

# The FDA and Drug Safety

## A Proposal for Sweeping Changes

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**T**he current Food and Drug Administration (FDA) system of regulating drug safety has serious limitations and is in need of changes. The major problems include the following: the design of initial preapproval studies lets uncommon, serious adverse events go undetected; massive underreporting of adverse events to the FDA postmarketing surveillance system reduces the ability to quantify risk accurately; manufacturers do not fulfill the majority of their postmarketing safety study commitments; the FDA lacks authority to pursue sponsors who violate regulations and ignore postmarketing safety study commitments; the public increasingly perceives the FDA as having become too close to the regulated pharmaceutical industry; the FDA's safety oversight structure is suboptimal; and the FDA's expertise and resources in drug safety and public health are limited. To address these problems, we urge Congress, which is ultimately responsible for the FDA's performance, to implement the following 5 recommendations: (1) give the FDA more direct legal authority to pursue violations, (2) authorize the adoption of a conditional drug approval policy, at least for selected drugs, (3) provide additional financial resources to support the safety operations, (4) mandate a reorganization of the agency with emphasis on strengthening the evaluation and proactive monitoring of drug safety, and (5) require broader representation of safety experts on the FDA's advisory committees.

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*People just don't want to think about the risks of this inherently risky business. Doctors don't want to scare their patients or draw attention to their own prescribing mistakes. Serious safety questions about a major drug can threaten the survival of a large drug company. As a result, companies often wage aggressive campaigns against safety critics. Even the FDA [Food and Drug Administration] has a dilemma. Every time it moves to restrict or withdraw a dangerous drug, it has to face questions about why it allowed the drug to reach the market in the first place.*

Thomas J. Moore<sup>1</sup>

Drug safety continues to be a major public health concern in the United States. Lazarou et al<sup>2</sup> estimated that, in 1994, there

were over 100 000 fatal drug reactions among 33 million hospital admissions; this estimate was supported by a later report.<sup>3</sup> Sadly, there is no evidence that the adverse drug reaction (ADR) problem in the United States is diminishing. A recent Harris poll showed a sharp decline in public confidence in the FDA.<sup>4</sup> The negative ratings were 58% compared with 37% two years ago.

One main reason is that there has been no meaningful change in our regulatory approach to drug safety during the past decades. When recommendations for improvements have been made, these tended to be only small changes in the status quo rather than a fundamental effort to fix the problems. Many of the problems at the FDA are well known. Yet, the FDA lacks the authority and resources to correct these vexing problems on its own. The solutions must come from Congress, which controls both the FDA's legal authority and its funding. This report summarizes the underlying concerns about the FDA and drug safety and calls for sweeping changes.

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The Food and Drug Administration Safety Act of 2005 (S 930), introduced by Senators Grassley and Dodd, would, if passed, establish the authority and independence of postmarketing safety that are essential to the restructuring of the FDA. It would also authorize additional funding to the FDA for carrying out the Act.

The Fair Access to Clinical Trials Act of 2005 (S 470) would, if passed, require that clinical trials be registered and their results be reported. Civil monetary penalties would be charged for noncompliance. A requirement to register trials would make it more difficult to suppress unfavorable trial results.

The Pharmaceutical Research and Manufacturers Accountability Act of 2005 (HR 879), introduced by Representatives Stark and Berry, would, if passed, send drug industry CEOs and other executives to jail for a minimum of 20 years if they knowingly conceal serious adverse drug experiences. A fine of up to \$2 million could also be imposed on an individual found to be in violation. In addition, the CEOs would be required by the bill to annually attest that all evidence of serious adverse effects for an approved drug has been disclosed. Also, failure to complete postmarketing studies within the time specified would lead to fines of up to \$5 million for each month the study goes unfinished.

## RESPONSES TO THE SAFETY PROBLEM

The news media's attention to drug safety increased after the revelation in 1997 that fenfluramine-phentermine (fen-phen) caused valvular heart disease.<sup>5,6</sup> However, the problem with unsafe drugs is much older.<sup>1,7</sup> The key features of the stories of the present are the same as with previous drug tragedies. New drugs are introduced on the market with inadequate safety documentation, serious ADRs are reported from the marketplace, and a large number of patients are injured before the drugs are withdrawn or better managed. The only difference is the name of the culprit drug. Recent drug safety concerns have focused on cyclooxygenase-2 (COX-2) inhibitors in pain relief, selective serotonin reuptake inhibitors for depression, and stimulants for treatment of attention deficit hyperactivity disorder.

The US Congress has responded by having high-profile hearings.<sup>8,9</sup> Several important bills related to drug safety were introduced in 2005 (see Box at the top of this page), but to date they have gone nowhere. Another Senate bill sponsored by Senators Enzi and Kennedy was announced in mid-2006. A major dilemma for the health care community is that solving the nation's drug safety problem requires congressional involvement. Through the FDA, Congress is responsible for protecting the public from harmful effects of drugs. The urgency to take immediate action ought to be a bipartisan issue.

Every tragic safety lapse is followed by litigation, often on behalf of hundreds or thousands of injured patients. An important conse-

quence has been public access to confidential internal documents circulated by drug company employees. It appears from these documents that the companies sometimes knew much more about their product's safety problems than they revealed to the FDA, the medical profession, and/or the public.<sup>10,11</sup>

Medical professionals, including ourselves, have often called into question the effectiveness of the FDA's approach to drug safety.<sup>12-17</sup> Moore et al<sup>12</sup> concluded that it was "time to act on drug safety." In a call for safer medicines, Wood et al<sup>13</sup> emphasized the need for an independent drug safety board. Ray and Stein<sup>14</sup> went a step further and called for reforming drug regulations. They highlighted many of the FDA's well-known limitations and concluded that the newly established Drug Safety Oversight Board is unlikely to succeed because of its lack of authority, resources, and independence from the FDA. Strom<sup>15</sup> suggested, among other things, that new drugs with potential safety problems be subject to conditional approval. This proposal also addresses the problem of unfulfilled industry commitments to conduct postmarketing safety studies (see problem 4 in the following section). Roth-Cline<sup>16</sup> proposed that safety problems could be reduced if stricter statistical criteria for documenting efficacy were required. In an accompanying editorial, Avorn<sup>17</sup> disagreed with that approach and pointed out many of the recognized problems at the FDA. His recommended solution was a 2-step approval process similar to that embraced by some European countries, which requires a re-review 2 to 3 years after the initial

approval. In general, these commentaries have focused on 1 or 2 specific weaknesses in the FDA's drug safety efforts rather than presenting a more thorough review of the limitations of the drug safety assessment and assurance status quo. As a result, the recommended solutions tend to be limited in scope and rarely recognize that the US Congress holds the key to a markedly improved and comprehensive national drug safety program.

## PROBLEMS WITH THE CURRENT SYSTEM

We see 8 major problems with the current system of assessment and assurance of drug safety at the FDA.

1. The initial review for approval often fails to detect serious ADRs. A study by the US General Accounting Office (GAO) concluded that 51% of all approved drugs had at least 1 serious ADR that was not recognized during the approval process.<sup>18</sup> Some of this results from the conduct of short-term trials in small numbers of low-risk patients. The FDA's reluctance or inability to require long-term trials focusing on those most likely to use a drug contributes to the problem. Another critical weakness appears to be the lack of effective review of preapproval trial protocols as it relates to drug safety.

2. The FDA's primary resource for identifying drug safety issues after marketing is the Adverse Event Reporting System.<sup>19,20</sup> It receives about 400 000 reports annually, primarily from drug manufacturers who are required to report serious, unexpected safety events within 15

days. A minor proportion of Adverse Event Reporting System data comes directly from health care providers and patients.<sup>20</sup> The surveillance system is plagued by massive underreporting and insensitivity to distinguishing between drug-induced and naturally occurring serious events. It has been estimated that only about 1% of all ADRs and about 10% of all serious ADRs are reported.<sup>20,21</sup>

3. Setting a threshold for action in response to ADR reports is subjective. Although many drug withdrawals have occurred simultaneously around the world, the FDA has been slow compared with the action by European regulatory agencies in some recent cases (eg, problems involving troglitazone, trovafloxacin, and tolcapone). When underreporting is combined with a high threshold for action, it has the troubling consequence of unnecessarily exposing a large number of patients to drug-related harm over a long period before regulatory action (eg, restriction or withdrawal) is taken. For example, an estimated 4 million patients were exposed to each of the 5 drugs (bromfenac, dexfenfluramine, fenfluramine, mibefradil, and terfenadine) withdrawn from the market between September 1997 and September 1998.<sup>22</sup>

4. Performance of postmarketing safety studies is virtually out of the FDA's control, with the majority of study commitments never initiated by the pharmaceutical industry and not pursued by the FDA. The Food and Drug Administration Modernization Act of 1997<sup>23</sup> required the FDA to annually report the status of postmarketing commitments made by product sponsors. According to the most recent report, there were 1231 as yet unsatisfied commitments through September, 2005.<sup>24</sup> Almost two thirds of them (n=797) were "pending" (ie, not initiated), and only 21% were ongoing or delayed. Many pending study commitments lacked any deadline for completion. The FDA has neither authority to take direct legal action against the violators nor a policy to grant conditional approval for drugs with an incomplete safety record.

5. In addition, the FDA lacks direct legal authority to hold account-

able drug companies that violate its recommendations or suppress or delay submission of unfavorable trial information. Rarely does the FDA involve the Department of Justice in taking action against a drug company.

6. The FDA's intrinsic structure is viewed by some as presenting a potential conflict of interest because the Center for Drug Evaluation and Research, the FDA center that reviews and approves drugs, also has responsibility for taking regulatory action against the drugs it previously approved when safety problems emerge in the postmarketing period. According to a recent GAO report,<sup>25</sup> the FDA's Office of Drug Safety, currently located within the Center for Drug Evaluation, has an unclear role in safety actions with no independent regulatory authority. Also, this report found that communication between the Office of Drug Safety and the Office of New Drugs is insufficient, and the Office of Drug Safety staff are sometimes excluded from important meetings.

7. Another problem may relate to the source of FDA funding. Critics of the FDA have claimed that the agency has gotten too close to the industry it is supposed to regulate, in part because of its dependence on user fees. Indeed, each of the past 3 iterations of the Prescription Drug User Fee Act<sup>26</sup> has required that the FDA produce or perform something of value to the pharmaceutical industry in exchange for which the industry would agree to pay the fees. Until the last iteration, the FDA was prohibited from using any funds from user fees to support postmarketing studies of safety.

8. The shortage of FDA expertise in drug safety and public health and in its advisory committees is a limiting factor. In the cases of troglitazone, cisapride, and most recently the selective COX-2 inhibitors, recommendations by some members of the FDA's drug safety staff were not followed, illustrating the weakness of the voices for safety. The adherence to the congressional requirement that the FDA must "promote diversity of viewpoints among appointed members"<sup>27</sup> is inadequate. Only the Drug Safety and Risk Management Advisory Committee has appropriate expertise in public health, drug safety, and eth-

ics. Symptomatic to the limited role of drug safety at the FDA, this committee is often not consulted in discussions or evaluations of potential safety problems. As the institution ultimately responsible for the public's health, the burden is primarily on Congress to take action to improve drug safety.

## RECOMMENDATIONS

### Authority

Experience has shown that the FDA needs more direct legal authority than it has been granted. The FDA should play a more active role in decisions about the design of preapproval trials and studies. For example, medicines for chronic conditions should be evaluated in large, long-term trials. Also, to achieve the medical dictum "first do no harm," a higher priority must be given to regulating drug safety. The FDA should exercise clearer authority to require that adequately powered safety trials be completed prior to drug approval. The regulations need to be very specific on this point. Safety evaluation should be given the same priority as efficacy evaluation. The new authority should also include the unilateral right of the FDA to suspend marketing or to mandate immediate withdrawal of harmful drugs.

Also, expanded authority should be given to the FDA regarding drug labeling changes in the face of postmarketing safety concerns. The FDA should be able to require changes to a drug label, including the addition of black box warnings, restriction of use in selected patients, and modification of approved indications. In the absence of such authority, the FDA must engage in often protracted labeling negotiations with drug manufacturers.

For postmarketing studies, the FDA needs additional and clearer authority to hold manufacturers to their commitments and to adherence to a fundamental of sound science that all study results, whether favorable or unfavorable, must be reported to the FDA in a timely manner, accompanied by disclosure to the public and/or other follow-up action. Failure to meet postmarketing commitments should have clear consequences for the offenders, which could include

finances, probation, public embarrassment, or even drug withdrawal. Senate Bill 930 (see Box on page 1939) strongly supports these recommendations.

### Independence

The FDA is generally effective at reviewing and approving drugs, especially for efficacy. To strengthen the drug safety program, a high priority should be the establishment of a Center for Drug Safety. We support Senate Bill 930 that proposes the establishment of 2 independent, collaborating centers within the FDA, one responsible for premarketing review and evaluation and the other for continuous postmarketing surveillance and regulation. In each case, the responsible center should collaborate closely with the other to avoid loss of expertise. However, we believe that this separation will help restore public confidence by bringing safety to equal standing with efficacy.

### Operations

In a number of respects, changes in FDA operations are needed to enhance its drug safety efforts. Some may require new regulations, while others require regular and much closer performance monitoring of the FDA by Congress.

- First, the FDA should have a “conditional approval” policy for new drugs that, at the initial hearing for approval, have clear benefits but unanswered questions regarding serious adverse events. A time-limited, conditional approval status would place pressure on the sponsors to conduct and report recommended safety studies. The European Medicine Evaluation Agency is expected to introduce new regulations in spring 2006 making 1-year conditional approval a regulatory option. An alternative would be to follow the model used in France, Japan, and Norway and have scheduled, routine reviews of all approved drugs 2 to 4 years after the initial approval. Another alternative would be for drugs to remain conditionally approved until certain data are available, providing an incentive to collect those postmarketing data.<sup>15</sup>

- Second, through the proposed Center for Drug Safety, the surveillance approach now consisting primarily of the Adverse Event Reporting System database should be shifted from passive/reactive to active/proactive. The FDA should be given the resources (ie, funding and staff) by Congress to take better advantage of large, available, private and public administrative databases. These could include the Department of Veterans Affairs, Department of Defense, and large electronically sophisticated health plans such as Kaiser-Permanente and Group Health Cooperative. In a few years, the new Medicare drug benefit program (Part D) could provide critically important safety information by linking pharmacy databases with clinical patient information. Benefit would be derived if the FDA would routinely review past drug withdrawals for lessons to be learned.

- Third, an updated approach to surveillance would also benefit from the establishment of a permanent network of collaborating drug safety centers across the United States. This program could build on the existing Centers for Education and Research in Therapeutics sponsored by the Agency for Healthcare Research and Quality (<http://www.certs.hhs.gov/>). Funding should preferably come from Congress through the appropriations process, rather than from the pharmaceutical industry in the form of user fees. The recent announcement from the FDA<sup>28</sup> that 4 awards were made, giving the agency access to external databases, is a good start but is far too limited in scope and funding. Another approach to securing funding could involve imposing a prescription fee of a few cents per prescription to be collected from the pharmaceutical companies.<sup>11,29</sup> Given the estimate of 4 billion prescriptions in 2006, this would generate substantial funding for safety monitoring.

- Fourth, the recommended active surveillance program could benefit further by learning from the experience in other countries. Adverse event surveillance, relying on large population-based, disease-specific registries, could focus on conditions such as acute liver or renal failure,

sudden cardiac death, or birth defects. The clear overrepresentation of use of suspected drugs in these disease-specific databases would be potential signals of harmful drug effects. Similarly, registries could be drug based and setting based. This approach would complement the MedWatch program.

- Fifth, the current MedWatch program, which has been characterized as “fundamentally a 1950-era approach,”<sup>30</sup> ought to be streamlined by refocusing on its strength—the detection of rare, serious conditions.

- Sixth, the composition of all FDA advisory committees should be changed. At present, the committees are made up mostly of subspecialty experts who often receive significant support from pharmaceutical companies for clinical investigations and expert opinions. This introduces a potential for conflicts of interest and bias. For example, whether such biases were present at the FDA hearings on selective COX-2 inhibitors and roflumilast cannot be definitively determined.<sup>31-33</sup> Nevertheless, when the votes at the COX-2 inhibitor hearings were analyzed, a significant relationship was apparent between voting patterns and industry ties,<sup>34</sup> although this observation could also have been due to different perspectives based on professional backgrounds.

Although subspecialty experts and investigators are critical to understanding the benefits and utility of a new drug under consideration, they should comprise no more than half of the committee members. The other half of each advisory committee should be made up of experts with diverse perspectives including risk management, drug safety, public health, epidemiology, health services research, and ethics. This should help ensure more objective and balanced recommendations from advisory committees and improve public confidence in the new drug approval and postmarketing safety surveillance processes.

### CONCLUSIONS

The drug industry and research community can point with pride to the development and diffusion of inno-

### Editor's Note

The article by Furberg et al was submitted by the authors through the standard unsolicited manuscripts mechanism. It underwent outside peer review and was accepted as a Special Article. We welcome comments from readers regarding other possible assessments and approaches.

Philip Greenland, MD  
Editor

vative drugs that have helped ameliorate deadly and debilitating medical conditions. However, the public health benefit of these products will be negated if they cause substantial harm to users and if the public lacks trust in their safety. Therefore, assuring the safety of medical products and restoring the public's trust that the medical products they rely on are safe for their intended use are critically important public health objectives. We have outlined a large number of current problems at the FDA and an aggressive action plan to solve them. It is now up to Congress to take the steps necessary to reinvigorate the FDA's ability to assure the public that approved medical products are safe. For Congress not to act now would be, in our opinion, an unfortunate missed opportunity for positive change.

We urge Congress, which is ultimately responsible for the FDA's performance, to implement the following 5 recommendations: (1) give the FDA more direct legal authority to pursue violations, (2) authorize the adoption of a conditional drug approval policy, at least for selected drugs, (3) provide additional financial resources to support the safety operations, (4) mandate a reorganization of the agency with emphasis on strengthening the evaluation and proactive monitoring of drug safety, and (5) require broader representation of safety experts on the FDA's advisory committees.

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**Disclaimer:** The authors are current or former members of the FDA Drug Safety and Risk Management Advisory Committee. The opinions expressed herein are their personal views.

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