

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.

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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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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 Pharmacoeconomics 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

¹⁰Adverse 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.

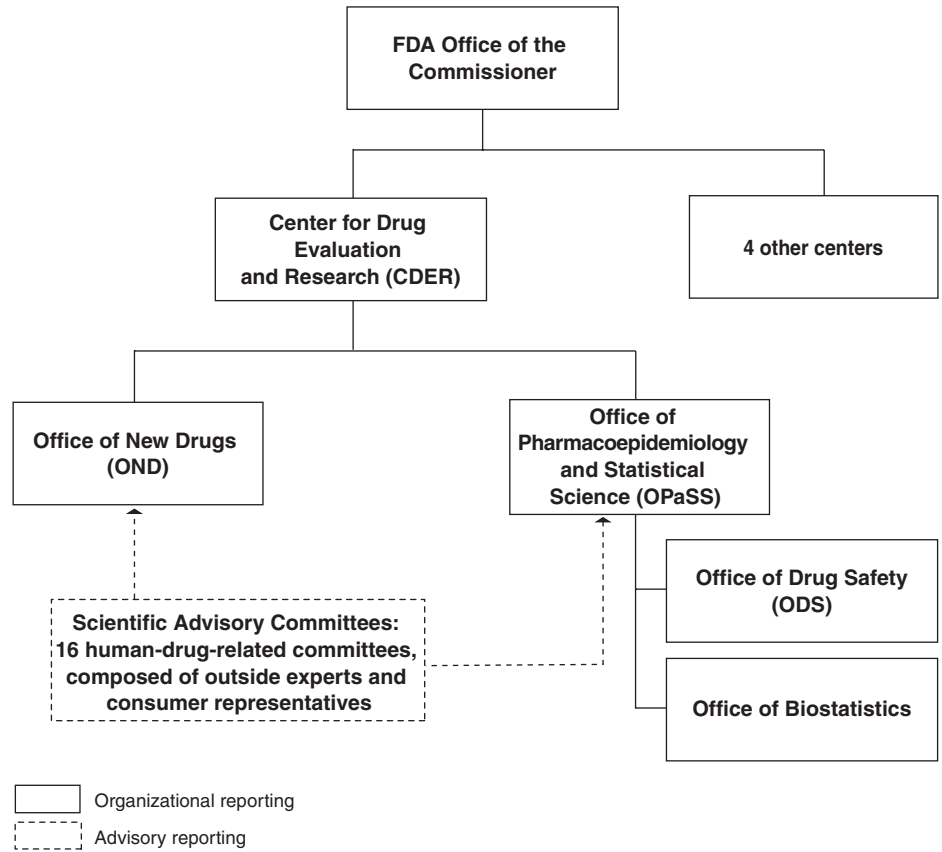
An important part of the drug approval and postmarket monitoring process is the advice FDA receives from 16 human-drug-related scientific advisory committees, composed of experts and consumer representatives from outside FDA.¹⁶ Considered by FDA as important in helping the agency accomplish its mission 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.

Figure 1: FDA Organizational Structure for Postmarket Drug Safety



Source: Based on FDA's and CDER's organizational charts.

Note: The scientific advisory committees referred to in this report include the following: Drug Safety and Risk Management Advisory Committee, Psychopharmacologic Drugs Advisory Committee, and Arthritis Advisory Committee.

FDA's Postmarket Drug Safety Authority

In terms of postmarket drug safety surveillance, FDA has the authority to require that drug sponsors report adverse events to FDA with different reporting schedules based on the seriousness of the event and whether the event has been previously identified and is included in the drug's label. Sponsors must report serious, unlabeled adverse events to FDA within 15 days of learning about them. Sponsors are required to report other adverse events quarterly for 3 years, then annually thereafter in the form of periodic adverse event reports. In addition, health care providers and

patients can voluntarily submit adverse event reports to FDA through its MedWatch program.¹⁷ Adverse event reports become part of FDA's computerized database known as the Adverse Event Reporting System (AERS).¹⁸

FDA has the authority to withdraw the approval of a drug on the market for safety-related and other reasons, although it rarely does so.¹⁹ Since 2000 there have been 10 drug withdrawals for safety reasons, and in all of these cases the drug's sponsor voluntarily removed the drug from the market. FDA does not have explicit authority to require that drug sponsors take other safety actions; however, when FDA identifies a potential problem, sponsors generally negotiate with FDA to develop a mutually agreeable remedy to avoid other regulatory action. For example, if FDA determines that an approved drug may produce adverse events not previously identified, FDA and the sponsor may negotiate on revised labeling for the drug,²⁰ and then FDA may issue an accompanying Public Health Advisory for patients and health care providers that describes the safety information. FDA may also request that the sponsor restrict the distribution of the drug in order to minimize a significant risk associated with the drug.

¹⁷MedWatch is an FDA program for receiving reports of adverse events from and providing safety information to healthcare professionals and the public. MedWatch provides clinical information about safety issues involving medical products, including prescription and over-the-counter drugs, biologics, medical and radiation-emitting devices, and special nutritional products (e.g., medical foods, dietary supplements, and infant formulas).

¹⁸FDA receives over 400,000 reports of adverse events each year. Some adverse event reports are not entered into AERS, such as periodic reports for drugs that have been approved for more than 3 years and that are considered nonserious.

¹⁹21 U.S.C. § 355(e). FDA may propose withdrawal when, for example, it determines through experience, tests, or other data that a drug is unsafe under the conditions of use approved in its application, there is a lack of substantial evidence that the drug will have the effect that it purports to have or that is suggested in its labeling, or required patent information is not timely filed. Prior to withdrawal, FDA would need to notify the affected parties and provide an opportunity for a hearing. Approval may be suspended immediately, prior to a hearing, if the Secretary of Health and Human Services finds that continued marketing of a particular drug constitutes an imminent hazard to the public health. FDA used this authority once, to withdraw the drug phenformin from the market in 1977. Phenformin was used to treat diabetes and was associated with a life-threatening buildup of lactic acid in the blood.

²⁰The labeling of a drug can be changed, for example, by adding information to the "Warnings Section."

FDA has limited authority to require that sponsors conduct postmarket safety studies; it may impose such a requirement during the premarket phase of drug development in two situations, and in one during the postmarket phase. In two situations, FDA has the authority to require that sponsors commit to conducting postmarketing studies as a condition of approval. First, FDA's program for accelerated approval of new drugs for serious or life-threatening illnesses (referred to as "subpart H drugs") allows FDA to more quickly approve drugs showing meaningful therapeutic benefit with the caveat that the sponsor will conduct or finish studies after the drug is marketed.²¹ Such drugs may be made available to the public sooner but with less complete safety information than the normal review process requires for approval. Second, in cases where human efficacy studies of a drug may not be ethical or feasible, FDA may rely on animal studies alone to approve the use of a drug and require postmarket studies as a condition of approval when studies on humans become feasible and ethical.²² For example, FDA approved a drug in 2003 that is used as a treatment for patients who have been exposed to a chemical nerve agent called Soman. Evidence of the effectiveness of this drug was obtained from animals alone because it is unethical to perform such studies in humans. In either situation, FDA may withdraw approval of these drugs if, for example, postmarket clinical studies fail to verify clinical benefits, the sponsor fails to perform postmarketing studies with due diligence, or postmarketing restrictions (for example, restricted distribution) are inadequate to assure safe use of the drug.²³ Finally, under certain conditions, after a drug is approved, FDA can also require that drug sponsors conduct postmarket studies of marketed drugs when such

²¹21 C.F.R. § 314.510 (2005).

²²21 C.F.R. § 314.610(b)(1) (2005).

²³21 C.F.R. § 314.530(a)(1)–(3); 21 C.F.R. § 314.620(a)(1)–(3) (2005).

studies are needed to provide adequate labeling to ensure the safe and effective use of these drugs in children.²⁴

Two Distinct FDA Units Involved in Postmarket Drug Safety Activities

Two distinct FDA offices are involved in postmarket drug safety activities. While there is some overlap in their activities, they have different organizational characteristics and perspectives on postmarket drug safety. OND is involved in postmarket drug safety activities as one aspect of its larger responsibility to review new drug applications, and it has the decision-making responsibility for postmarket drug safety. ODS has a primary focus on postmarket drug safety and provides consultation to OND. ODS has been reorganized several times over the years, and there has been an absence of stable leadership. FDA's postmarket drug safety decision-making process is complex, involving iterative interactions between OND and ODS.

OND Has Decision-making Responsibility for Postmarket Drug Safety

Since OND is responsible for approving or disapproving drug applications, its staff are involved in safety activities throughout the life cycle of a drug (that is, premarket and postmarket), and it has the ultimate responsibility to take regulatory action concerning the postmarket safety of drugs. OND is organized into six offices that evaluate drugs and drug products, and within these offices are 17 review divisions organized by medical specialty (for example, oncology or dermatology). OND's staff includes physicians, pharmacologists, toxicologists, and microbiologists. The key decision makers in OND—division directors and office directors—are physicians. In general, OND staff take a clinical perspective in their work. According to the Director of the office, OND's medical staff have expertise in medical specialties as well as drug regulation, which he said gave them the ability to integrate issues related to the disease, available therapy, effectiveness of the drug, and relative safety. He also told us that OND staff are focused on meeting patient needs and providing health care practitioners and

²⁴According to the Pediatric Research Equity Act of 2003, FDA may require drug manufacturers to develop information regarding the safety, effectiveness, dosing, and administration of marketed drugs if (1) the drug is used by a substantial number of pediatric patients for the labeled indications, and the absence of adequate labeling could pose significant risks to pediatric patients; or (2) the drug would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients. 21 U.S.C. § 355c. This authority may be used only after FDA has been unsuccessful in obtaining necessary pediatric information under other authority. These studies have resulted in new pediatric labels with important dosing or safety information.

patients with a range of drugs for treatment of a specific disease or condition. Finally, an important characteristic of OND's organization is that OND's work and its pace are driven in part by PDUFA goals to complete its review of drug applications within certain time frames.

FDA estimates that 51 percent of OND's work time is devoted to drug safety, either premarket or postmarket.²⁵ In the drug development or premarket phase, OND staff review safety and efficacy data from sponsors' animal studies and human clinical trials to decide whether or not to approve a drug. In some cases OND identifies safety concerns at the time of approval that it believes can be managed, for example, by educating patients and providers or restricting distribution to certain populations. In these cases, OND works with ODS and the sponsor to develop a risk management plan to outline these strategies. OND may also request, or in cases where FDA has the authority, require that a sponsor conduct a postmarketing study as a condition of approval.

After a drug is on the market, OND receives information about safety issues related to a drug's use and takes appropriate regulatory action. OND receives information about safety issues in several ways. First, OND staff receive notification of adverse event reports for drugs to which they are assigned and they review the periodic adverse event reports that are submitted by drug sponsors. Second, OND staff review safety information that is submitted to FDA when a sponsor seeks approval for a new use or formulation of a drug, and monitor completion of postmarket studies. OND also partners with ODS and other CDER offices for information and analysis to help it make postmarket drug safety decisions. When considering postmarket drug safety issues, OND staff use evidence found in clinical trials. For example, one OND manager told us that OND staff typically review adverse event data related to a drug, obtain a consult from ODS, and then review any clinical trial data. Then, if necessary, OND makes a decision about what action should be taken, which may include negotiating with a sponsor to change a drug's label, restricting its distribution, or proposing to withdraw the drug's approval.

²⁵Theresa M. Mullin, Ph.D., Office of Planning, Office of Commissioner, FDA, "Estimating CDER Resources Devoted to Safety" (presentation to FDA Science Board Advisory Committee, Apr. 15, 2005).

ODS Serves as a Consultant to OND

ODS serves primarily as a consultant to OND and has an overall goal of reducing preventable deaths and injuries associated with the use of drugs with a primary focus on postmarket drug safety. ODS also provides consultation to OND on premarket safety issues, including risk management issues.²⁶ Although FDA's postmarket drug safety office has been reorganized several times over the years, the consultant role of the office has remained consistent. ODS was formed in 2002 when FDA combined the Office of Postmarketing Drug Risk Assessment with the MedWatch program (from the Office of Training and Communications) and with patient labeling and risk communication functions (from the Division of Drug Marketing, Advertising, and Communications). ODS was established within the new Office of Pharmacoepidemiology and Statistical Science (OPaSS). OPaSS was made equivalent to OND within the CDER organizational structure.

ODS is composed of a small management team and three divisions. According to the ODS Director, the management team consists of the director, deputy director, an associate director for regulatory affairs, and an associate director for science and medicine. ODS's three divisions are: the Division of Drug Risk Evaluation (DDRE), the Division of Surveillance, Research, and Communication Support, and the Division of Medication Errors and Technical Support. The Division of Surveillance, Research, and Communication Support is involved with the acquisition and analysis of data related to drug safety. This division also reviews consumer-oriented materials for content and patient-friendly language, such as medication guides, which are dispensed with drugs that have serious safety concerns. This division also disseminates safety information to the medical community and general public through the MedWatch Web site. The Division of Medication Errors and Technical Support is responsible for conducting premarketing reviews of all proprietary names and labels of drugs in order to minimize medication errors due to similar names or confusion related to the labeling and packaging of drugs. This division also provides postmarketing review and analysis of medication errors.

ODS's DDRE is the primary unit responsible for postmarket drug safety surveillance. Its staff of 47 include safety evaluators, who are generally pharmacists, and epidemiologists, with many having either a Ph.D. in epidemiology or an M.D. with epidemiologic training. The division's safety evaluators are assigned to cover specific groups or classes of marketed

²⁶PDUFA goals apply to ODS's premarket consultative work.

drugs. They primarily review reports of individual adverse events from AERS in order to detect safety signals. The division's epidemiologists work collaboratively with the safety evaluators, using population-level data to analyze potential safety signals and put them into context. They also review the published literature and conduct research through the use of contracts and other agreements with researchers outside of government, health care utilization databases, and surveillance systems.²⁷ Finally, safety evaluators and epidemiologists interact with international colleagues on drug safety issues.

ODS operates primarily in a consultant capacity to OND and does not have any independent decision-making responsibility. When there is a safety concern, ODS staff conduct an analysis and produce a written report for OND called a consult. Safety consults conducted by DDRE staff include analyses of adverse event reports and assessments of postmarket study designs and risk management plans.²⁸ In fiscal year 2004, DDRE completed approximately 600 safety consults. A majority of DDRE's consults are requested by OND. In fiscal year 2004, 71 percent of DDRE's consults were requested by OND; 22 percent were requested by other sources;²⁹ and 7 percent were self-initiated by DDRE. Over time, the proportion of DDRE-initiated consults has declined while the proportion of OND-requested consults has increased.

In general, ODS staff take a population-based perspective in their work, which ODS staff we spoke with contrasted with the clinical perspective of OND. They look at how a drug is being used in the general population and its side effects, and they base their safety analyses on adverse event reports, observational studies, and other population-based data sources. ODS staff do not typically use clinical trial data for their safety analyses and conclusions. In their postmarket work, ODS staff also do not operate under PDUFA drug review goals and therefore do not face the same kinds

²⁷For example, FDA has used data from the IMS Health National Prescription Audit database and the National Electronic Injury Surveillance System: Cooperative Adverse Drug Events Surveillance System (NEISS-CADES).

²⁸In addition to these safety consults, ODS's Division of Medication Errors and Technical Support provides consults on medication errors, drug names, and labeling, while ODS's Division of Surveillance, Research, and Communication Support provides consults on drug use data.

²⁹ODS has also done consults for other FDA centers (for example, Center for Devices and Radiological Health), other federal agencies (for example, National Institutes of Health), international health agencies (for example, World Health Organization), and others.

of deadlines that OND staff face. Furthermore, ODS staff have sometimes taken an academic research approach to safety work, for example, publishing case reports about adverse events or safety analyses in peer-reviewed journals.

There has been high turnover of ODS directors—there have been eight different directors of the office and its various predecessors—in the past 10 years. Four of the directors have been “acting” directors, not permanent ones. From February to September 2002 and again from October 2003 to January 2005, the Director of OPaSS also served as the Acting Director of ODS. The Director of CDER, as well as staff within and outside of ODS, told us that the lack of consistent leadership of ODS has had a negative effect on the work and morale of staff. One ODS staff member told us that since drug safety issues often take a fair amount of time to resolve, it is important to have consistency in leadership so that the leaders are knowledgeable of ongoing issues. In October 2005 FDA appointed a permanent director of ODS from within the organization, the first permanent director since October 2003.

Postmarket Drug Safety Decision Making Is Complex and Iterative

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. As we have described, ODS safety consults can be initiated within ODS or requested by OND, but typically OND requests them. OND often requests an analysis because of information it receives from the drug’s sponsor about a safety concern. ODS safety evaluators then search AERS for all relevant cases and develop a summary of individual cases from the reports. The safety evaluators assess the cases to determine whether the adverse events are drug-related and whether there are any common trends or risk factors. ODS epidemiologists sometimes collaborate with the safety evaluators by estimating how frequently an adverse event occurs among the population exposed to a particular drug,³⁰ and they compare this estimate with how frequently the same event occurs in a population not treated by the drug. The epidemiologists also might use information from observational studies and drug use analyses to analyze the safety issue. When completed, ODS

³⁰This is called a “reporting rate” and is calculated by dividing the number of reported cases of a particular adverse event by a measure of the drug’s utilization, such as the number of dispensed prescriptions. FDA has contracts with outside companies to obtain information about drug utilization across various health care settings.

staff summarize their analysis in a written consult. The ODS division director of the staff who worked on the consult typically reviews the consult and either signs it, indicating agreement, or writes a memorandum explaining what part he or she disagrees with and why. According to FDA officials, OND staff within the review divisions usually decide what regulatory action should occur, if any, by considering the results of the safety analysis in the context of other factors such as the availability of other similar drugs and the severity of the condition the drug is designed to treat. Several CDER staff, including OND and ODS staff, that we interviewed told us that most of the time there is agreement within FDA about what safety actions should be taken. At other times, however, OND and ODS disagree about whether the postmarket data are adequate to establish the existence of a safety problem or support a recommended regulatory action. In those cases, sometimes OND requests additional analyses by ODS and sometimes there is involvement from other FDA organizations. In some cases, OND seeks the advice of FDA's scientific advisory committees, including DSaRM, for decisions about postmarket drug safety. The recommendations of the advisory committees do not bind the agency to any decision. According to FDA officials, if a decision is made by OND that a safety action is warranted, then OND staff generally work with the drug's sponsor to implement it.

There was sometimes a lack of consensus in our drug case studies, and we observed that ODS often performed a series of related analyses about the same safety concerns for OND over a significant period of time.³¹ As an illustration of this iterative decision-making process, OND requested in 2002 that ODS analyze cases of serious skin reactions associated with the pain reliever Bextra after the drug's sponsor had communicated with OND about this potential risk. ODS staff searched the AERS database and found several related cases for review. They estimated the occurrence of reported cases of serious skin reactions among Bextra users by using the cases and drug utilization data. On the basis of their analysis, ODS recommended that Bextra's label be updated to include this risk, and OND followed the recommendation by working with the sponsor to update the label in 2002. Between 2002 and 2004, ODS staff conducted five other analyses of the occurrence of serious skin reactions associated with Bextra, including two that were requested by OND. In March 2004, ODS staff recommended that Bextra carry a boxed warning about its risks of

³¹For more information on events related to FDA's decision-making processes on Arava, Baycol, Bextra, and Propulsid, see apps. I-IV.

serious skin reactions. The ODS staff based their recommendation on their finding that Bextra's risk for serious skin reactions was 8 to 13 times higher than that for other similar drugs and 20 times higher than the incidence rate in the population.³² The ODS Division Directors who reviewed the analysis and recommendation agreed, but the OND review division responsible for Bextra did not initially agree. About 5 months later, the OND review division decided a boxed warning was warranted, after ODS performed another analysis requested by OND, comparing Bextra's risk with several other similar drugs, including Mobic.³³ ODS found no reported cases of serious skin reactions associated with Mobic. In 2005, a joint meeting of FDA's Arthritis Advisory Committee and DSaRM was held to discuss the postmarket safety of several anti-inflammatory drugs including Bextra, with a focus on their cardiovascular risks. The committees recommended, after presentations by FDA staff and others, that Bextra should remain on the market. A few months later, FDA asked the sponsor to withdraw the drug from the market because, in part, its risk for serious skin reactions appeared to be greater than for other similar anti-inflammatory drugs.³⁴

FDA Lacks a Clear and Effective Decision-making Process for Postmarket Drug Safety

FDA's postmarket drug safety decision-making process has been limited by a lack of clarity, insufficient oversight by management, and data constraints. We observed that there is a lack of established criteria for determining what safety actions to take and when. Aspects of ODS's role in the process are unclear, including its role in participating in scientific advisory committee meetings organized by OND. A lack of communication between ODS and OND's review divisions and limited oversight of postmarket drug safety issues by ODS management has hindered the decision-making process. FDA relies primarily on three types of data sources—adverse event reports, clinical trial studies, and observational studies—in its postmarket decision making. Each data source has

³² A boxed warning is placed in a prominently displayed box on a drug's label when there are serious safety problems associated with a drug, such as those that may lead to serious injury or death. Advertisements that serve to remind health care professionals of a drug's availability (called "reminder ads") are not allowed for drugs with boxed warnings.

³³ In April 2004, prior to the boxed warning, the label was changed to include a statement in the warnings section that fatalities due to serious skin reactions had been reported. This change did not include a boxed warning.

³⁴ The OND and OPaSS Directors posted a memorandum on FDA's Web site explaining this decision.

weaknesses, however. FDA also faces constraints in requiring certain studies and obtaining data.

Decision-making Process on Drug Safety Lacks Clarity about Criteria for Action and the Role of ODS

While acknowledging the complexity of the postmarket drug safety decision-making process, we observed in our interviews with OND and ODS staff and in our case studies that the process lacked clarity about how drug safety decisions are made and about the role of ODS. If FDA had established criteria for certain postmarket drug safety decisions, then some of the disagreements we observed in our case studies could have possibly been resolved more quickly. For example, in the case of Bextra, as described earlier, ODS and OND staff disagreed about whether the degree of risk warranted a boxed warning, the most serious warning placed in the labeling of a prescription medication. As another example, there were differing opinions over taking stronger actions against Propulsid, the nighttime heartburn medication which was associated with cardiovascular side effects, or whether to modify the label. Between 1995 and 1997, Propulsid's label had been modified, including the addition of a boxed warning, to warn consumers and professionals about the cardiovascular side effects of the drug. In June 1997 a task force within FDA, including OND and ODS staff, was convened to further evaluate the efficacy and safety of Propulsid. FDA staff, including task force members, later met to discuss several regulatory options, including proposing further label modifications, presenting the agency's concerns to an advisory committee, and proposing to withdraw approval of Propulsid. According to a former OND manager, as a result of this meeting, FDA decided to seek further label modifications. Some staff, from both OND and ODS, however, supported stronger actions at this time, including proceeding with proposing a withdrawal of approval.³⁵ According to several FDA officials, in the absence of established criteria, decisions about safety actions are often based on the case-by-case judgments of the individuals reviewing the data.

Our observations are consistent with previous FDA reviews. In 2000, two internal CDER reports based on interviews that FDA conducted with staff indicated that an absence of established criteria for determining what safety actions to take, and when, posed a challenge for making postmarket

³⁵Subsequent changes to the boxed warning were made in 1998 and a medication guide was implemented in 1998. FDA decided in November 1999 that an advisory committee meeting would be scheduled to discuss how to reduce the occurrence of adverse events with Propulsid, but before it was held the drug's sponsor withdrew the drug from the market.

drug safety decisions. The reports recognized the need to establish criteria to help guide such decisions. In a review of the safety issues concerning Propulsid, CDER staff recommended that a standardized approach to postmarket drug safety issues be established, by addressing various issues such as how to determine when to incorporate safety issues into labeling and when stronger actions should supersede further labeling changes. According to the report, several staff noted frustration with the numerous changes made to Propulsid's label that were mostly ineffective in reducing the number of cardiovascular adverse events.³⁶ Similarly, after the diabetes drug Rezulin was removed from the market in 2000 because of its risk for liver toxicity, a CDER report focused on Rezulin also recommended that a consistent approach to postmarket drug safety be developed, including what regulatory actions should occur to address postmarket drug safety concerns, and when they should occur.

In addition to a lack of criteria for safety actions, we observed a lack of clarity related to ODS's recommendations. In practice, ODS often makes written recommendations about safety actions to OND but there is some confusion over this role, according to several ODS managers, and there is no policy that explicitly states whether ODS's role includes this responsibility. The case of Arava illustrates this confusion. In 2002, the OND review division responsible for Arava, a drug used to treat rheumatoid arthritis, requested that ODS review postmarket data for cases of serious liver toxicity associated with its use. The ODS staff who worked on this analysis recommended that Arava be withdrawn from the market because they concluded that the risk for serious liver toxicity exceeded its benefits. The OND Division Director responsible for Arava felt that ODS should not have included a recommendation in its consult because he argued that this was the responsibility of OND, not ODS. Some of the confusion may be the result of ODS's evolving role in postmarket drug safety. A current and a former ODS manager told us that in the past, ODS's safety consults were technical documents summarizing adverse events with minimal data analysis and few recommendations. Over time the consults have become more detailed with sophisticated data analyses and more recommendations about what safety action is needed (for example, label change, medication guide, drug withdrawal).

³⁶One staff member noted that the numerous labeling changes made it increasingly difficult to use Propulsid as labeled because of the numerous contraindications.

ODS's role in scientific advisory committee meetings is also unclear. According to the OND Director, OND is responsible for setting the agenda for the advisory committee meetings, with the exception of DSaRM. This includes who is to present and what issues will be discussed by the advisory committees. For the advisory committees (other than DSaRM) it is unclear when ODS staff will participate. While ODS staff have presented their postmarket drug safety analyses during some advisory committee meetings, our case study of Arava, and another case involving antidepressant drugs, provide examples of the exclusion of ODS staff. For example, in March 2003, the Arthritis Advisory Committee met to review the efficacy of Arava, and its safety in the context of all available drugs to treat rheumatoid arthritis.³⁷ The OND review division responsible for Arava presented its own analysis of postmarket drug safety data at the meeting, but did not allow the ODS staff—who had recommended that Arava be removed from the market—to present their analysis because it felt that ODS's review did not have scientific merit. Specifically, the OND review division felt that some of the cases in the ODS review did not meet the definition of acute liver failure, the safety issue on which the review was focused. The OND division also believed that in some of the cases ODS staff inappropriately concluded that liver failure resulted from exposure to Arava.³⁸ After the meeting, ODS epidemiologists and safety evaluators asked the ODS and OPaSS Directors to clarify ODS's role involving postmarket drug safety issues, including its role at advisory committee meetings.³⁹ According to an FDA official, there was no written response to this request.

As another example of ODS's unclear role in scientific advisory committees, in February 2004 an ODS epidemiologist was not allowed to present his analysis of safety data at a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee that was held to discuss reports of suicidal thoughts and actions in children with

³⁷The committee was asked to consider whether the data presented by the drug's sponsor supported improvement in physical function and whether the drug's labeling needed to be updated to add any additional warning about liver toxicity.

³⁸Similarly, other senior-level CDER staff, including ODS and OND managers, did not agree with the ODS staff's conclusions and recommendation.

³⁹Specifically, they recommended that as a matter of policy, ODS staff should present postmarket safety data at these meetings or if such data are presented by a non-ODS staff member, then ODS staff should play an integral role in preparing the presentation content.

major depressive disorder during clinical trials for various antidepressant drugs. According to statements by FDA officials at a congressional hearing, OND believed that the ODS staff member's analysis, which showed a relationship between the use of antidepressants and suicidal thoughts and behaviors in children, was too preliminary to be presented in detail. The analysis was based on pediatric clinical trial data that FDA requested from the sponsors of several antidepressant drugs. FDA had asked the sponsors to identify suicide-related events using specific methods, and then ODS was asked to analyze all of the submitted data. OND later decided that the sponsors may have been inconsistent in their classification approaches and asked outside experts to perform additional reviews of all the cases by rating whether particular events could be classified as suicidal. The staff member who performed the ODS review, however, believed that the available data were sufficient to conclude a relationship between the use of antidepressants and suicidal thoughts and behaviors in pediatrics and to recommend further safety actions. In his consult, the ODS staff member also concluded that while additional analyses would yield valuable information, they would also take several more months to complete. In light of this delay, he recommended an interim plan to discourage the use of all but one antidepressant in the treatment of pediatric major depressive disorders.⁴⁰ In December 2004, ODS epidemiologists communicated to the CDER Director their position that ODS's role should include the responsibility of presenting all relevant ODS data at advisory committee meetings. According to an FDA official, there was no written response to this request. However, in our interviews, the Directors of CDER and OND told us that in retrospect they felt it was a mistake for FDA to have restricted the ODS epidemiologist from presenting his safety information at the meeting.

Several ODS managers that we interviewed told us that there is also a lack of clarity regarding the role of the epidemiologist in postmarket drug safety work. Despite the fact that ODS's epidemiologists have some

⁴⁰In March 2004, FDA asked drug sponsors of 10 antidepressants to include stronger cautions and warnings about the need to monitor pediatric and adult patients for the worsening of depression and the emergence of suicidal thoughts and behavior. The additional review of the clinical trial data, performed by an expert panel assembled at Columbia University, was completed in July 2004. In September 2004, a joint meeting was held with the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee to discuss FDA's analysis of the reclassified data. FDA announced in October 2004 that it had requested that drug sponsors of all antidepressants add a boxed warning to the labels describing the increased risk of suicidal thoughts and behaviors in pediatric patients.

defined responsibilities, there appears to be some confusion about the scope of their activities and a lack of understanding on the part of OND about their role and capabilities. A prior review of postmarket drug safety identified similar issues.⁴¹ For example, in that review some epidemiologists indicated that they should be able to maintain an independent approach to their research and the publication of their research. However, some OND review division directors indicated that the work of the epidemiologists should be considered within the context of CDER's overall regulatory mission. Further, the epidemiologists' research conclusions do not necessarily reflect the conclusions of FDA but may be perceived as such by the medical community. ODS managers indicated that a current challenge for FDA is to determine how it should use its epidemiologists and what their work products should be. According to the current ODS Director, efforts are needed to help OND better understand what epidemiologists can do. The epidemiologists themselves have asked for greater clarity about their role and a stronger voice in decision making.

A Lack of Communication and Limited Oversight Hinders the Decision-making Process

A lack of communication between ODS and OND's review divisions and limited oversight of postmarket drug safety issues by ODS management have also hindered the decision-making process. The frequency and extent of communication between ODS and OND's divisions on postmarket drug safety vary. ODS and OND staff often described their relationship with each other as generally collaborative, with effective communication. But both ODS and OND staff said sometimes there were communication problems, and this has been an ongoing concern. For example, according to some current and former ODS staff, OND does not always adequately communicate the key question or point of interest to ODS when it requests a consult, and as ODS works on the consult there is sometimes little interaction between the two offices. After a consult is completed and sent to OND, ODS staff reported that OND sometimes does not respond in a timely manner or at all. Several ODS staff characterized this as consults falling into a "black hole" or "abyss." OND's Director told us that OND staff probably do not "close the loop" in responding to ODS's consults, which includes explaining why certain ODS recommendations are not followed. In some cases CDER managers and OND staff criticized the methods used in ODS consults and told us that the consults were too lengthy and academic.

⁴¹FDA, *Program Review of the Division of Epidemiology and Surveillance (DES) in the Office of Epidemiology and Biometrics (OEB)*, (Washington, D.C.: 1993).

ODS management has not effectively overseen postmarket drug safety issues, and as a result, it is unclear how FDA can know that important safety concerns have been addressed and resolved in a timely manner. According to a former ODS Director, the small size of ODS's management team has presented a challenge for effective oversight of postmarket drug safety issues. Another problem is the lack of systematic information on drug safety issues. According to the ODS Director, ODS currently maintains a database of consults that can provide certain types of information such as the total count, the types of consults that ODS staff conducted, and the ODS staff that wrote the consults. But it does not include information about whether ODS staff have made recommendations for safety actions and how the safety issues were handled and resolved, including whether recommended safety actions were implemented by OND. For example, ODS was unable to provide us with a summary of the recommendations for safety actions that its staff made in 2004 because it was not tracking such information.

Data Constraints Contribute to Difficulty in Making Postmarket Safety Decisions

Data constraints—such as weaknesses in data sources and limitations in requiring certain studies and obtaining data—contribute to FDA's difficulty in making postmarket drug safety decisions. OND and ODS use three different sources of data to make postmarket drug safety decisions. They include adverse event reports, clinical trial studies, and observational studies. While data from each source have weaknesses that contribute to the difficulty in making postmarket drug safety decisions, evidence from more than one source can help inform the postmarket decision-making process. The availability of these data sources is constrained, however, because of FDA's limited authority to require drug sponsors to conduct postmarket studies and its resources.

While decisions about postmarket drug safety are often based on adverse event reports,⁴² FDA cannot establish the true frequency of adverse events in the population with AERS data. The inability to calculate the true frequency makes it hard to establish the magnitude of a safety problem,

⁴²Adverse event data are the primary basis for postmarket safety actions ranging from labeling changes to withdrawal.

and it makes comparisons of risks across similar drugs difficult.⁴³ In addition, it can be difficult to attribute adverse events to particular drugs when there is a relatively high incidence rate in the population for the medical condition.⁴⁴ For example, ODS staff analyzed adverse event reports of serious cardiovascular events among users of the anti-inflammatory drug Vioxx in a 2001 consult. However, because Vioxx was used to treat arthritis, which occurs more frequently among older adults, and because of the relatively high rate of cardiovascular events among the elderly, ODS staff concluded that the postmarket data available at that time were not sufficient to establish that Vioxx was causally related to serious cardiovascular adverse events.⁴⁵ With AERS data it is also difficult to attribute adverse events to the use of particular drugs because the AERS reports may be confounded by other factors, such as other drug exposures. For example, one AERS report described a patient who developed cardiac arrest after he was given the drug hyaluronidase⁴⁶ with two local anesthetics in preparation for cataract surgery. Because local anesthetics can lead to cardiac events, the ODS safety evaluator who reviewed this case concluded that the causal role of hyaluronidase alone could not be established.

FDA may also use data from clinical trials and observational studies to support postmarket drug safety decisions, but each source has weaknesses that constrain the usefulness of the data provided. Clinical trials, in particular randomized clinical trials, are considered the “gold standard” for assessing evidence about efficacy and safety because they are considered the strongest method by which one can determine whether

⁴³This is due, in part, to the underreporting of adverse events and inconsistency in how those reporting define cases. These limitations have been reported elsewhere. See, for example, David J. Graham, Patrick C. Waller, and Xavier Kurz, “A View from Regulatory Agencies,” in *Pharmacoepidemiology*, ed. Brian L. Strom (Chichester: John Wiley & Sons, Ltd., 2000), pp. 109–124.

⁴⁴AERS data are useful when an adverse event is relatively rare, such as liver toxicity. Drug-induced liver toxicity is the major reason for regulatory actions concerning drugs, including withdrawal from the market, restrictions on use, and warnings to physicians.

⁴⁵The sponsor of Vioxx voluntarily removed it from the market in 2004 because one of its postmarket clinical trials showed a causal relationship between the use of Vioxx and serious cardiovascular events. However, some researchers and some FDA staff believe that previous studies, including a clinical trial completed by the sponsor, supported an earlier withdrawal of Vioxx or restrictions on its use.

⁴⁶This drug promotes the dispersion of other drugs, for example, speeding the onset of action for an anesthetic.

new drugs work.⁴⁷ However, clinical trials also have weaknesses. Clinical trials typically have too few enrolled patients to detect serious adverse events associated with a drug that occur relatively infrequently in the population being studied. They are usually carried out on homogenous populations of patients that often do not reflect the types of patients who will actually take the drugs, including those who have other medical problems or take other medications. In addition, clinical trials are often too short in duration to identify adverse events that may occur only after long use of the drug.⁴⁸ This is particularly important for drugs used to treat chronic conditions where patients are taking the medications for the long term. Observational studies, which use data obtained from population-based sources, can provide FDA with information about the population effect and risk associated with the use of a particular drug. Because they are not controlled experiments, however, there is the possibility that the results can be biased or confounded by other factors.⁴⁹

Despite the weaknesses of clinical trials and observational studies, evidence from both types of studies helps inform FDA's postmarket drug safety decision-making process. For example, clinical trials conducted by drug sponsors for their own purposes sometimes provide information for FDA's evaluation of postmarket drug safety issues. For instance, drug sponsors sometimes conduct clinical trials for drugs already marketed in order to seek approval for a new or expanded use.⁵⁰ These studies may

⁴⁷In these trials, patients are randomly assigned to either receive the drug or a different treatment, and differences in results between the two groups can typically be attributed to the drug.

⁴⁸FDA has generally recommended that 1500 patients be exposed to a drug intended for long-term treatment of non-life-threatening conditions. While between 300 and 600 of these patients should be exposed for 6 months and 100 exposed for 1 year, others will have shorter-term exposure. See HHS, FDA, *Guidance for Industry: Premarketing Risk Assessment* (Rockville, Md.: 2005).

⁴⁹The limitations of observational studies have been discussed and debated in the literature and were recently illustrated in the case of hormone replacement therapy (HRT). While observational studies had indicated a positive effect of HRT, in 2002 the Women's Health Initiative study, a clinical trial, demonstrated the opposite, and found that HRT may in fact increase the risk of heart disease, cancer, and other diseases. A review of the observational studies suggested that selection bias probably accounted for the positive effect of HRT, that is, women who chose to take the hormone replacement drug were different from women who did not. For example, they tended to be healthier and better educated.

⁵⁰In such cases, clinical trial data, including adverse event reports from trials, are submitted to FDA while at the same time FDA receives postmarket adverse event reports from sponsors or from other sources, such as health care providers, and all of this information is factored into decisions about whether to approve new or expanded uses for the drug.

also be conducted to support claims about the additional benefits of a drug, and their results sometimes reveal safety information about a marketed drug. For example, to support the addition of a claim for the lower risk of gastrointestinal outcomes (such as ulcers and bleeding), Vioxx's sponsor conducted a clinical trial that found a greater number of heart attacks in patients taking Vioxx compared with another anti-inflammatory drug, naproxen. This safety information was later added to Vioxx's labeling.⁵¹ In addition to relying on sponsors, ODS partners with researchers outside of FDA to conduct postmarket observational studies through cooperative agreements and contracts. For example, several cooperative agreements supported a study of Propulsid using population-based databases from two managed care organizations and one state Medicaid program, before and after warnings on contraindications were added to the drug's label in 1998.⁵² The cooperative agreement researchers, which included ODS staff, measured the prevalence of contraindicated use of Propulsid, and found that a 1998 labeling change warning about the contraindication did not significantly decrease the percentage of users who should not have been prescribed this drug.⁵³

FDA's access to postmarket clinical trial and observational data, however, is limited by its authority and available resources. As described previously, FDA does not have broad authority to require that a drug sponsor conduct an observational study or clinical trial for the purpose of investigating a specific postmarket safety concern. One senior FDA official and several outside drug safety experts told us that FDA needs greater authority to

⁵¹This study was not designed to study cardiovascular events but it has been proposed that FDA could use the studies that sponsors conduct for marketed drugs to explicitly study emerging safety concerns.

⁵²A boxed warning was first added to Propulsid's label in 1995, which contraindicated its use in patients taking drugs that affected Propulsid's metabolism. FDA expanded the boxed warning in 1998 to include additional contraindicated drugs. The boxed warning also stated that the use of Propulsid was contraindicated in patients with certain medical conditions, such as heart disease, that could predispose them to cardiac arrhythmias. FDA also issued a press release about the changes, and the drug's sponsor distributed a letter to 800,000 health care professionals informing them of the revised label. In 2000 FDA announced the decision to hold an advisory committee meeting to discuss the safety of Propulsid and ways to reduce the occurrence of adverse events associated with Propulsid. The sponsor withdrew the drug in 2000, before the scheduled meeting, but ODS staff told us that they were planning to present the study findings at the meeting.

⁵³See W. Smalley, D. Shatin, D.K. Wysowski, et al., "Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action," *Journal of the American Medical Association*, vol. 284, no. 23 (2000).

require such studies. Long-term clinical trials may be needed to answer safety questions about risks associated with the long-term use of drugs, such as those that are widely used to treat chronic conditions. For example, during a February 2005 scientific advisory committee meeting, some FDA staff and members of the Arthritis Advisory Committee and DSaRM indicated that there was a need for better information on the long-term use of anti-inflammatory drugs and discussed how a long-term trial might be designed to study the cardiovascular risks associated with the use of these drugs. As another example, FDA approved Protopic and Elidel, both eczema creams, in December 2000 and December 2001, respectively. Since their approval, FDA has received reports of lymphoma and skin cancer in children and adults treated with these creams. In March 2005, FDA announced that it would require label changes for the creams, including a boxed warning about the potential cancer risk. An ODS epidemiologist told us that FDA has been trying for several years to get the sponsor to do long-term studies of these drugs, but that it has been difficult to negotiate.

In the absence of specific authority, FDA often relies on drug sponsors voluntarily agreeing to conduct such postmarket studies. But the postmarket studies that drug sponsors agree to conduct have not consistently been completed. For example, one study estimated that the completion rate of postmarket studies, including those that sponsors have voluntarily agreed to conduct, rose from 17 percent in the mid-1980s to 24 percent between 1991 and 2003.⁵⁴ FDA has little leverage to ensure that these studies are carried out, for example, by imposing administrative penalties.

In terms of resource limitations, several FDA staff (including CDER managers) and outside drug safety experts told us that in the past ODS has not had enough resources for cooperative agreements to support its postmarket drug surveillance program. Annual funding for this program was less than \$1 million from fiscal year 2002 through fiscal year 2005. In October 2005 FDA awarded four contracts to replace the cooperative agreements, and FDA announced that these contracts would allow FDA to more quickly access population-level data and a wider range of data sources. The total amount of the contracts, awarded from 2005 to 2010, is

⁵⁴Postmarket studies for approved drugs and biologics are included in the percent calculations. See: Tufts Center for the Study of Drug Development (Kenneth I. Kaitin, ed.), "FDA Requested Postmarketing Studies in 73% of Recent New Drug Approvals," *Impact Report: Analysis and Insight into Critical Drug Development Issues*, vol. 6, no. 4 (2004).

about \$5.4 million, which averages about \$1.1 million per year, a slight increase from fiscal year 2005 funding. The new contracts will provide access to data from a variety of health care settings including health maintenance organizations, preferred provider organizations, and state Medicaid programs.

According to an FDA official, FDA does not conduct its own clinical trials because of the high cost associated with carrying out such studies and because FDA does not have the infrastructure needed to conduct them. It was recently estimated that clinical trials designed to study long-term drug safety could cost between \$3 million and \$7 million per trial.⁵⁵ The estimated cost of just one such trial would exceed the amount FDA has currently allocated (\$1.1 million) for its contracts with researchers outside of FDA.

FDA Initiatives Are an Improvement, but Will Not Address All Gaps

FDA has undertaken several initiatives to improve the postmarket drug safety decision-making process, but these are unlikely to address all the gaps. FDA's newly created Drug Safety Oversight Board (DSB) may help provide oversight of important, high-level safety decisions, but it does not address the need for systematic tracking of ongoing safety issues. Other initiatives, such as FDA's draft policy on major postmarket drug safety decisions and communication initiatives may help improve the clarity and effectiveness of the process, but they have not been fully implemented. FDA's dispute resolution processes to help resolve disagreements over safety decisions have not been used and may not be viewed as sufficiently independent. FDA is taking steps to identify additional data sources for postmarket drug safety studies, and expects to use additional funds for this purpose, but FDA still faces data constraints.

DSB May Provide Broad Oversight, but Systematic Tracking Is Still Needed

FDA's DSB, created in the spring of 2005, may help provide oversight of important, high-level safety decisions within CDER; however, there is still a need for systematic tracking of ongoing safety issues. FDA established the DSB to help provide independent oversight and advice to the CDER Director on the management of important safety issues. The DSB reports directly to the head of CDER and consists primarily of FDA officials from

⁵⁵See D. Carpenter, "A Proposal for Financing Postmarketing Drug Safety Studies By Augmenting FDA User Fees," *Health Affairs*—Web Exclusive, <http://content.healthaffairs.org/cgi/content/full/hlthaff.w5.469/DC1> (downloaded October 18, 2005).

within CDER and other FDA centers. According to an FDA policy document, the DSB includes 11 voting members from CDER, with 3 representatives from ODS and 3 from OND. Currently the OND and ODS Directors are voting members. It also includes representatives from other federal agencies.⁵⁶ DSB members who conducted the primary preapproval review of the drug or who were involved with a drug's approval or postmarket safety review will not be allowed to vote on issues concerning that drug. As of February 2006, the DSB was meeting regularly and an FDA official told us that it is expected to meet monthly. The meetings are not open to the public, but FDA posts abbreviated summaries of the meeting minutes on its Web site.⁵⁷

According to an FDA policy document, the DSB will identify, track, and oversee the management of important drug safety issues. Important drug safety issues include serious side effects identified after a drug's approval that have the potential to significantly alter the drug's benefit-to-risk analysis or significantly affect physicians' prescribing decisions. According to an FDA official, ODS and OND submit monthly reports of safety issues for discussion by the DSB to be used in setting the agenda for the meetings. In addition, at any time individuals within and outside of FDA can submit issues to be considered by contacting a DSB member or the executive director. The FDA official said that the DSB will not be involved in the ongoing process of postmarket surveillance and decision making about drug safety issues, but rather will be involved with ensuring that broader safety issues—such as ongoing delays in changing a label—are effectively resolved. The DSB may also develop standards for certain kinds of safety-related actions, such as when a drug warrants a boxed warning or a medication guide.⁵⁸ The FDA official acknowledged that safety-related decisions are still based on individual judgments and lack consistency. The

⁵⁶According to FDA policy documents, the DSB will have representation from outside FDA, including a member from another HHS agency (for example, National Institutes of Health) and a non-HHS health care providing agency (for example, Department of Veterans Affairs). The board may also consult with other scientific experts and representatives of patient and consumer groups as needed.

⁵⁷FDA also makes information publicly available concerning certain emerging safety information through its Web page, which reflects the input of the DSB.

⁵⁸Used primarily for outpatient drugs that have serious safety concerns, medication guides are required to be dispensed with each prescription. They contain safety information specifically for the patient, such as the most important information the patient should know about a drug.

DSB has plans to form subcommittees to look at policy development in this and other areas.

The DSB may help provide high-level oversight of safety issues, but it does not address the problem of the lack of systematic tracking of safety issues and their resolution. Information about the resolution of safety issues identified by ODS staff is still not available to ODS management nor to the DSB.

Other Process and Organizational Initiatives Are Promising, but Not Fully Implemented

FDA's draft policy on major postmarket drug safety decision making and other process and organizational initiatives may make the process clearer and more effective, but these efforts have not been fully implemented. Several years ago, FDA drafted a policy entitled "Process for Decision-Making Regarding Major Postmarketing Safety-Related Actions" that could help improve the decision-making process, but as of February 2006, this policy has not been finalized and implemented. The draft policy was designed to ensure that all major postmarket safety recommendations, such as the market withdrawal of a drug, would be discussed by involved CDER managers, starting at the division level.⁵⁹ The draft policy states that CDER staff, including ODS staff, are to write a detailed memorandum describing their recommendation for a major safety action.⁶⁰ If the immediate supervisor disagrees, he or she prepares a memorandum explaining the nature of the differences, and then the division director prepares a memorandum indicating how the issue should be resolved. In some cases the supervisor and division director may be the same person. A Division Consensus Meeting is to be convened for every recommendation regardless of whether there is initial agreement between the staff member making the recommendation and the supervisor and division director.⁶¹ The process stops at the division level if a decision is

⁵⁹According to the draft policy, major postmarket safety-related actions also include restrictions on a drug's distribution and boxed warnings. Some recommendations included in risk minimization action plans are also considered major postmarket safety-related actions under this draft policy, such as reminder systems that are intended to facilitate reduced-risk prescribing and use.

⁶⁰ODS staff (and staff from other consultant divisions) are to discuss their intended recommendation with the appropriate OND review division before drafting the memorandum. The draft policy states that these discussions are not intended to unduly influence the recommendation, but should be viewed as opportunities to exchange information and enhance communication.

⁶¹This meeting includes staff and managers from the involved divisions, such as the OND review division responsible for the drug and the ODS division making the recommendation.

reached that a major safety action is not needed.⁶² Otherwise, the recommendation is discussed at higher levels of management in CDER. An Office Action Meeting would then be held to recommend a course of action to the CDER director, although it is possible that there still could be disagreement at the office level. A final meeting, called the Decisional Meeting, would then be held to decide a course of action, and would include the CDER director as well as office- and division- level staff. It is not clear how the new DSB will be integrated into the draft policy on major postmarket drug safety decision making, and FDA officials told us they are still trying to determine how to do this.

Other initiatives may improve the decision-making process, but these efforts have not been fully implemented. For example, ODS has established a Process Improvement Team to assess the safety consult process, including how OND asks questions about postmarket safety concerns and how ODS should answer the questions. OND has established a similar team to assess the overall process for reviewing postmarket safety information, including the consult process. Both teams plan to make recommendations; for example, the OND representative chairing the OND team told us the OND team plans to recommend which office (OND or ODS) should have responsibility for certain postmarket tasks, such as reviewing periodic adverse event reports. According to the OND chair, the OND team expects to finalize its recommendations by the end of March 2006. According to the ODS Director, the ODS team's work was still in progress as of January 2006 and would not be completed for about 6 months. In February 2006, ODS established a new Process Improvement Team to identify best practices for safety evaluators in order to make sure there is standardization of their work (for example, reviewing of adverse event reports). The ODS Director estimated that the work of this team would be completed in 3 to 4 months.

FDA officials told us that they have proposed reorganizing CDER to dissolve OPaSS and have the director of ODS report to the CDER director. FDA plans to implement this reorganization in May 2006. In the meantime, ODS has taken some other steps to improve communication and oversight of safety issues. According to the ODS Director, the DDRE Director

⁶²Management above the division level, including the OND, ODS, and CDER directors, would be briefed about the matter even if division-level officials decide not to proceed with a safety action. The process would continue, however, if the CDER director does not agree with the decision that a major safety action is not needed. In addition, the process would continue if the decision is appealed.

recently instituted regular meetings between the safety evaluators in his division and the OND review divisions in order to discuss drug safety issues, including ongoing consults, issues that DDRE staff have not yet provided consultation on, and how safety issues have been resolved. According to the DDRE Director, over half of OND's review divisions have participated in these regular meetings to date. The Director of ODS also acknowledged that ODS needs to have a better way to track safety issues as they are emerging. He told us that ODS is developing a tracking system that is currently being tested and is expected to become operational in 2006. The Director also said he had plans to build up the immediate office of ODS by adding an associate director of operations and staff responsible for working on relationships with other federal agencies (for example, National Institutes of Health) and contractors. He has decided to hold regular meetings with the ODS deputy director and division directors for the specific purpose of discussing the status of drug safety problems.

Despite the efforts that FDA has made to improve its postmarket drug safety decision-making process, the role of ODS in advisory committee meetings (other than DSaRM) has not been clarified. The role of ODS in scientific advisory committee meetings is not discussed in the draft policy on major postmarket drug safety decisions or in other policy documents. In addition, according to the ODS Director, the role of epidemiologists in ODS requires further clarification. A Process Improvement Team that was formed to address this issue was suspended, and the ODS Director said that other ways to approach this issue are being evaluated.

Dispute Resolution Processes Have Not Been Used

The DSB and a pilot program have not been used as of February 2006 to help resolve organizational and individual disagreements that occur within CDER over safety decisions and may not be viewed as sufficiently independent. According to an FDA policy document, the DSB will resolve organizational disputes over approaches to drug safety. According to an FDA official, as of February 2006, however, the DSB had not handled any such formal disputes. An FDA official told us that, as an example, ODS might believe that a drug should come off the market but OND does not agree, and resolving this matter could be handled by the DSB. Although DSB members who were involved with a drug product's approval or safety review will be recused from the DSB's decision-making process concerning that drug, the current DSB membership includes CDER managers who oversee the drug approval and safety review processes, which may limit the ability of the DSB to provide neutral, independent advice in the handling of organizational disputes. In addition, decisions made by the DSB will serve as recommendations to the CDER director,

who is the final decision maker. This reporting chain may further limit the independence of the DSB since the CDER director manages the overall drug approval and safety review processes.

In addition to the DSB, a pilot program for dispute resolution procedures has not been used by CDER staff as of February 2006. In November 2004 FDA implemented a pilot program for dispute resolution that is designed for individual CDER staff to have their views heard when they disagree with a decision that could have a significant negative effect on public health, such as a proposed safety action or the failure to take a safety action. Any CDER employee can initiate the process, but the CDER ombudsman,⁶³ in consultation with the CDER director, determines whether a dispute warrants formal review. If the CDER director and ombudsman decide to proceed, the CDER director would establish a panel of three or four members, one of which the CDER employee initiating the process would nominate. The panel would review the case and make a recommendation to the CDER director, who would then decide how the dispute should be resolved. Like the DSB, the pilot program also does not offer employees an independent forum for resolving disputes. The CDER director decides whether the process should be initiated, appoints the chair of the panel, and is the final adjudicator.

FDA Is Taking Steps to Identify Additional Data Sources, but Constraints Remain

FDA is taking steps to identify additional data sources that it may obtain with its current authority and resources. In fiscal year 2006, FDA expects to use \$10 million for this purpose consistent with direction in the Conference Report accompanying FDA's fiscal year 2006 appropriation.⁶⁴ The Conference Report specified that a \$10 million increase over the prior year was provided for drug safety activities, including \$5 million for ODS and \$5 million for drug safety activities within CDER. The conferees intended for the increases to be used for FDA's highest-priority drug safety needs that were not funded in fiscal year 2005, such as acquiring access to additional databases beyond those that will be accessed through its new contracts.⁶⁵ The ODS Director told us that ODS plans to use the \$5 million

⁶³Created in 1995, the role of the CDER ombudsman includes investigating complaints and resolving issues and disputes. The CDER ombudsman receives complaints directly from the drug industry, the public, and CDER staff.

⁶⁴See H.R. Conf. Rep. No. 109-255, at 100 (2005) (accompanying H.R. 2744).

⁶⁵The conferees directed FDA to report to the Appropriations Committees on its proposed use of the funds. The report is currently under review within FDA.

to hire staff, specifically safety evaluators and technical support staff. The other \$5 million is to be used for postmarket drug safety work throughout CDER and those plans had not been finalized as of February 2006. The Director of ODS said that given the high cost of planning and conducting observational studies, only one or two studies can be funded each year.

According to the ODS Director, FDA has started to work with the Centers for Medicare & Medicaid Services to obtain access to data on Medicare beneficiaries' experience with prescription drugs covered under the new prescription drug benefit, which began in 2006. This data source may provide information about drug utilization for a very large population of Medicare recipients and can potentially be linked to claims data, providing information about patients' medical outcomes. According to the ODS Director, a team of ODS staff has been working with the Centers for Medicare & Medicaid Services to determine what data elements ODS would seek to access; however, it is uncertain how useful the data will be because there are potential data reliability issues. For example, it is unclear whether ODS will be able to do medical chart reviews to verify medical outcomes. Additionally, in April 2005 FDA requested information⁶⁶ from other organizations about their active surveillance programs⁶⁷ in the United States for identifying serious adverse events. In its request, FDA noted that it was seeking information related to these programs because active surveillance would strengthen and complement the tools it currently has to monitor postmarket drug safety. As an example, FDA noted interest in learning about systems that can identify specific acute outcomes for which a drug is frequently considered as a potential cause, such as acute liver failure and serious skin reactions. According to the ODS Director, a working group within ODS is currently evaluating the responses to the request for information; however, it is unlikely that they will fund any of these active surveillance systems in 2006 because FDA needs to ensure that such systems are able to identify drug safety concerns earlier compared to other data sources before the agency invests in them.

⁶⁶Department of Health and Human Services, Food and Drug Administration, Office of Acquisitions and Grants Services, "Request for Information on Active Surveillance Programs in the United States for the Identification of Clinically Serious Adverse Events Associated with Medical Products," published on April 11, 2005, <http://www.fbo.gov/servlet/Documents/R/1154711> (downloaded February 27, 2006).

⁶⁷Active surveillance has been defined by others as the regular periodic collection of case reports from health care providers or facilities. By contrast, passive surveillance refers to adverse event reports provided at the discretion of a health care provider.

The working group's review of the request for information was still ongoing as of March 2006.

Conclusions

Postmarket drug safety decision making at FDA is a complex process that sometimes results in disagreements, as observed in our case studies. Scientific disagreements may be expected in a large regulatory agency, especially given the different professional orientations of the key players, OND and ODS, and the inherent limitations of the available data. However, because of the potential public health consequences of FDA's decisions about postmarket drug safety issues, it is important to come to a decision quickly. In our review, we observed opportunities for improving the clarity and oversight of the process and strengthening the information used for decision making. FDA has recently made some important organizational and policy changes, but more could be done to improve management oversight of postmarket drug safety issues, to improve the dispute resolution process, and to strengthen the collaboration between OND and ODS. In order to address the serious limitations of the data, FDA will need to continue its efforts to develop useful observational studies and to access and use additional healthcare databases. However, even if FDA is successful in expanding its data sources for postmarket drug safety surveillance, it would still benefit from information from long-term clinical trials of certain drugs and the additional authority to require that these studies be carried out.

Matter for Congressional Consideration

To improve the decision-making process for postmarket drug safety, the Congress should consider expanding FDA's authority to require drug sponsors to conduct postmarket studies, such as clinical trials or observational studies, as needed, to collect additional data on drug safety concerns.

Recommendations for Executive Action

To improve the postmarket drug safety decision-making process, we recommend that the Commissioner of FDA take the following four actions:

- establish a mechanism for systematically tracking ODS's recommendations and subsequent safety actions;
- with input from the DSB and the Process Improvement Teams, revise and implement the draft policy on major postmarket drug safety decisions;
- improve CDER's dispute resolution process by revising the pilot program to increase its independence; and

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- clarify ODS's role in FDA's scientific advisory committee meetings involving postmarket drug safety issues.

Agency Comments and Our Evaluation

FDA reviewed a draft of this report and provided comments, which are reprinted in appendix V. FDA also provided technical comments, which we incorporated as appropriate.

FDA commented that our conclusions were reasonable and consistent with actions that it has already begun or planned. FDA did not comment on our recommendations. In addition, FDA made six comments about specific aspects of our draft report. First, concerning our description of the complexity of the postmarket decision-making process, FDA stated that the draft report implied the process is too complex and that FDA should not be criticized for its difficult task of weighing the risks and benefits associated with drugs with the data available to the agency. We agree with FDA that postmarket drug safety issues are inherently complex. For that reason, we believe that FDA needs to have greater clarity about how decisions are made and to establish more effective oversight of the decision-making process. Furthermore, we believe that our report fairly characterizes the limitations of the data that FDA relies on in this complex process. Because of the data limitations, we believe that FDA needs greater authority to access certain kinds of postmarket safety data. Second, FDA noted that factors other than PDUFA goals influence OND's work and its pace. FDA also stated that ODS plays a role in certain premarket safety activities and that PDUFA goals also apply to these activities. We clarified these points in the report. Third, FDA stated that referring to ODS as a consultant to OND understates the role of ODS in drug safety and that CDER considers ODS and OND to be equal partners in the identification and timely resolution of drug safety issues. As we stated in the draft report, we found that the central focus of the process is the iterative interaction between OND and ODS. Nonetheless, ODS does not have any independent decision-making responsibility while OND has the ultimate responsibility to make decisions about regulatory actions concerning the postmarket safety of drugs. Further, both OND and ODS refer to ODS reports on drug safety as consults. For these reasons, we believe that our description of ODS as a consultant to OND is accurate.

Fourth, FDA agreed with our statements about the role of the DSB and indicated that the DSB has reviewed current mechanisms for identifying safety issues and discussed ways to enhance the tracking of those issues. Fifth, FDA commented that our examples of ODS staff being excluded from advisory committee meetings imply that such disagreements occur

frequently. FDA stated that this is not the case, and that OND and ODS work cooperatively in the vast majority of cases. However, our work demonstrates a need for further clarification of ODS's role. Finally, FDA commented that our case study chronology for Arava was incomplete because it did not describe two meetings. We provided additional clarification in the report about the meetings in the chronology for Arava.

As we agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days from the date of this letter. We will then send copies to others who are interested and make copies available to others who request them.

If you or your staffs have any questions about this report, please contact me at (202) 512-7119 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix VI.



Marcia Crosse
Director, Health Care

Appendix I: Regulatory History and FDA Decision-making Process for Arava

Background and Summary

Arava was approved for marketing in 1998. Arava is indicated in adults for the treatment of active rheumatoid arthritis to reduce the signs and symptoms of the disease, slow down damage to joints, and improve physical function. Arava has been associated with cases of serious liver injury, some of which have been fatal.

In this case, the Office of Drug Safety (ODS)¹ identified a serious safety signal—hepatic failure and fatal hepatitis—associated with Arava in March 2001. A citizen’s petition in 2002 spurred further inquiry into the issue. An ODS analysis of adverse event reports concluded that Arava was associated with a substantial increased risk of liver failure and recommended removal from the market, but the Office of New Drugs (OND) disagreed. OND established an internal panel of senior staff and hired outside consultants to further review the reports of liver failure, and both the panel and outside consultants concluded that in most cases Arava was not causally related to liver failure. In 2003 a Food and Drug Administration (FDA) advisory committee meeting was held to discuss Arava and ODS staff were not allowed to present their analysis. FDA approved revised labeling of Arava in 2003 that strengthened the drug’s warnings, and it remained on the market as of February 2006.

Chronology

September 1998

FDA approved Arava for marketing. At approval there was a known risk of liver toxicity (hepatotoxicity); in clinical trials Arava was associated with elevated liver enzymes in a significant number of patients. This information was included in the original label.

March 2001

During routine surveillance of incoming adverse event reports, an ODS safety evaluator had identified 11 cases of hepatic failure and fatal hepatitis associated with the use of Arava. The safety evaluator recommended that Arava’s label mention more extensive liver damage, such as liver-related fatalities. The ODS Division Director who reviewed the consult concurred with the findings and recommendation, but the OND Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug

¹The names of the postmarket safety and new drug offices changed during the time period studied. For the sake of clarity and consistency we used ODS and OND—the current names—when referring to these offices.

	<p>Products² did not. OND did not agree with the findings or recommendation because officials were uncertain about the causal relationship between Arava and liver damage in the case reports and they believed that the current label was adequate for communicating risk about hepatotoxicity.</p>
March 2002	<p>Public Citizen, a national nonprofit public interest organization, filed a petition requesting that FDA immediately remove Arava from the U.S. market. Public Citizen said that a significantly higher number of serious adverse events, including fatal liver toxicity, had been associated with Arava, compared with another drug used to treat patients with rheumatoid arthritis. In response to the petition, OND requested that ODS review postmarket data for serious hepatic events and liver failure since the approval of Arava.</p>
August 2002	<p>ODS and OND staff met to discuss ODS's preliminary work in response to the Public Citizen request. ODS's preliminary review concluded that Arava was associated with a substantially increased risk for acute liver failure and recommended removal from the market. OND disagreed with the review.</p>
October 2002	<p>Because of the disagreements about causality, OND established a panel of senior-level Center for Drug Evaluation and Research (CDER) staff, which included managers from OND and ODS. The panel met twice to review U.S. postmarket reports of 16 cases of acute liver failure and to vote on the probability that Arava caused the liver injury. The majority of panel members voted that Arava was likely to be causally related to liver failure in only 2 of the cases.</p>
November 2002	<p>ODS staff finalized their review on Arava and sent the consult to OND. The report included the recommendation to remove Arava from the market because the authors believed that the risks of Arava greatly exceeded its benefits³ and because the available risk management strategies (for example, label changes and periodic liver enzyme monitoring) had been shown to be ineffective in minimizing risk for other drugs. The ODS Division Director who reviewed the consult concurred with the findings</p>

²This division is now called the Division of Anesthesia, Analgesia, and Rheumatology Products.

³This conclusion was based on an analysis of Adverse Event Reporting System (AERS) reports, the usage of Arava in the population, and a review of the literature and efficacy from preapproval clinical trials.

and recommendation. The ODS Director and the Office of Pharmacoepidemiology and Statistical Science (OPaSS) Director also reviewed the consult. Both disagreed with the findings and recommendation.

December 2002

At the request of OND, an ODS safety evaluator reviewed adverse event reports of liver injury associated with Arava from outside the United States. The ODS safety evaluator, who did not work on the prior analysis of the U.S. cases, analyzed 13 cases of liver failure and concluded that there was a possible association between the use of Arava and the development of liver failure. The safety evaluator also concluded that these findings were consistent with the earlier ODS findings in the 16 U.S. liver failure cases. The ODS Division Director who reviewed the consult concurred with the findings.

Because of the disagreement on Arava's safety, OND had hired outside consultants, including two hepatologists, to further review Arava's safety profile. The hepatology consultants completed their analysis, which included a review of the U.S. reports of acute liver failure, by mid-December 2002. They identified no definite cases of Arava-induced liver failure, but found some cases to be possibly related to Arava.

March 2003

FDA's Arthritis Advisory Committee met to review Arava's benefit-to-risk profile and ways to improve risk management, and to discuss whether Arava should be approved for a claim of improvement in physical function. OND presented its own analysis of the postmarket safety data,⁴ and did not allow ODS staff to present their analysis of postmarket safety data. A former OND manager told us that OND believed that the ODS analysis did not have scientific merit.

FDA's Advisory Committee voted unanimously that Arava's benefits in rheumatoid arthritis outweighed its potential risks and that its risks were no greater than other similar drugs. The committee also voted that Arava should be approved for a claim of improvement in physical function.

ODS's epidemiologists and safety evaluators submitted a letter to the ODS and OPaSS Directors, expressing their concerns with the Arthritis Advisory Committee meeting. They recommended that ODS staff should

⁴The presentation also included a summary of data from other sources including the sponsor, and an analysis of AERS called data mining.

present postmarket safety data at advisory committee meetings and that there should be a policy that defines the role of ODS at all advisory committee meetings involving postmarket safety issues.

CDER's Director and Deputy Director sent a memo about ODS's November 2002 consult to the ODS Director, an ODS Division Director, and the OPaSS Director. The memo criticized the quality of ODS's consult and stated that ODS had analyzed postmarket data on Arava with a "bias toward concluding that the risk is as large as possible." The memo also included the general expectations for an ODS consult. For example, it stated that consults should include a summary of the strengths and weaknesses of the analytic approach used to evaluate postmarket data.

June 2003

FDA approved revised labeling of Arava to support the claim of improved physical function. The revised labeling also stated that rare cases of severe liver injury, including cases with fatal outcomes, had been reported in Arava users. OND decided that although the liver toxicity risk was very rare, the accumulated evidence provided support for strengthening the warnings on the label.

OND asked the sponsor to submit liver-related adverse events within 15 days rather than annually, on the basis of an ODS request.

October 2003

The sponsor issued a Dear Healthcare Professional letter explaining the labeling changes approved in June 2003.

March 2004

Information was added to Arava's label about the use of Arava in pediatric populations, including instances of liver-related adverse reactions from pediatric study reports.⁵

FDA sent a letter to Public Citizen denying its request to remove Arava from the U.S. market.

⁵FDA requested information about the use of Arava in children from its sponsor, on the basis of the Pediatric Research Equity Act of 2003.

Appendix II: Regulatory History and FDA Decision-making Process for Baycol

Background and Summary

Baycol was approved for marketing in 1997. Baycol is a member of the class of drugs known as statins that lower cholesterol levels in the body. Baycol was associated with rhabdomyolysis, a severe adverse reaction involving the breakdown of muscle fibers, which can lead to death.

In this case, the Office of Drug Safety (ODS) and the Office of New Drugs (OND) agreed from the outset (spring 2001) that adverse event reports received for high-dose Baycol were alarming.¹ At the request of OND, ODS conducted an analysis that verified the increased safety risk associated with Baycol, but it did not make specific recommendations for action. Shortly thereafter, OND and ODS met with the sponsor and the Food and Drug Administration (FDA) communicated to the sponsor that it was considering withdrawing the high-dose Baycol from the market. In August 2001 the sponsor voluntarily withdrew all doses of Baycol.

Chronology

June 1997

FDA approved Baycol for marketing (doses up to 0.3 mg).² The original label stated that rhabdomyolysis had been reported with the use of other statins.

January 1999

FDA approved a change in the warnings section of Baycol's label to indicate that rare cases of rhabdomyolysis had been reported with Baycol and other drugs in the class. FDA also approved adding a new subsection—postmarketing adverse event reports (including rhabdomyolysis)—to the label.

May 1999

FDA approved the 0.4 mg dose of Baycol.

December 1999

FDA approved a change in Baycol's label, requested by the sponsor, to include a contraindication with gemfibrozil (a member of a class of drugs called fibrates, which also lower cholesterol). The combined use of Baycol and gemfibrozil was contraindicated because of the risk for rhabdomyolysis. The sponsor issued a Dear Healthcare Professional letter shortly thereafter, explaining the labeling changes.

¹The names of the postmarket safety and new drug offices changed during the time period studied. For the sake of clarity and consistency we used ODS and OND—the current names—when referring to these offices.

²The sponsor only marketed the 0.2 and 0.3 mg doses in the United States.

June 2000	At the request of OND's Division of Endocrine and Metabolic Drug Products, ³ ODS completed a postmarketing safety review of rhabdomyolysis resulting from the combined use of statins and fibrates. OND requested the review because sponsors of other statins (not Baycol) were seeking over-the-counter status for their drugs. ODS safety evaluators and an epidemiologist analyzed reports from the Adverse Event Reporting System (AERS) and calculated reporting rates of rhabdomyolysis for Baycol and other statins when taken alone, and in combination with gemfibrozil. The reporting rate for Baycol combined with gemfibrozil was higher than that of other statins combined with gemfibrozil. But the reporting rate for Baycol alone was only slightly higher compared with the other statins. On the basis of their findings and the severity of rhabdomyolysis as a clinical diagnosis, the ODS staff recommended that the statins not be granted over-the-counter designation. The ODS Division Director who reviewed the consult concurred. In agreement with ODS's position, OND decided to discuss with the sponsor sending stronger messages to healthcare professionals about the adverse reaction.
July 2000	FDA approved the 0.8 mg dose of Baycol.
November 2000	FDA approved the addition of a patient package insert for Baycol. ⁴
April 2001	An ODS safety evaluator contacted the OND medical officer responsible for Baycol about reports of fatal rhabdomyolysis associated with Baycol, especially at the 0.8 mg dose, since ODS's last consult in 2000. The medical officer agreed the data were alarming and asked for more analysis. At about the same time, the sponsor notified OND about a dose-related occurrence of adverse events.
May 2001	FDA approved several revisions to labeling for Baycol, including an emphasis that the correct starting dose of Baycol should be 0.4 mg because of the increased risk of rhabdomyolysis at higher doses. The

³The Division of Endocrine and Metabolic Drug Products is now called the Division of Metabolism and Endocrinology Products.

⁴A patient package insert is an additional part of the professional labeling of a drug that provides important information to the consumer and may be distributed to patients when the drug is dispensed. It is required for a few drugs, such as oral contraceptives, and voluntary for other drugs.

sponsor issued a Dear Healthcare Professional letter explaining the changes.

July 2001

OND and ODS staff met with the sponsor to discuss concerns over the safety of Baycol. An ODS epidemiologist presented an analysis of fatal cases of rhabdomyolysis associated with the 0.8 mg dose of Baycol compared with Lipitor, another statin, and compared with the 0.4 mg dose of Baycol. ODS found that the risk of fatal rhabdomyolysis was higher for Baycol than for Lipitor. ODS also found that the risk appeared to be dose-related, with twice as many of the fatalities among patients taking the highest daily dose—0.8 mg—of Baycol (without concomitant gemfibrozil) compared with the lower dose—0.4 mg.⁵

At the meeting, FDA communicated to the sponsor that it was considering several safety actions to address its concerns about Baycol, including the withdrawal of the 0.8 mg dose, and a boxed warning with information about not exceeding a dosage of 0.4 mg daily and a contraindication with gemfibrozil.

August 2001

OND and ODS staff met with the sponsor again to discuss their ongoing concerns over the safety of Baycol, particularly concerns about the risk of rhabdomyolysis at higher doses or in combination with gemfibrozil. The sponsor proposed to (1) voluntarily withdraw the 0.8 mg dose in the United States, (2) add a boxed warning on the label about not exceeding a dose of 0.4 mg daily, and (3) add a boxed warning on the label for contraindicated use of Baycol and gemfibrozil. FDA asked the sponsor for a comprehensive analysis of the 0.4 mg dose.

A week later, FDA announced that the sponsor voluntarily withdrew all doses of Baycol from the United States market and the sponsor issued a Dear Healthcare Professional letter explaining its decision.

⁵ODS's analysis was finalized on August 17, 2001. It did not contain a recommendation for regulatory action. The safety review included a critique of two epidemiologic studies that the sponsor conducted to examine the risk of myopathy (for example, muscle aching or muscle weakness) subsequent to statin use in a managed care organization, using its automated claims data. The ODS staff who wrote the consult concluded that the studies did not alleviate the concerns raised by the spontaneous report data. The Acting Division Director of ODS who reviewed the consult concurred with the review.

Appendix III: Regulatory History and FDA Decision-making Process for Bextra

Background and Summary

Bextra was approved for marketing in 2001. Bextra was part of the class of drugs known as the COX-2 selective nonsteroidal anti-inflammatory drugs (NSAID). Bextra was approved to relieve the symptoms of osteoarthritis and rheumatoid arthritis in adults, and to relieve painful menstrual cycles. Bextra was associated with serious, potentially fatal skin reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis. Bextra was also later associated with an increased risk of serious cardiovascular events, similar to the other approved COX-2 drugs.

In this case, after the Office of Drug Safety (ODS)¹ did an analysis of serious skin reactions associated with Bextra in 2002, Bextra's label was modified. ODS continued to do a series of analyses of adverse events associated with Bextra from 2003 to 2004, recommending in 2004 that there be a boxed warning, the most serious warning, on the label, but the Office of New Drugs (OND) disagreed. OND changed its position after ODS did a comparison, at OND's request, of Bextra's rate of serious skin reactions with the reporting rates of other similar drugs. A boxed warning was added to Bextra's label in late 2004. In February 2005, two scientific advisory committees that met primarily about the cardiovascular risks associated with the COX-2 NSAIDs voted that Bextra's overall risk-to-benefit profile supported continued marketing. But a few months later the Food and Drug Administration (FDA) came to a different conclusion and announced that the overall risk-to-benefit profile of Bextra was not favorable, and as a result requested that it be withdrawn from the market, which it was in April 2005.

Chronology

November 2001

FDA approved Bextra for marketing.

September 2002

The sponsor had identified the occurrence of serious skin reactions, proposed adding information about this risk to the label, and proposed issuing a Dear Healthcare Professional letter. At the request of OND's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products,²

¹The names of the postmarket safety and new drug offices changed during the time period studied. For the sake of clarity and consistency we used ODS and OND—the current names—when referring to these offices.

²The Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products is now called the Division of Anesthesia, Analgesia, and Rheumatology Products.

ODS staff reviewed reports of serious skin reactions in the Adverse Event Reporting System (AERS) for Bextra. They compared Bextra's reporting rate of serious skin reactions with rates for Vioxx and Celebrex (other COX-2 NSAIDs), and the incidence in the general population. The ODS staff agreed that the label should be changed and that a Dear Healthcare Professional letter should be issued because the rates for Bextra were higher than those for Vioxx, Celebrex, and the general population. The ODS Division Director that reviewed the consult and OND concurred with the findings.

November 2002

FDA announced an updated label describing the risk for serious skin reactions associated with Bextra and that Bextra was contraindicated in patients with histories of allergic reactions to sulfa, a substance that Bextra contains. The sponsor issued a Dear Healthcare Professional letter explaining the updated label.

April 2003

The Division of Pediatrics and Therapeutics³ had asked ODS for a recommendation on whether Bextra should be studied in pediatric populations for the treatment of acute pain, as proposed by the sponsor. ODS staff recommended that Bextra not be studied in pediatric populations because of its risk of serious skin reactions in the adult population. In addition, ODS staff analyzed data from the National Center for Health Statistics and found that serious skin reactions generally occur more commonly in children than adults. The ODS Acting Division Director that reviewed the consult agreed with the analysis and recommendation as did the Division of Pediatrics and Therapeutics. However, OND disagreed with the recommendation and supported the study of Bextra in pediatric populations because staff in OND felt this drug could have value in certain pediatric populations, such as patients who cannot tolerate other NSAIDs. Ultimately, Bextra was not studied in children in part because, according to a former OND manager, OND deferred to ODS's judgment on this recommendation.

July 2003

ODS staff updated their original analysis and concluded that the reporting rates for serious skin reactions associated with Bextra remained markedly elevated above the incidence in the general population and above the rates for Celebrex and Vioxx. ODS staff recommended adding another skin

³This division is now called the Division of Pediatric Drug Development and is located within CDER's Office of Counter-Terrorism and Pediatric Drug Development. This division has responsibility for determining what kinds of pediatric studies are needed to develop information about certain marketed drugs, such as the appropriate dosing for pediatric use.

reaction to the warnings in the label and the ODS Acting Division Director that reviewed the consult concurred. Although OND did not respond to the consult, a former OND manager told us that it would not have been important to add this skin reaction to the label since the label already included the most severe forms of skin reactions.

March 2004

ODS staff updated their assessment of the risks of serious skin reactions associated with Bextra, on the basis of additional AERS reports, and commented on a risk management plan submitted by the sponsor. They recommended to OND several stronger safety actions, including a boxed warning and a medication guide,⁴ because the risk remained elevated compared with the incidence in the general population and relative to Celebrex and Vioxx (for example, 13-fold relative to Vioxx). The ODS staff stated that very little was known about the risk factors for serious skin reactions, making them difficult to avoid. In addition, they recommended that OND consider the clinical circumstances in which Bextra had a favorable benefit-to-risk profile relative to other treatment alternatives. Two ODS Division Directors that reviewed the consult concurred, but OND did not agree that Bextra needed stronger safety actions at this time.

April 2004

Bextra's label was changed to include the statement that fatalities due to serious skin reaction had been reported.

June 2004

At the request of OND, ODS staff compared Bextra's reporting rate of serious skin reactions with an antibiotic drug's reporting rate because both Bextra and the antibiotic contained sulfa and both drugs were contraindicated in patients with known allergies to sulfa. ODS staff compared the reporting rates, but indicated in their consult that it was inappropriate to compare an antibiotic marketed for more than 30 years and was used for acute, potentially life-threatening illnesses with a recently marketed pain reliever that was generally used for a chronic non-life-threatening illness. The ODS Division Director that reviewed the consult concurred. However, the OND medical officer involved in the case maintained it was an appropriate comparison. ODS staff found a higher reporting rate for serious skin reactions associated with Bextra when compared with the rate for the antibiotic drug.

⁴Used primarily for outpatient drugs that have serious safety concerns, medication guides are required to be dispensed with each prescription. They contain information specifically for the patient, such as the most important information the patient should know about a drug.

August 2004	At the request of OND, ODS staff compared Bextra's rate of serious skin reactions with the reporting rates of Celebrex, Vioxx, and Mobic, anti-inflammatory drugs that are used to treat arthritis. ODS staff concluded that Bextra's reporting rate continued to be elevated compared with the other drugs, including Mobic, which had no reported cases of serious skin reactions. As a result of this analysis, and the reports of death (at least four deaths have been associated with Bextra), OND asked Bextra's sponsor for a boxed warning about this risk, which it previously did not support.
October 2004	The sponsor issued a Dear Healthcare Professional letter summarizing the serious skin reactions associated with Bextra and stated that it had proposed an updated label to FDA to expand previous warnings about the skin reactions.
December 2004	FDA announced that Bextra would carry a boxed warning for serious skin reactions. ⁵ The sponsor also issued a Dear Healthcare Professional letter explaining these changes.
February 2005	A joint meeting of FDA's Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held. The meeting was focused primarily on the cardiovascular risks of the COX-2 selective NSAIDs, including Bextra. The advisory committees voted (17 yes, 13 no, 2 abstentions) that Bextra's overall risk-to-benefit profile supported continued marketing.
April 2005	After reviewing information from multiple sources, which included specific votes and recommendations that the advisory committees made in February 2005, FDA announced its conclusion that Bextra's overall risk-to-benefit profile was not favorable and, as a result, requested that the sponsor voluntarily withdraw Bextra from the market. ⁶ FDA concluded that in addition to its cardiovascular risk (similar to the other COX-2 drugs), Bextra already carried a boxed warning for serious skin reactions. While the other COX-2 drugs also had a risk for these serious skin reactions, the reporting rate appeared to be greater for Bextra. In addition,

⁵A new warning regarding Bextra's cardiovascular risk was also added to Bextra's label at this time.

⁶FDA posted a memo on its Web site, written by the Directors of OND and OPaSS, explaining why FDA decided to ask Bextra's sponsor to withdraw the drug from the market.

the occurrence of the skin reactions was unpredictable, for example, occurring after both short- and long-term use, making attempts to manage this risk difficult. Also, there were no data supporting a unique therapeutic benefit for Bextra over other available NSAIDs, which could have offset the increased risk of serious skin reactions.

The sponsor agreed to withdraw the drug in the United States.

Appendix IV: Regulatory History and FDA Decision-making Process for Propulsid

Background and Summary

Propulsid was approved for marketing in 1993. Propulsid was indicated for use in adults for the symptomatic relief of nighttime heartburn due to gastroesophageal reflux disease. Propulsid was associated with serious cardiac arrhythmias, including reports of death, and most of these adverse events occurred in patients who were taking other medications or suffering from underlying conditions known to increase the risk of cardiac arrhythmia.

In this case there was general agreement about the safety concern between the Office of New Drugs (OND) and the Office of Drug Safety (ODS),¹ but differing opinions within the Food and Drug Administration (FDA) over what safety actions should be taken regarding the drug. In 1997 FDA decided to continue to work with the sponsor to make changes to the drug's label, which included a boxed warning, but some staff felt stronger actions were needed. An FDA-supported study later found that the boxed warning did not significantly deter use of the drug with contraindicated drugs or medical conditions. During this case, a task force within FDA was formed to help evaluate Propulsid's safety and efficacy, and ODS staff conducted numerous analyses and made multiple recommendations for stronger safety actions, including a market withdrawal. The sponsor voluntarily removed the drug from the market in 2000. Propulsid is currently available through a limited-access program to ensure that only certain patients receive the medication.

Chronology

July 1993

FDA approved Propulsid for marketing in tablet form.

January 1995

The sponsor submitted information to the Center for Drug Evaluation and Research (CDER) about reports of cardiac arrhythmias associated with the use of Propulsid. Subsequently, an ODS safety evaluator identified and reviewed 12 reports of torsade de pointes² in FDA's MedWatch Spontaneous Reporting System (SRS)³ and identified potential risk factors, including cardiac history and the concomitant use of several other drugs.

¹The names of the postmarket safety and new drug offices changed during the time period studied. For the sake of clarity and consistency we used ODS and OND—the current names—when referring to these offices.

²Torsade de pointes is a type of serious cardiac arrhythmia.

³FDA now maintains adverse event reports in the Adverse Event Reporting System (AERS).

OND's Division of Gastrointestinal and Coagulation Drug Products⁴ agreed with ODS that this was a safety concern.

February 1995

Propulsid's label was revised to state that it was contraindicated with certain other drugs⁵ which, when taken with Propulsid, can increase the concentration of Propulsid and lead to arrhythmias. A clinical study conducted by the sponsor provided this evidence. The label was also revised to include information about other risk factors, including a history of cardiac disease. The sponsor issued a Dear Healthcare Professional letter with similar information.

September 1995

FDA approved Propulsid for marketing in liquid form.

A boxed warning was added to Propulsid's label, specifying its contraindication with other drugs. The boxed warning also included the statement that some of the reported adverse events had resulted in death. The sponsor issued a Dear Healthcare Professional letter in October with similar information.

January 1996

An ODS epidemiologist identified and analyzed 46 adverse event reports of patients who developed serious cardiac arrhythmias while using Propulsid, from July 1993 through early October 1995, and concluded that many patients who developed arrhythmias had histories of cardiac and renal conditions. Most patients who developed arrhythmias were not taking contraindicated medications; as a result, the epidemiologist concluded that Propulsid may itself cause arrhythmias.⁶ The epidemiologist recommended that risk factors, such as histories of significant cardiac and renal disease, should be displayed in the label's warning with the same emphasis as the contraindicated drugs. The ODS Division Director concurred with the consult.

August 1996

At the request of OND, an ODS safety evaluator searched SRS for all adverse event reports associated with Propulsid in children aged 19 years and younger. Although Propulsid was not approved for use in children, it had been prescribed to children (for example, in newborn infants for

⁴The division is now called the Division of Gastroenterology Products.

⁵Nizoral tablets, Sporanox capsules, Monistat IV, and Tao capsules were contraindicated with Propulsid.

⁶A few reports and studies in the medical literature also suggested that Propulsid may cause cardiac arrhythmias.

feeding problems such as reflux). Six children were reported to have had cardiac arrhythmias with the use of Propulsid and several other children had other cardiovascular events. The safety evaluator also reported that the estimated usage of Propulsid in children was increasing steadily.

FDA rejected the sponsor's application for a pediatric indication for Propulsid.

June 1997

OND established a task force within FDA to evaluate the safety and efficacy of Propulsid. The task force included members from OND and ODS. At its initial meeting, the task force decided to gather information from several sources, including the reviews done by ODS, in order to accurately assess the safety of Propulsid.

August 1997

As agreed in the June 1997 Propulsid task force meeting, an ODS epidemiologist reviewed adverse event reports of Propulsid users with serious arrhythmias. The epidemiologist found that in about half of the cases, patients had taken contraindicated drugs with Propulsid and that a high proportion of the remaining cases had medical problems that may have predisposed them to arrhythmias. The epidemiologist recommended that the risk factors, such as predisposing medical problems, should be displayed in the label's warning with the same emphasis as the contraindicated drugs and that the recommended dosage should not be exceeded. The ODS Division Director who reviewed the consult concurred.

September 1997

The task force on Propulsid met for the second time. The group discussed information that was gathered on the safety of Propulsid. An ODS epidemiologist summarized her August 1997 consult, including her recommendation that predisposing medical problems should be displayed in the label's warnings similar to the contraindicated drugs and that the recommended dosage should not be exceeded. She also noted that Propulsid was primarily being prescribed for off-label use.⁷ Other relevant studies were discussed, including a clinical trial study where 3 out of 32 healthy elderly volunteers had abnormal electrocardiogram results after exposure to Propulsid alone.

⁷Any use of a drug not described in the label is termed off-label use.

October 1997	An ODS safety evaluator reported that there were additional cases of serious, cardiovascular adverse events among children who were prescribed Propulsid.
November 1997	FDA approved a rapidly disintegrating tablet form of Propulsid for marketing. The task force on Propulsid met and decided to seek further input from a CDER-wide group about pursuing the following regulatory actions: adding the risk for cardiac arrhythmias with the use of Propulsid alone (for example, without taking contraindicated drugs) to the label; holding an advisory committee meeting; and withdrawing approval of all Propulsid formulations.
December 1997	OND's Division of Gastrointestinal and Coagulation Drug Products consulted another OND division that was responsible for the drug Seldane to find out what information would be required to withdraw the approval of a drug since FDA had initiated proceedings to withdraw its approval of Seldane in 1996 for a similar cardiovascular side effect. That division recommended that data be gathered to support the assertion that Propulsid was still being coprescribed with contraindicated drugs despite the boxed warning and Dear Healthcare Professional letters. At the request of OND, an ODS epidemiologist evaluated the sponsor's epidemiological study on risk of serious cardiac arrhythmias among Propulsid users. In this study the researchers concluded that serious cardiac arrhythmias were not associated with Propulsid. The ODS epidemiologist outlined several major limitations with the study, including the potential for the misclassification of arrhythmia in patients not diagnosed by an electrocardiogram. A meeting was held in CDER to discuss FDA's regulatory options for Propulsid. This meeting included some senior-level managers in CDER and an FDA attorney. The OND medical officer responsible for Propulsid presented his concerns, including his conclusion that Propulsid should be removed from the market. Proceeding with a withdrawal from the market was discussed at the meeting. FDA continued to work with the sponsor to change Propulsid's label. Some staff believed that stronger safety actions were needed.
May 1998	An ODS epidemiologist summarized reports of 186 patients who developed serious cardiac disorders and arrhythmias (including deaths) with and without contraindicated drugs from July 1993 through early May 1998. The

ODS epidemiologist recommended to OND that the boxed warning should state that serious arrhythmias had occurred in Propulsid users who had not been taking contraindicated drugs, and that an accompanying Dear Healthcare Professional letter should be issued.

The ODS epidemiologist also recommended that Propulsid's labeling should state that the safety and effectiveness of Propulsid had not been demonstrated in pediatric patients for any indication.

June 1998

FDA announced revisions to the boxed warning that strengthened its warnings and precautions, and the sponsor issued a Dear Healthcare Professional letter explaining the revisions. The changes included the statement that Propulsid was contraindicated in patients with medical problems known to predispose them to arrhythmias, such as heart disease. The revision also stated that other therapies for heartburn should be used before Propulsid, and that the safety and effectiveness in pediatric patients had not been established. Also, the revised boxed warning included the statement that cardiac adverse events, including sudden death, had occurred among Propulsid users who were not taking contraindicated drugs.

July 1998

An ODS epidemiologist summarized cardiac adverse event reports from the beginning of Propulsid's marketing (July 1993) through May 1998. There were 187 reports, including 38 deaths.

November 1998

FDA implemented a medication guide⁸ and unit-dose packaging⁹ for Propulsid.

May 1999

An ODS epidemiologist worked on a study to evaluate labeling compliance among Propulsid users, which was carried out through ODS's cooperative agreement program. The study ultimately found that the boxed warning

⁸Used primarily for outpatient drugs that have serious safety concerns, medication guides are required to be dispensed with each prescription. They contain information specifically for the patient, such as the most important information the patient should know about a drug.

⁹Unit-dose packaging includes a single dose, individually packaged and labeled. According to an FDA official, this type of packaging is believed to help prevent medication errors.

did not significantly deter the use of Propulsid with contraindicated drugs or medical conditions.¹⁰

June 1999

The sponsor issued a Dear Healthcare Professional letter with information about revisions to the boxed warning. The revisions included two new contraindications and a new drug interaction. Similar revisions were incorporated into the medication guide.

An ODS epidemiologist analyzed and summarized the reports of Propulsid users who developed cardiovascular problems, including deaths, in four separate consults. The reports included adult and pediatric patients who took Propulsid with and without contraindicated drugs and medical conditions. The ODS epidemiologist recommended to OND that other contraindications should be added to the label, including one for patients with structural heart defects.

The ODS epidemiologist recommended that OND consider several safety actions, including asking the sponsor to conduct a clinical or epidemiological study on the association between Propulsid and cardiac adverse events in its users, and removing Propulsid from the market.

November 1999

ODS and OND staff and the CDER Director met to discuss further options for regulatory actions. It was decided that FDA would hold a public advisory committee meeting to discuss ways to reduce the occurrence of adverse events with Propulsid. The preliminary results of the cooperative agreement study were going to be presented at the advisory committee meeting.

January 2000

FDA announced further revisions to the boxed warning and that a public advisory committee meeting was scheduled for April. The label revision included new recommendations for performing diagnostic tests and a new contraindication for patients with electrolyte disorders. Similar revisions were incorporated into the medication guide. The sponsor issued a Dear Healthcare Professional letter explaining these revisions.

¹⁰The study was published in 2000. See W. Smalley, D. Shatin, D.K. Wysowski, et al., "Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action," *Journal of the American Medical Association*, vol. 284, no. 23 (2000).

March 2000	FDA announced that the sponsor would withdraw Propulsid from the U.S. market as of July 14, 2000. ¹¹ FDA also announced that its scheduled public advisory committee meeting was cancelled.
April 2000	The sponsor announced that it would make Propulsid available to certain patients through an investigational limited-access program, approved by FDA.
March 2002	An ODS epidemiologist summarized reports of adverse events, including cardiovascular events, among patients enrolled in the limited-access program. The epidemiologist recommended that the availability of Propulsid should not be expanded from the limited-access program to a restricted distribution. The ODS Division Director who reviewed the consult agreed. The drug's availability was not expanded.

¹¹In April 2000, the sponsor announced that it would make Propulsid available to patients who met specific eligibility criteria through an investigational limited-access program.

Appendix V: Comments from the Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 14 2006

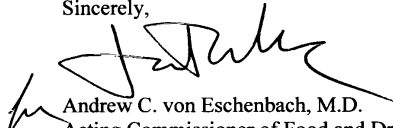
Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
Washington, DC 20548

Dear Ms. Crosse:

Enclosed are the Food and Drug Administration's (FDA) comments on the U.S. Government Accountability Office's draft report entitled, "DRUG SAFETY: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process" (GAO-06-402). These comments represent the tentative position of the agency and are subject to reevaluation when the final version of this report is received.

FDA appreciates the opportunity to comment on this draft report before its publication.

Sincerely,



Andrew C. von Eschenbach, M.D.
Acting Commissioner of Food and Drugs

Enclosure

Comments by CDER on the Government Accountability Office's (GAO) Draft Report, DRUG SAFETY: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process (GAO-06-402)

Introduction

The Center for Drug Evaluation and Research (CDER) appreciates the opportunity to comment on GAO's draft report which focuses on postmarketing drug safety issues. This document has two sections: general comments about topics discussed in the document and specific comments related to items of fact in the report.

Overall, CDER believes that the report is well done and that the conclusions reached are reasonable and consistent with actions we already have underway or planned. In particular, CDER has several initiatives that are discussed in the GAO report and are in the process of being implemented. These initiatives are aimed at strengthening the management of identified safety issues to assure that the decisions are made promptly, and are based on all of the relevant expertise in CDER, including the staff in the Office of New Drugs (OND) and the Office of Drug Safety (ODS).

General Comments by CDER on the Government Accountability Office's (GAO) Draft Report, DRUG SAFETY: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process (GAO-06-402)

Complexity of Decisionmaking and Quality of Data

Throughout the report, GAO makes statements that appear critical of CDER's drug safety processes, implying that they are too complex and the data on which they rest are sometimes unreliable. For example, GAO states that the decision-making process for postmarket drug safety is complex, and is limited by a lack of clarity, insufficient oversight by management, and data constraints. CDER believes that the evaluation of drug safety (i.e., determining whether a drug is likely to have caused an event and how often that occurs), and then weighing that against a drug's value is intrinsically complex. This complex balancing of risks and benefits, based upon whatever data are available, is the task CDER is required to perform every day. This cannot be changed, and CDER should not be criticized for the task it faces. Although there is no single formula for how best to make such important determinations, as GAO recognizes in the report, CDER is working to improve its processes for addressing these complex issues.

Role of PDUFA Goals in the Drug Review Process

The GAO refers to OND's work and its pace being driven by PDUFA goals. We believe that this is a bit misleading and should be changed to state that OND's work and its pace are driven "in part" by PDUFA goals. OND has other statutory and regulatory drivers of

their work, as well as a mission to protect the public health, which all of the staff in OND take very seriously.

In addition, this section of your report focuses on ODS' role in postmarket drug safety. ODS is also active in premarket safety review. For example, OND and ODS are required to meet to discuss drug safety before each new drug is approved. The purpose of the meeting is to discuss the safety database at the time of each drug's approval and facilitate postmarketing safety assessment. In addition, ODS is involved throughout the premarket review when there are specific safety issues, risk management issues, and risk management programs under consideration. For example, ODS was involved in the premarket reviews of Bosentan, Revlimid, Palladone, and Exubera.

When ODS' work occurs during the premarket period, ODS works with OND to meet the PDUFA goals. The goals, therefore, apply when ODS is reviewing a risk management plan for a drug yet to be approved, as illustrated by the examples above.

Role of ODS and OND in Drug Safety

Throughout, the report refers to the ODS as a "consultant to OND." This understates the importance and value that ODS adds in evaluating drug safety issues. CDER considers ODS and OND to be co-equal partners in the identification and timely resolution of drug safety issues. One goal of the processes that CDER is putting into place around drug safety (processes you summarize in your document) is to foster that partnership.

Role of the Drug Safety Oversight Board (DSB) in Drug Safety

CDER agrees with many of the comments about the potential impact of the DSB on the management of postmarketing safety issues, including standard setting. The DSB has reviewed current mechanisms CDER has for identifying drug safety concerns and discussed ways to enhance tracking of safety by CDER. Because the DSB membership includes balanced representation from OND and ODS leadership, these discussions can facilitate the implementation of CDER-wide actions on safety.

Role of ODS and OND in Advisory Committee Meetings

The report recommends that the ODS role in Advisory Committee meetings be 'clarified'. For instance, it states that ODS sets the agenda for the Drug Safety and Risk Management Advisory Committee (DSaRM) meetings and OND sets the agenda for all other scientific advisory committee meetings. In many cases, however, ODS and other groups in CDER are actively involved in the setting of the agendas for meetings of other committees besides DSaRM. For example, FDA's Office of Pediatric Therapeutics sets the agenda for the Pediatric Advisory Committee with OND and ODS input. The agenda for the Peripheral and Central Nervous System Drugs Advisory Committee meeting for Tysabri (natalizumab), and the presentations by both OND and ODS reflected the partnership between OND and ODS, despite the fact that this meeting was not a joint

meeting with DSaRM. The reality is that when safety issues arise in CDER today where ODS expertise is important, they are included in the planning of Advisory Committee meetings.

The GAO report also includes two cases where OND and ODS did not agree on what ODS should present to the advisory committee. It is implied that such disagreements occur frequently, but this is not, in fact, the case. When appropriate, ODS staff present their postmarketing safety reviews at advisory committee meetings organized by OND (see the example cited above for Tysabri). ODS also presented at a recent Peripheral and Central Nervous System Drugs Advisory Committee meeting on August 4, 2005, that discussed the NDA for MT 100 (naproxen sodium and meteclopramide hydrochloride) for the acute treatment of migraine headache with or without aura. In the vast majority of cases, OND and ODS work cooperatively on advisory committee presentations, regardless of who organized the meeting.

Arava Case Study

There is additional information regarding Arava that was not reflected in GAO's case study. In two meetings attended by approximately 20 people from OND and ODS, there was a wide-ranging discussion of the postmarketing cases of liver injury, with a full opportunity for discussion by all participants. ODS' concerns were taken very seriously, and in the end the consensus of the group was that the reports were unconvincing and represented at most a few drug-related injuries. These conclusions were also supported by the Advisory Committee and outside experts. This case study is one example of how the process in CDER can work to achieve consensus around a complicated safety issue.

Appendix VI: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7119 or crosssem@gao.gov

Acknowledgments

In addition to the contact named above, Martin T. Gahart, Assistant Director; Anne Dievler; Pamela Dooley; Cathleen Hamann; and Julian Klazkin made key contributions to this report.

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