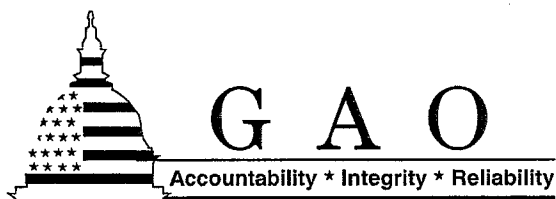


March 2006

DRUG SAFETY

Improvement Needed in FDA's Postmarket Decision-making and Oversight Process





Highlights of GAO-06-402, a report to the Chairman, Committee on Finance, United States Senate and the Chairman, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

In 2004, several high-profile drug safety cases raised concerns about the Food and Drug Administration's (FDA) ability to manage postmarket drug safety issues. In some cases there have been disagreements within FDA about how to address safety issues. In this report GAO (1) describes FDA's organizational structure and process for postmarket drug safety decision making, (2) assesses the effectiveness of FDA's postmarket drug safety decision-making process, and (3) assesses the steps FDA is taking to improve postmarket drug safety decision making. GAO conducted an organizational review and case studies of four drugs with safety issues: Arava, Baycol, Bextra, and Propulsid.

What GAO Recommends

To improve the decision-making process for postmarket drug safety, GAO suggests that the Congress consider expanding FDA's authority to require drug sponsors to conduct postmarket studies when needed. GAO also recommends that FDA systematically track postmarket drug safety issues, revise and implement its draft policy on major postmarket safety decisions, improve the dispute resolution process, and clarify ODS's role in scientific advisory committees. In its comments on a draft of this report, FDA stated that GAO's conclusions were reasonable. FDA did not comment on GAO's recommendations.

www.gao.gov/cgi-bin/getrpt?GAO-06-402.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse, (202) 512-7119, crossem@gao.gov.

DRUG SAFETY

Improvement Needed in FDA's Postmarket Decision-making and Oversight Process

What GAO Found

Two organizationally distinct FDA offices, the Office of New Drugs (OND) and the Office of Drug Safety (ODS), are involved in postmarket drug safety activities. OND, which holds responsibility for approving drugs, is involved in safety activities throughout the life cycle of a drug, and it has the decision-making responsibility to take regulatory actions concerning the postmarket safety of drugs. OND works closely with ODS to help it make postmarket decisions. ODS, with a primary focus on postmarket safety, serves primarily as a consultant to OND and does not have independent decision-making responsibility. ODS has been reorganized several times over the years. There has been high turnover of ODS directors in the past 10 years, with eight different directors of the office and its predecessors. In the four drug case studies GAO examined, GAO observed that the postmarket safety decision-making process was complex and iterative.

FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints. GAO observed that there is a lack of criteria for determining what safety actions to take and when to take them. Certain parts of ODS's role in the process are unclear, including ODS's participation in FDA's scientific advisory committee meetings organized by OND. Insufficient communication between ODS and OND has been an ongoing concern and has hindered the decision-making process. ODS does not track information about ongoing postmarket safety issues, including the recommendations that ODS staff make for safety actions. FDA faces data constraints in making postmarket safety decisions. There are weaknesses in the different types of data available to FDA, and FDA lacks authority to require certain studies and has resource limitations for obtaining data.

Some of FDA's initiatives, such as the establishment of a Drug Safety Oversight Board, a draft policy on major postmarket decision making, and the identification of new data sources, may improve the postmarket safety decision-making process, but will not address all gaps. FDA's newly created Drug Safety Oversight Board may help provide oversight of important, high-level safety decisions, but it does not address the lack of systematic tracking of ongoing safety issues. Other initiatives, such as FDA's draft policy on major postmarket decisions and regular meetings between OND divisions and ODS, may help improve the clarity and effectiveness of the process, but they are not fully implemented. FDA has not clarified ODS's role in certain scientific advisory committee meetings. FDA's dispute resolution processes for disagreements about postmarket safety decisions have not been used. FDA is taking steps to identify additional data sources, but data constraints remain.

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Figure 1: FDA Organizational Structure for Postmarket Drug Safety

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Abbreviations

AERS	Adverse Event Reporting System
CDER	Center for Drug Evaluation and Research
DDRE	Division of Drug Risk Evaluation
DSaRM	Drug Safety and Risk Management Advisory Committee
DSB	Drug Safety Oversight Board
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
HRT	Hormone Replacement Therapy
NSAID	Nonsteroidal Anti-inflammatory Drug
ODS	Office of Drug Safety
OND	Office of New Drugs
OPaSS	Office of Pharmacoepidemiology and Statistical Science
PDUFA	Prescription Drug User Fee Act
SRS	Spontaneous Reporting System

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United States Government Accountability Office
Washington, DC 20548

March 31, 2006

The Honorable Charles E. Grassley
Chairman
Committee on Finance
United States Senate

The Honorable Joe Barton
Chairman
Committee on Energy and Commerce
House of Representatives

In 2004, several high-profile drug safety cases raised concerns about the Food and Drug Administration's (FDA) management of safety issues concerning drugs that have been approved for marketing.¹ At congressional hearings in September 2004, FDA was criticized for taking too long to tell physicians and patients about studies linking the use of antidepressants among children to an increased risk of suicidal behavior. Similarly, at a congressional hearing in November 2004, it was alleged that FDA did not act quickly enough on evidence it obtained in 2001 about the cardiovascular risks of Vioxx, an anti-inflammatory drug.² In these cases and others there were disagreements within FDA about how to address safety issues. There were also reports that some FDA scientists were discouraged by supervisors from raising questions about the safety of certain drugs.

Problems with FDA's postmarket drug safety program have been raised before. There have been numerous reviews by external and internal groups dating back over 30 years that have identified problems with the federal government's postmarket drug surveillance program and that have

¹FDA is an agency within the Department of Health and Human Services (HHS).

²Vioxx was voluntarily withdrawn from the market by its manufacturer in September 2004.

made recommendations for improvement.³ Following passage of the Prescription Drug User Fee Act of 1992 (PDUFA),⁴ additional concerns were raised about drug safety. Under PDUFA, drug companies (“sponsors”) began paying fees to FDA, which used the funds to hire more drug application reviewers and make other changes in order to speed up the drug review process. As a result, FDA was able to review drug applications and approve new drugs for marketing more rapidly than before. However, the increased attention to timely drug approval decisions led to increased attention to monitoring of postmarket safety as well, which was reflected in the 2002 reauthorization of PDUFA.⁵ The 2002 act states that FDA should continue to strengthen and improve the review and monitoring of drug safety, and the PDUFA goals, incorporated by reference into the act, state that FDA will allocate almost \$71 million over a 5-year period for postmarket drug safety. FDA subsequently increased its risk management activities,⁶ drafted guidance for industry to help drug companies assess and minimize drug risks, and used PDUFA revenues to upgrade its system for adverse event reporting and to acquire external sources of data. In late 2004 and 2005, in response to the safety issues raised in the case of Vioxx and other drugs, FDA announced plans to further strengthen its management of postmarket drug safety. These initiatives, some of which are in an early stage of implementation, include launching a new Web page to make public information on emerging drug safety issues while FDA evaluates them, finalizing the risk management

³See, for example, National Research Council, *Report of the International Conference of Adverse Reactions Reporting Systems* (Washington, D.C.: National Academies of Science, 1971); FDA, *Program Review of the Division of Epidemiology and Surveillance (DES) in the Office of Epidemiology and Biometrics (OEB)* (Washington, D.C.: 1993); HHS, Office of Inspector General, *Review of the Food and Drug Administration’s Handling of Adverse Drug Reaction Reports* (Washington, D.C.: 1999). In November 2004, FDA announced that it would contract with the Institute of Medicine to evaluate the current drug safety system. This study is currently in progress.

⁴Pub. L. No. 102-571, 106 Stat. 4491.

⁵Pub. L. No. 107-188, 116 Stat. 594.

⁶In an effort to address drug risks, FDA works with industry to develop risk management plans and postapproval risk management studies. Risk management plans may include labeling, targeted education and outreach such as medication guides and training programs, reminder systems such as consent forms and special data collection systems, and performance-linked access systems such as restricted distribution and limited prescribing or dispensing.

guidance for industry,⁷ and making other organizational and policy process changes.

In light of the recent controversy about drug safety, you asked us to conduct a review of FDA's current organizational structure and decision-making process for postmarket drug safety. In this report we (1) describe FDA's organizational structure and process for postmarket drug safety decision making, (2) assess the effectiveness of the postmarket drug safety decision-making process, and (3) assess steps FDA is taking to improve postmarket drug safety decision making.

To describe FDA's organizational structure and process for postmarket drug safety decision making, we analyzed FDA's organizational charts and annual reports, the roles and responsibilities of staff working on drug safety, documents describing internal FDA policies and procedures, and other relevant FDA documents. Our review focused on two offices within FDA's Center for Drug Evaluation and Research (CDER) that are involved in postmarket drug safety activities: the Office of New Drugs (OND) and the Office of Drug Safety (ODS). We interviewed ODS, OND, and other CDER managers and staff about their roles, responsibilities, workloads, and the process for postmarket drug safety decision making. We also interviewed former FDA officials and drug safety experts from outside FDA. To assess the effectiveness of the postmarket drug safety decision-making process, we analyzed documents describing internal FDA policies and procedures and interviewed FDA officials. In order to obtain an in-depth understanding of FDA's policies and procedures, we conducted case studies of four drugs—Arava, Baycol, Bextra, and Propulsid—that help to illustrate the current decision-making process.⁸ Each of these drugs presented significant postmarket safety issues that FDA acted upon in recent years, and they reflect differences in the type of adverse event or potential safety problem associated with the drug, the safety actions taken,

⁷In March 2005, FDA issued three guidance documents for industry: HHS, FDA, *Guidance for Industry: Premarketing Risk Assessment*; *Guidance for Industry: Development and Use of Risk Minimization Action Plans*; and *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (Rockville, Md.: 2005).

⁸FDA approved Arava to treat arthritis; Baycol to treat high cholesterol; Propulsid to treat nighttime heartburn; and Bextra to relieve pain. Baycol, Bextra, and Propulsid have since been withdrawn from the market (in August 2001, April 2005, and March 2000, respectively), and the warnings on Arava's label were strengthened (most recently in March 2004). In this report we also refer to other drugs that had safety issues for purposes of illustration, but they were not part of our case studies.

and the OND and ODS staff involved. For our case studies we reviewed relevant FDA documents and conducted interviews with OND and ODS staff and former FDA staff who were directly involved in the cases. We focused on (1) significant postmarket drug safety regulatory actions; (2) analyses that ODS conducted on the safety concerns; and (3) internal FDA meetings, especially those that involved ODS.⁹ We did not examine other elements of the postmarket drug safety decision-making process, such as internal OND meetings. In some cases there may be gaps in our description of events because there was no documentation available about that point in the process. We also did not evaluate the scientific validity of FDA's data, methodologies, or decisions in these or other cases. Our cases cannot be generalized to FDA's deliberations about postmarket drug safety issues for other drugs. Finally, to assess FDA's actions to improve postmarket drug safety decision making, we reviewed relevant FDA documents and interviewed FDA officials and outside drug safety experts. We conducted our review from December 2004 through March 2006 in accordance with generally accepted government auditing standards.

Results in Brief

Two organizationally distinct FDA offices, OND and ODS, are involved in postmarket drug safety activities. OND, which holds responsibility for approving drugs, is involved in safety activities throughout the life cycle of a drug, and it has the decision-making responsibility to take regulatory actions concerning the postmarket safety of drugs. OND staff include physicians, pharmacologists, toxicologists, and microbiologists who are focused on providing health care practitioners and patients with a range of drugs for treatment of a specific disease or condition. OND's work and its pace are driven by PDUFA goals that FDA make drug approvability decisions within certain time frames. OND works closely with ODS to make postmarket drug safety decisions. In contrast to OND's broad perspective, ODS's primary focus is on postmarket drug safety. ODS serves primarily as a consultant to OND and does not have independent decision-making responsibility. ODS has been reorganized several times over the years, and its Division of Drug Risk Evaluation (DDRE) is the primary unit responsible for postmarket safety surveillance. The Division's safety evaluators, who are generally pharmacists, review and analyze adverse event reports. Its epidemiologists, taking a population-based

⁹FDA verified the major postmarket regulatory actions we identified for each drug. ODS and OND staff also told us which internal meetings were significant in the decision-making process.

perspective, analyze adverse events in the context of drug utilization, and conduct postmarket drug safety research in collaboration with scientists outside of FDA. There has been high turnover of ODS directors in the past 10 years, with eight different directors of the office and its various predecessors. In our case studies we observed that the decision-making process for postmarket drug safety is complex, involving input from a variety of FDA staff and organizational units and information sources, but the central focus of the process is the iterative interaction between OND and ODS.

FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints. We observed that there is a lack of criteria for determining what safety actions to take and when to take them. Certain parts of ODS's role in the process are unclear, including ODS's participation in scientific advisory committee meetings that are organized by OND to discuss specific drugs. While ODS staff have presented their analyses during some of these meetings, our case studies and others provide examples of the exclusion of ODS staff. Insufficient communication between ODS and OND's divisions has been an ongoing concern and has hindered the decision-making process. Specifically, ODS does not always know how OND has responded to ODS's safety analyses and recommendations. ODS management does not systematically track information about the recommendations its staff make and OND's response to them. This limits the ability of ODS management to provide effective oversight so that FDA can ensure that safety concerns are addressed and resolved in a timely manner. FDA faces data constraints that contribute to the difficulty in making postmarket safety decisions. For example, FDA relies on clinical trials, reports of adverse drug reactions, and studies following the use of drugs in ongoing medical care in order to evaluate safety concerns and support its decisions, but each type of data has weaknesses. FDA also lacks authority to require certain studies and has resource limitations for obtaining data.

Some of FDA's initiatives, such as the establishment of a Drug Safety Oversight Board (DSB), a draft policy on major postmarket drug safety decision making, and the identification of new data sources, may improve the postmarket drug safety decision-making process, but they will not address all the gaps we identified. FDA's newly created DSB may help provide oversight of important, high-level safety decisions; however, it does not address the lack of systematic tracking of safety issues and their

resolution. Other initiatives such as FDA's draft policy on major postmarket decisions and regular meetings between OND divisions and ODS may help improve the clarity and effectiveness of the process, but they are incomplete, and do not clarify ODS's role in certain scientific advisory committee meetings. FDA's dispute resolution processes to help resolve organizational and individual disagreements over postmarket drug safety decisions have not been used and may not be viewed as sufficiently independent. FDA is taking steps to identify additional data sources, including data on Medicare beneficiaries using drugs covered by the new prescription drug benefit, but data constraints remain.

To help improve the decision-making process for postmarket drug safety, we suggest that the Congress consider expanding FDA's authority to require drug sponsors to conduct postmarket studies when additional data are needed. We are also making recommendations to the Commissioner of FDA to improve the process by establishing a mechanism for systematically tracking postmarket drug safety issues, revising and implementing FDA's draft policy on major postmarket drug safety decisions, improving CDER's dispute resolution process, and clarifying ODS's role in FDA's scientific advisory committee meetings.

In commenting on a draft of this report, FDA stated that the conclusions reached by GAO were reasonable and consistent with actions that it has already begun or planned. FDA did not comment on our recommendations.

Background

Postmarket Drug Safety and FDA's Role

Before a drug can be marketed in the United States, its sponsor must demonstrate to FDA that the drug is safe and effective for its intended use. Because no drug is absolutely safe—there is always some risk of an adverse reaction—FDA approves a drug for marketing when the agency judges that its known benefits outweigh its known risks. After a drug is on the market, FDA continues to assess its risks and benefits. FDA reviews reports of adverse drug reactions (adverse events)¹⁰ related to the drug and information from studies about the drug, including clinical trials and studies following the use of drugs in ongoing medical care (observational

¹⁰ Adverse event is the technical term used by FDA to refer to any untoward medical event associated with the use of a drug in humans.

studies),¹¹ conducted by the drug's sponsor, FDA, or other researchers. If FDA has information that a drug on the market may pose a significant health risk to consumers, it weighs the effect of the adverse events against the benefit of the drug to determine what actions, if any, are warranted. This decision-making process is complex and encompasses many factors, such as the medical importance and utility of the drug, the drug's extent of usage, the severity of the disease being treated, the drug's efficacy in treating this disease, and the availability of other drugs to treat the same disorder.¹²

CDER, the largest of FDA's five centers, is the organizational entity within FDA that oversees the review of marketing applications for new drugs and the postmarket monitoring of drugs once they are marketed.¹³ Within CDER there are several key offices involved in activities related to postmarket drug safety. OND is the largest of the offices with fiscal year 2005 expenditures of \$110.6 million and 715 staff. In fiscal year 2005, more than half of OND's expenditures, or \$57.2 million, came from PDUFA funds. OND's staff evaluate new drugs for efficacy and safety to decide if a drug should be approved for marketing. OND also makes decisions about actions to take when there are postmarket safety issues with a drug (for example, revising the label to include adverse event information or having FDA withdraw approval for marketing). For safety questions, OND interacts with several FDA offices and divisions, but primarily with ODS.¹⁴

¹¹Observational studies can provide information about the association between certain drug exposures and adverse events. In observational studies, the investigator does not control the therapy, but observes and evaluates ongoing medical care. In contrast, in clinical trials the investigator controls the therapy to be received by participants and can test for causal relationships.

¹²The risk/benefit calculation is different for each drug. For example, FDA is likely to be more tolerant of adverse events if the drug is the only drug that treats a life-threatening condition than it is for a drug that is one of many drugs for treating a less serious condition.

¹³CDER also oversees the review of marketing applications for therapeutic biological products, such as antibodies that are produced in a laboratory to eliminate foreign substances such as bacteria or toxins.

¹⁴Other FDA offices and divisions that are involved in safety activities include: the Division of Drug Marketing, Advertising, and Communication, which assesses whether drug information provided by drug sponsors is truthful, balanced, and accurately communicated; the Office of Pediatric Therapeutics, which is responsible for pediatric ethical, and safety issues that arise either before or after a drug has been approved for use in children; and the Office of Compliance, which is responsible for inspections of drug sponsors and manufacturers to ensure adherence to current good manufacturing practices and appropriate monitoring of adverse events.

ODS is currently located within the Office of Pharmacoepidemiology and Statistical Science (OPaSS), which is organizationally parallel to OND and also contains the Office of Biostatistics.¹⁵ ODS is a much smaller office than OND, with fiscal year 2005 expenditures of \$26.9 million and 106 staff. In fiscal year 2005, \$7.6 million of ODS's expenditures were from PDUFA funds. ODS staff evaluate and monitor drug risks and promote the safe use of drugs. While ODS is involved in both premarket and postmarket drug safety issues, its primary focus is on postmarket safety.

An important part of the drug approval and postmarket monitoring process is the advice FDA receives from 16 human-drug-related scientific advisory committees, composed of experts and consumer representatives from outside FDA.¹⁶ Considered by FDA as important in helping the agency accomplish its mission and maintaining public trust, these advisory committees provide expert advice to the agency on a range of issues, including safety. The committees are largely organized according to specialized medical areas or conditions such as cardiovascular disease, gastrointestinal conditions, or oncology. In 2002, FDA established the Drug Safety and Risk Management Advisory Committee (DSaRM), 1 of the 16 human-drug-related scientific advisory committees, to specifically advise FDA on drug safety and risk management issues. The committee is composed of individuals from outside FDA with experience in the areas of medication errors, risk communication, risk perception, risk management, clinical trial methodology, evidence-based medicine, biometrics, and pharmacoepidemiology. Since it was established, DSaRM has met nine times, with four of those meetings held jointly with another drug-related scientific advisory committee. DSaRM members have also been asked to participate in other scientific advisory committees when safety issues were discussed. ODS sets the agenda for DSaRM meetings, whereas OND sets the agenda for the other scientific advisory committee meetings.

Figure 1 describes the offices and external advisory committees involved in postmarket drug safety at FDA.

¹⁵The Office of Biostatistics provides support on research methods and statistics.

¹⁶These committees are either mandated by legislation or are established at the discretion of HHS.