

The review article by Psaty et al²² is unusual in that much of the data were derived from company documents and is even more unusual in that the authors gained access to some of these internal documents during their participation as plaintiffs' experts during litigation against Bayer Corporation, the manufacturer of cerivastatin. Recognizing the potential for different interpretations of such documents, considering the serious implications of the study by Psaty et al, and wanting to ensure fairness and balance in coverage of this important issue, *JAMA* took the unusual step of asking Bayer to review the manuscript by Psaty et al²² and furthermore, in an even more unusual step, invited the company to provide its perspective on the findings.

In response, the company sent 2 manuscripts.^{23,24} The first, by Strom²³ places the findings of the report by Psaty et al²² in the context of the current postmarketing system environment, describes the limitations of the spontaneous reporting system, and offers suggestions for enhancing the existing postmarketing surveillance system to help improve reporting of information on drug safety. In the second article,²⁴ Piorkowski, a physician-attorney representing Bayer, suggests that the company views the article by Psaty et al²² as "the publication of a disputed position taken in ongoing litigation," points out what he suggests are several "errors of the article," and maintains that Bayer "complied with its disclosure obligations." In their invited response to the manuscript by Piorkowski,²⁴ Psaty et al²⁵ point out that evidence of the increased risk of rhabdomyolysis with cerivastatin was available to Bayer well before the drug was finally withdrawn from the market, but also emphasize that their review of cerivastatin should serve to demonstrate some of the problems with the current postmarketing surveillance system.

It is noteworthy that both Psaty and coauthors²⁵ and Piorkowski²⁴ were involved in the *Haltom* trial (the case from which the documents used by Psaty et al were obtained) and that Piorkowski was involved with the depositions of Psaty, Furberg, and Ray. Given the potentially contentious nature of their interactions in this litigation, and to present our readers with full information about this situation, we decided to publish the response by Piorkowski²⁴ and the reply by Psaty et al²⁵ with no substantive editing to provide

insight into the defensive stances taken by Piorkowski and the company involved in this litigation, to allow Psaty et al the opportunity to present their position, and to ensure that any claims of editorial tampering would be without merit.

Taken together, these articles²²⁻²⁵ epitomize several fundamental problems with the current postmarketing surveillance system. First, in some cases, serious adverse drug events are quite uncommon, and detecting them accurately and using them to determine incidence rates can be difficult with the existing passive system for voluntary reporting of adverse drug events. As illustrated in another article in this issue, Graham and colleagues²⁶ used data from more than 250 000 patients treated with lipid-lowering agents from January 1998 through June 2001 in 11 managed care health plans, and identified 24 patients who were hospitalized with rhabdomyolysis during treatment. By virtue of having data from drug-specific, population-based inception cohorts, the authors estimated an incidence of rhabdomyolysis of 5.34 per 10 000 person-years for cerivastatin monotherapy, and 1035 per 10 000 person-years for combined cerivastatin-fibrate use (ie, risk of rhabdomyolysis of approximately 1 in 10 patients treated with the combined therapy per year).

Second, because of conflicts of interest or perhaps other reasons, some companies may neglect to fully acknowledge reports that indicate harm and fail to initiate proper studies to determine risk. As the review article by Psaty et al²² suggests, companies may be well aware of analyses of serious adverse drug event data but may fail to report them in a timely manner. An important question is whether, when, or how fully some of the information and data on cerivastatin would have come to light had it not been for the litigation against Bayer. Companies also have financial incentives and economic pressures that may influence interpretation of adverse event data and may delay full reporting to the FDA. As the investigations and litigation proceed against the manufacturer of rofecoxib, similar unreported information and data demonstrating adverse cardiovascular events may be revealed.

Third, pharmaceutical companies, like other for-profit entities, are motivated to protect their interests. For example, if the response by Piorkowski²⁴ is any indication, companies will continue to use highly defensive articles as well as other tactics, such as threats and attempts at intimidation,^{18,27,28} to protect their interests and attempt to defend against dissemination of negative information about their products. With pharmaceutical and biotechnology companies accounting for 9 of the top 50 largest public companies in the world,²⁹ the resources for continuing these types of approaches seem more than sufficient.

Six years ago, Moore, Psaty, and Furberg³⁰ drew attention to the woefully underfunded, understaffed, and haphazard system whereby postmarketing information on drug safety and adverse events is gathered, despite marketed drugs causing thousands of deaths each year. In his article in this issue, Strom²³ aptly describes the spontaneous voluntary re-

porting system as “fundamentally a pre-1950s-era approach” and, despite his serving as an expert for defense attorneys in litigation about cerivastatin, he clearly acknowledges that “there is indeed a conflict of interest in asking industry to monitor its own drugs.”

In the wake of major criticism about its recent handling of safety issues surrounding antidepressants and risk of teenage suicide and rofecoxib and cardiovascular risk, the FDA has just announced that it is taking several measures to attempt to strengthen the safety program for marketed drugs.^{31,32} These include a commitment to (1) sponsor an Institute of Medicine study of the drug safety system; (2) implement a program for adjudicating differences of professional opinion by FDA staff and by outside experts; (3) appoint a director for the Office of Drug Safety (a position that has been vacant for 13 months); (4) conduct drug safety/risk management consultations with other agencies, academia, pharmaceutical industry, and the health care community; and (5) publish risk management guidelines “to help pharmaceutical firms in identifying and assessing potential safety risks.”

The Institute of Medicine is the most appropriate body to critically and objectively examine the US drug review and safety issue, but it will take time to conduct a thorough study and prepare a report. In the meantime, while the other measures announced by the FDA are important, these initial steps are inadequate to restore the trust and confidence necessary to convince physicians and other health professionals and the public that the FDA's first absolute priority is to protect the public health, and certainly are insufficient to dispel the perceptions that the agency appears to be unduly influenced by industry and seems overly concerned about its own public image and relations.^{21,32}

To improve the necessary measures to monitor the safety of marketed drugs, the drug approval process must be decoupled from the postmarketing safety and surveillance system. It is unreasonable to expect that the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek evidence to prove itself wrong (ie, that the decision to approve the product was subsequently shown to be incorrect). One option worth strong consideration, as others have suggested,^{30,33,34} is to establish an independent drug safety board or independent agency for drug safety, specifically to oversee postmarketing surveillance for drugs and devices. This agency should be given full authority to ensure compliance with regulations and sufficient funding to establish an effective national active surveillance system with a prospective, comprehensive, and systematic approach for monitoring, collecting, analyzing, and reporting data on adverse events. Above all, the agency must be completely independent of influence from the pharmaceutical industry, biotechnology firms, and medical device manufacturers.

To enhance effectiveness of the postmarketing safety system, several guidelines should be considered. Manufacturers should be required to conduct clinical studies to assess

safety for all new products, not only for the 2 categories for which postmarketing studies are now mandatory (ie, fast-track products approved on an accelerated basis, and products for which deferred pediatric studies are needed to establish safe use in children).³⁵

Protocols for adequately powered postmarketing studies would be mandated at the time a new drug is launched and the studies must be completed at least within the first 2 years after the new drug or device is marketed, with additional studies conducted as deemed necessary by the independent drug agency. The conduct and progress of these studies would be monitored by the independent drug agency, and all data from these investigations as well as all reports and data on serious adverse drug events would be required to be reported expeditiously and directly to the independent agency by the researchers conducting the studies, with summary data reported at least annually. Companies that withhold or conceal data, including data from any studies conducted before or after drug approval, would be subject to legal penalties. In addition, if adverse events are detected, especially early after marketing and even if at low frequency, the manufacturer would be required to make information about those adverse events widely available, with clear information about those risks included on the drug label and on package information, communicated directly to physicians and other health professionals, and prominently mentioned in all product promotional materials, including direct-to-consumer advertising.

The postmarketing surveillance system requires a long overdue major restructuring. Until that occurs—as indicated by the articles in this issue of *JAMA*, as epitomized by recent evidence of serious harms from widely used and heavily promoted medications, as demonstrated by the influence of industry over postmarketing data, and as illustrated by the lengths to which some manufacturers will go to protect their interests—the United States will still be far short of having an effective, vigilant, and trustworthy system of postmarketing surveillance to protect the public.

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