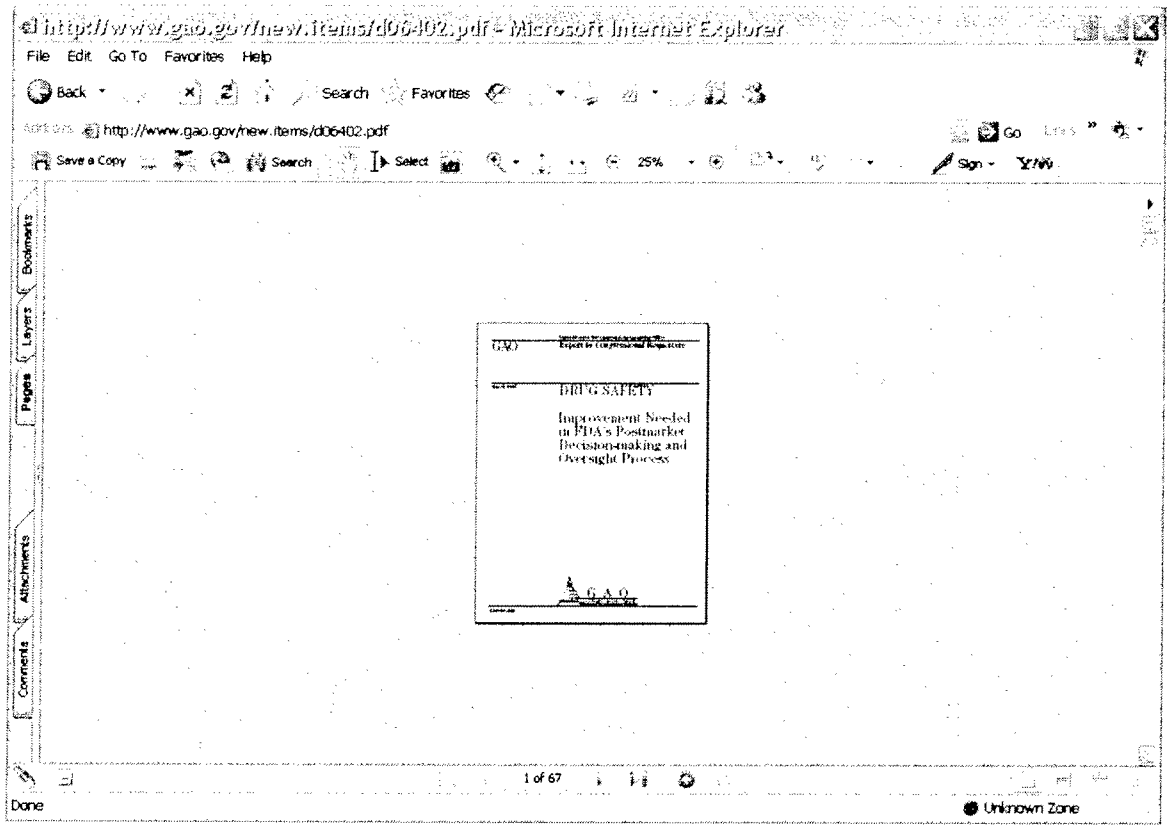
http://www.gao.gov/new.items/d06402.pdf - Microsoft Internet Explorer
File Edit Go To Favorites Help
Back
Search
Favorites
http://www.gao.gov/new.items/d06402.pdf
Go
Save a Copy
Search
Select
25%
Sign
Bookmarks
Layers
Pages
Attachments
Comments
GAO
DRUG SAFETY
Improvement Needed in FDA's Postmarket Decision-making and Oversight Process
GAO
1 of 67
Done
Unknown Zone

United States Government Accountability Office

GAO

Report to Congressional Requesters

March 2006

DRUG SAFETY

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

G A O

Accountability * Integrity * Reliability

GAO-06-402

March 2006

GAO
Accountability · Integrity · Reliability

Highlights

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

DRUG SAFETY

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

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.

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.

Contents

Letter		1
	Results in Brief	4
	Background	6
	Two Distinct FDA Units Involved in Postmarket Drug Safety Activities	12
	FDA Lacks a Clear and Effective Decision-making Process for Postmarket Drug Safety	18
	FDA Initiatives Are an Improvement, but Will Not Address All Gaps	29
	Conclusions	36
	Matter for Congressional Consideration	36
	Recommendations for Executive Action	36
	Agency Comments and Our Evaluation	37
Appendix I	**Regulatory History and FDA Decision-making Process for Arava**	39
	Background and Summary	39
	Chronology	39
Appendix II	**Regulatory History and FDA Decision-making Process for Baycol**	43
	Background and Summary	43
	Chronology	43
Appendix III	**Regulatory History and FDA Decision-making Process for Bextra**	46
	Background and Summary	46
	Chronology	46
Appendix IV	**Regulatory History and FDA Decision-making Process for Propulsid**	51
	Background and Summary	51
	Chronology	51
Appendix V	**Comments from the Food and Drug Administration**	58

Appendix VI GAO Contact and Staff Acknowledgments 62

Figures

Figure 1: FDA Organizational Structure for Postmarket Drug Safety 9

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

GAO
Accountability * Integrity * Reliability

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

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

[2]Vioxx 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

[3]See, 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.

[4]Pub. L. No. 102-571, 106 Stat. 4491.

[5]Pub. L. No. 107-188, 116 Stat. 594.

[6]In 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,

[7]In 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).

[8]FDA 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

[9]FDA 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.