United States Government Accountability Office

Report to the Ranking Member, Committee on Finance, U.S. Senate

November 2009

DRUG SAFETY

FDA Has Begun Efforts to Enhance Postmarket Safety, but Additional Actions Are Needed

GAO

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GAO Highlights

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DRUG SAFETY

FDA Has Begun Efforts to Enhance Postmarket Safety, but Additional Actions Are Needed

Why GAO Did This Study

There have been long-standing concerns regarding the Food and Drug Administration's (FDA) oversight of postmarket drug safety. In 2006, GAO reported that FDA had not clearly defined the roles of two offices involved in making decisions about postmarket safety—the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE). GAO and others reported additional concerns such as limitations in the data FDA relies on to identify postmarket drug safety issues and the systems it uses to track such issues. At that time, GAO made recommendations, including that FDA improve the independence of its program for resolving scientific disputes related to postmarket drug safety. In 2007, legislation further expanded FDA's postmarket responsibilities. This report examines the steps that FDA is taking to (1) enhance its processes for making decisions about the safety of marketed drugs, (2) improve access to data that help the agency identify drug safety issues, and (3) build its capacity to fulfill its postmarket drug safety workload. GAO reviewed FDA policies and planning documents, and interviewed FDA officials.

What GAO Recommends

GAO recommends that FDA develop a comprehensive plan to prepare OSE for the transfer of additional regulatory authorities from OND. FDA agreed with GAO's recommendation.

What GAO Found

FDA is beginning to address previously identified weaknesses in its oversight of postmarket drug safety issues, but challenges remain. The agency is changing its postmarket decision-making process as part of its Safety First Initiative, which includes formalizing interactions between OND and OSE and providing OSE with added responsibilities. The one authority FDA transferred from OND to OSE is a premarket review responsibility. FDA officials said the agency plans to transfer authority for two postmarket responsibilities for reviewing certain types of drug safety studies, but the agency does not have a time frame for their transfer. Officials said that OSE must still gain experience leading the one transferred responsibility and expand its staff before it can assume these additional responsibilities. While most of the OSE and OND employees GAO interviewed indicated that OSE's role in managing safety issues has increased since 2006, most OSE employees GAO interviewed said that OND's perspective still carries more weight in decision making. OND recently created safety management positions in each of its 17 divisions; OSE expanded its similar positions from 9 to 25, although an employee said turnover has made it difficult for the OSE managers to gain experience. FDA is also revising its program for resolving scientific disputes, but these changes have not increased its independence, as GAO recommended.

FDA plans to implement new data systems and is increasing access to external data to assist with drug safety decisions. FDA plans to implement new systems in 2010 to improve the timeliness, quality, and analysis of reports of adverse events associated with human drug use. FDA has also increased funding for contracts with private companies and is in the early stages of forming partnerships with federal data holders to access external data. As mandated in the 2007 legislation, FDA is developing the Sentinel System, a network of external data providers intended to enhance drug safety surveillance, but the agency is in the early stages of developing it.

FDA faces challenges meeting an expanding workload. The agency indicated that expanded responsibilities resulting from the 2007 legislation increased its workload, and both OND and OSE employees described difficulties meeting their responsibilities. FDA indicated that since fiscal year 2008, OND staff increased from 736 to 928 and OSE staff increased from 114 to 193. However, an agency review suggests that OSE may still need to more than double its staff of 193 by fiscal year 2011 to meet its new responsibilities. Although OSE has increased its staff, officials cited hiring challenges, such as competition from the private sector, that may make it difficult to hire staff quickly enough to meet the increasing workload. FDA also expects to complete a growing number of drug safety studies, but technological and staffing challenges limit its capacity to conduct these studies. To assist its decision making, FDA has increasingly sought advice from members of its external drug safety advisory committee. However, the agency has encountered difficulty filling several committee vacancies. An official said FDA is reviewing candidates with the goal of filling these vacancies as soon as possible.

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Abbreviations

AERS	Adverse Event Reporting System
CDER	Center for Drug Evaluation and Research
CMS	Centers for Medicare & Medicaid Services
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DCI	data collection instrument
DOD	Department of Defense
DPO	differing professional opinion
DSaRM	Drug Safety and Risk Management Advisory Committee
ESG	Electronic Submissions Gateway
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HHS	Department of Health and Human Services
IOM	Institute of Medicine
MOA	memorandum of agreement
OIG	Office of Inspector General
OND	Office of New Drugs
OSE	Office of Surveillance and Epidemiology
PDUFA	Prescription Drug User Fee Act of 1992
REMS	Risk Evaluation and Mitigation Strategy
VA	Department of Veterans Affairs

GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

November 9, 2009

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

Dear Senator Grassley:

Concerns about the Food and Drug Administration's (FDA) management of safety issues for drugs approved for marketing have been long-standing.[1] Reviews dating back over 30 years have identified problems related to the agency's monitoring of postmarket drug safety.[2] In 2004, high-profile drug safety cases continued to raise concerns about FDA's process for evaluating postmarket safety and making decisions about what actions to take. For example, FDA was criticized for taking too long to inform patients of serious drug risks. There were also reports of disagreements within the agency about how to address certain safety issues and reports that some FDA scientists were discouraged by supervisors from raising questions about the safety of certain drugs. FDA's process for making postmarket drug safety decisions involves multiple offices, including the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE). OND is involved in drug review activities throughout the life cycle of a drug (that is, premarket and postmarket). For postmarket safety issues, OND's activities include interacting with OSE,[3] which evaluates and monitors drug risks and promotes the safe use of drugs.

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[1]FDA is an agency within the Department of Health and Human Services (HHS). Within FDA, the Center for Drug Evaluation and Research (CDER) is responsible for overseeing the safety and effectiveness of drugs.

[2]See, for example, National Research Council, *Report of the International Conference of Adverse Reactions Reporting Systems* (Washington, D.C.: National Academies of Science, 1971); FDA, *Program Review of the Division of Epidemiology and Surveillance (DES) in the Office of Epidemiology and Biometrics (OEB)* (Washington, D.C.: 1993); and HHS, Office of Inspector General, *Review of the Food and Drug Administration's Handling of Adverse Drug Reaction Reports* (Washington, D.C.: December 1999).

[3]OSE was formerly known as the Office of Drug Safety. The office was renamed in May 2006. In this report, we refer to the office by its current name.

GAO-10-68 Postmarket Drug Safety

Since these concerns were raised, we and other organizations have conducted reviews of FDA's process for monitoring the safety of marketed drugs. In 2006, we reported that FDA had not clearly defined the role of OSE in postmarket drug safety and communication problems between OND and OSE had hindered the decision-making process.[4] We also found weaknesses in the data that FDA relied on to identify postmarket drug safety issues and in the systems it used to track them once they were identified. In addition, a 2006 Institute of Medicine (IOM) report identified similar weaknesses. IOM also reported that FDA's resources for postmarket drug safety were inadequate and that this could impede the agency's ability to identify and take actions to address drug safety issues.[5] More recently, HHS's Office of Inspector General (OIG) identified oversight of drug safety as one of HHS's top management challenges and earlier this year we added FDA's oversight of drugs and other medical products to our list of high-risk federal programs.[6]

You raised questions about FDA's postmarket drug safety program and asked that we follow up on our 2006 report to examine the role of OND and OSE in the postmarket monitoring of drugs. This report examines the steps that FDA is taking to (1) enhance its processes for making decisions about the safety of marketed drugs, (2) improve access to data that help the agency identify drug safety issues, and (3) build its capacity to fulfill its postmarket drug safety workload.

To describe the steps FDA is taking to enhance its processes for making decisions about the safety of marketed drugs, we reviewed FDA policies and planning documents and interviewed officials to identify specific actions being taken by the agency.[7] We also interviewed all individuals

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[4]GAO, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, GAO-06-402 (Washington, D.C.: Mar. 31, 2006).

[5]A. Baciu, K. Stratton, and S. P. Burke, eds., Institute of Medicine of the National Academies, Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington, D.C.: Sept. 22, 2006).

[6]HHS, *Fiscal Year 2008 Agency Financial Report* (November 2008), http://www.hhs.gov/afr/ (accessed Dec. 17, 2008); and GAO, *High-Risk Series: An Update*, GAO-09-271 (Washington, D.C.: January 2009).

[7]Our work is focused on human drugs regulated by CDER and not on biologics. Biologics are materials, such as vaccines, derived from living sources such as humans, animals, and microorganisms. Some biologics are regulated by CDER and such products are included in the scope of our work.

who were members of FDA's drug safety advisory committee of external experts, the Drug Safety and Risk Management Advisory Committee (DSaRM), as of January 2009. In addition, we examined policies related to FDA's program for resolving professional scientific disputes and interviewed FDA officials about its utilization by employees. To describe steps FDA is taking to improve access to data that help the agency identify drug safety issues, we reviewed documentation describing the development and implementation of systems the agency uses for collecting and monitoring drug safety data. We also examined contracts FDA has entered into with external organizations and agreements with federal agencies to access information about drug use and patient outcomes. To describe the steps that FDA is taking to build its capacity to fulfill its postmarket drug safety workload, we reviewed staffing data provided by the agency and documents related to the agency's efforts to assess workload. We also interviewed FDA officials regarding hiring initiatives to meet its postmarket drug safety responsibilities.

In addition, to supplement our work for each of the three objectives, we conducted a series of interviews with small groups of OND and OSE employees with responsibilities involving postmarket drug safety. Each small group interview consisted of a group discussion to capture general themes about these activities. At the conclusion of each interview, we asked each employee to complete a written data collection instrument (DCI) to document their responses to specific questions about the agency's postmarket decision-making process. To select employees for our small group interviews, we obtained March 2009 staffing data from FDA and confirmed the accuracy of these data through discussions with officials from OND and OSE. We also used our discussions with the OND and OSE officials to help us identify employees with no management responsibilities and at least 4 years of experience in the Center for Drug Evaluation and Research (CDER). We selected these employees because they are directly engaged in postmarket safety activities and would be in a position to comment on changes made by the agency since our 2006 report.

- For OND, we selected employees from its four divisions with the largest number of employees,[8] which we identified using the March 2009 staffing

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[8]OND has a total of 17 review divisions. We selected individuals from the Divisions of Anesthesia, Analgesia, and Rheumatology Products; Drug Oncology Products; Gastroenterology Products; and Neurology Products.

data. We determined that these data were sufficiently reliable for the purpose of our report. For each division, we randomly selected to interview five medical reviewers, who are the individuals responsible for reviewing data on the safety and efficacy of drugs. In one division, we also spoke with a second group of reviewers because that division has established separate teams of general reviewers and reviewers with specific drug safety responsibilities.[9] Based on these selection criteria and the availability of employees, we conducted five small group interviews of four or five employees, each.

• For OSE, we selected all employees from each of the office's five divisions who met our criteria to interview. For one division, we divided employees into two interview groups because of the large number of employees meeting our selection criteria. Based on these selection criteria and the availability of employees, we conducted six small group interviews of between three and six employees, each.

Across all of the small groups, we interviewed a total of 52 employees, each of whom completed a DCI. The views expressed by these employees cannot be generalized to all employees working within these offices.

We conducted this performance audit from October 2008 through October 2009 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

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. FDA approves a drug for marketing when the agency judges that its known benefits outweigh its known risks. However, because premarket evaluations are limited in their ability to always predict safety and efficacy with absolute certainty, FDA continues to assess a drug's risks and benefits after it has been marketed. If the agency identifies a postmarket safety issue, it makes a decision regarding whether to take a regulatory

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[9]The Division of Neurology Products has medical reviewers who fulfill traditional review duties and those who are members of a safety review team. Therefore, we conducted separate interviews with each of these groups of medical reviewers.

action, such as withdrawing the approval of a drug, which it rarely does, or communicating new safety information to the public and healthcare providers.

FDA Organization Related to Postmarket Drug Safety Decision Making

The decision-making process for postmarket drug safety is complex, multidisciplinary, and relies on an iterative interaction between OND, OSE, and other FDA components.[10] OND, which primarily conducts premarket reviews of drug applications submitted by drug sponsors, also has postmarket drug safety as one of its responsibilities. Although it interacts with OSE and staff from other offices concerning the postmarket safety of drugs, OND has ultimate responsibility to decide whether to take regulatory action regarding these issues. The office is organized into 17 review divisions that generally reflect certain therapeutic areas, such as gastroenterology or oncology drugs. The review of safety and efficacy data from drug applications is conducted by OND medical reviewers, who typically are physicians who have expertise in specific therapeutic areas and are skilled in the review of clinical trials.

OSE's primary focus is on postmarket safety, although it is also involved in certain premarket drug safety issues. OSE has traditionally operated primarily in a consultant capacity to OND and has not had any independent decision-making responsibility. When a safety issue is identified, OSE staff may conduct an analysis and produce a written report called a "consult" to assist OND. Safety consults could include analyses of adverse event reports and assessments of postmarket study designs.[11] In contrast to OND's organization by therapeutic area, OSE is organized into five divisions that each reflect different areas of its drug safety responsibilities. Two divisions analyze adverse event reports, one division reviews epidemiologic studies completed by drug sponsors and conducts its own studies,[12] one division reviews risk management plans submitted by drug sponsors,[13] and one division reviews proposed proprietary drug

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[10]FDA indicated that, in addition to OND and OSE, other FDA offices and divisions, such as the Office of Compliance, the Office of Clinical Pharmacology, and the Office of Biotechnology Products, are routinely involved in postmarket decision making.

[11]The term "adverse event" is used by FDA to indicate any untoward medical event that is associated with the use of a drug, whether causally related to the drug or not.

[12]Epidemiologic studies are intended to provide information about the association between drug use and adverse events by allowing observation of care delivered in the population.

[13]Risk management plans are submitted by drug sponsors and document plans for developing and implementing tools to minimize a drug's risks while preserving its benefits.

names submitted by drug sponsors for their new products and postmarket studies of medication errors completed by drug sponsors and others.[14]

To help it provide oversight of important, high-level safety decisions, FDA established the Drug Safety Oversight Board in spring 2005.[15] The board is comprised primarily of FDA staff, including OND and OSE officials, but also includes officials from other federal agencies, such as the National Institutes of Health. It was established with the goal of providing independent oversight and making recommendations to the CDER Director about the management of important drug safety issues.[16]

An important part of the drug approval and postmarket monitoring process is the advice the agency receives from CDER's 16 drug-related scientific advisory committees composed of external experts.[17] The committees are generally organized into specific therapeutic areas, such as gastrointestinal drugs or oncologic drugs. In 2002, FDA established DSaRM, which is one of the 16 committees. In contrast to the committees focused on a specific therapeutic area, DSaRM was established to advise FDA on drug safety and risk management issues across therapeutic areas. The committee's charter states that DSaRM is to be composed of 14 members—13 voting members with drug safety expertise and 1 nonvoting member to represent the drug industry. DSaRM members can also be asked to participate in other scientific advisory committee meetings when safety issues are discussed. OSE sets the agenda for DSaRM meetings, whereas OND sets the agenda for meetings of the other 15 committees.

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[14]OSE provides premarketing reviews of proprietary drug names to minimize any potential conflicts with names of drugs already being marketed that could lead to a healthcare provider misprescribing or misinterpreting the correct name, and dispensing or administering the wrong product, or dispensing it incorrectly. The office also reviews drug labeling and packaging in order to reduce the potential for a medication error.

[15]The Drug Safety Oversight Board has since been mandated by law. See 21 U.S.C. § 355-1(j).

[16]The Drug Safety Oversight Board also has responsibility to, among other things, manage the dissemination of certain safety information through FDA's Web site to healthcare professionals and patients; establish policies regarding management of drug safety issues in CDER; and track important emerging safety issues and ensure that they are resolved in a timely manner.

[17]In addition, the Pediatric Review Committee, an FDA-wide committee, also focuses on postmarket safety for drugs and biologics. FDA advisory committee members can be medical professionals, scientists, researchers, industry leaders, consumers, or patients.

Advisory committees may make recommendations to FDA that are not binding on the agency's decision making.

If individuals within CDER have differences of professional opinion or scientific disputes regarding a decision taken by the agency, they are generally expected to try to resolve them through their supervisory chain. If staff cannot resolve the dispute through this process, they can access CDER's differing professional opinion (DPO) program.[18] First implemented as a pilot program in November 2004, it provides a process through which individuals can protest agency actions or inaction when they believe there is a risk of a significant negative impact on public health. Under this process, a dispute filed by a CDER employee could be reviewed by an ad hoc panel of three to four employees.[19] The panel chair, who is appointed by the CDER Director, appoints the additional members, one of whom is nominated by the employee initiating the dispute. The panel would make a recommendation for resolving the dispute to the CDER Director. Several elements of this process are overseen by the CDER Ombudsman's Office, in consultation with the CDER Director.[20]

Data That Inform FDA's Postmarket Decision-Making Process

FDA uses evidence from multiple data sources to inform its postmarket decision-making process, each of which has certain strengths and weaknesses. FDA uses randomized clinical trial data to assess drug safety prior to approval. However, these data have inherent weaknesses. Therefore, the agency uses other data to continue to assess drug safety once drugs are on the market. One method of assessing postmarket drug safety is through the collection and analysis of reports of adverse events associated with drug use. FDA requires drug sponsors to submit adverse

[18]In our prior report, we referred to multiple FDA processes for resolving scientific disputes as "dispute resolution processes," including what FDA terms as its DPO program. See GAO-06-402. For the purposes of this report, we use the term "dispute resolution" to refer to the broad category of processes involved in resolving scientific disputes, including the review of the dispute by the supervisory chain and DPO program.

[19]When appropriate and feasible, a member with relevant technical expertise who is external to the agency could also be chosen.

[20]In addition to these duties, CDER's Ombudsman receives inquiries and investigates complaints from the drug industry, consumers, and healthcare professionals and provides general information on product development and regulation. In 2008, 94 percent of the contacts received by the Ombudsman were from the drug industry and consumers and 6 percent were from FDA employees.

event reports for the drugs they market.[21] In addition, healthcare providers and patients may voluntarily submit adverse event reports to FDA's Medwatch program by telephone, by mailing or faxing a paper form, or through a Web-based application on the Medwatch Web site. In 1997, CDER implemented the Adverse Event Reporting System (AERS), which it uses to store reports of adverse events. Adverse events are often a basis for postmarket safety actions; however, adverse event reporting has limitations that make it hard to establish the magnitude of a safety problem or to compare risks across similar drugs. Therefore, once a "safety signal" is identified for a marketed drug,[22] FDA may use data from observational epidemiologic studies to further examine relationships between a drug's use and reported adverse events. To conduct these studies, the agency seeks data from large, external databases of electronic health information—including claims data collected by health insurance companies and electronic medical records of care provided through large healthcare systems. (See table 1 for a description of these data sources used to inform drug safety decision making before and after approval.)

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[21]See 21 C.F.R. §§ 310.305, 314.80, 314.98, 600.80 (2009).

[22]Safety signals, which are potential relationships between drug use and adverse events, are sometimes the first indicator of a potential drug safety problem.

Table 1: Selected Data Sources FDA Uses to Inform Its Drug Safety Decision Making

	Market status		
	Premarket: approval	Postmarket: signal generation	Postmarket: signal confirmation
Data source	Randomized clinical trials	Adverse event reports	Observational studies
Description	Studies that randomly assign patients to either a treatment group that receives a drug or a control group that does not receive that drug.	Reports of adverse events received from patients, healthcare providers, and drug manufacturers once a drug is on the market.	Studies in which patients are not assigned to groups, but are studied as they receive treatment, such as, epidemiologic studies using data from large databases of electronic health information (insurance or medical records).
Use	To assess drug safety and efficacy.	To generate "safety signals," which are potential relationships between use of a drug and an adverse event.	To confirm safety signals by further investigation of the relationship between the drug and the adverse event.
Strengths	Randomization minimizes differences between the groups at the outset, which typically allows outcome differences to be attributed to the treatment.	Provides valuable information on rare, unexpected adverse events, including events that occur in patients other than those tested in clinical trials.	May involve larger groups of typical patients over longer periods of time, in more "real world" settings.
Weaknesses	• Generally involve a small group of patients relative to the population that will ultimately use the drug. • Patients typically receive the drug over a short duration. • Elderly persons, pregnant women, and patients who have other medical problems may be excluded, thus enrolled patients may not reflect the patients who will take the drug.	• Not effective for attributing common events, such as heart attack, to drug use. • Adverse events are underreported and, for some drugs, FDA may not have access to the total number of people exposed, which makes estimating the magnitude of a safety problem difficult.	• There could be systematic differences between the treatment and control groups at the outset that account for outcome differences. • Concomitant use of other products, such as over-the-counter drugs or herbal supplements, may not be recorded in the databases, which could affect study results.

Source: GAO.

Note: This table presents examples of data sources that FDA may consult during the life cycle of a drug. FDA may use multiple data sources to evaluate a safety issue at any given time. For example, although clinical trial data are used to evaluate premarket safety, FDA also uses clinical trial data to evaluate postmarket drug safety.

Recent Reviews of FDA's Postmarket Drug Safety Oversight

In 2006, we reported that FDA's process for overseeing postmarket drug safety was limited by a lack of clarity about OSE's role in decision making. For example, while OSE often made recommendations to OND in the consults that it completed, the agency had no policy explicitly stating whether this was part of OSE's role. OSE staff also reported that these consults sometimes fell into a "black hole" or "abyss" and OSE staff would not be informed of the results of their recommendations. Also in 2006, IOM noted that an imbalance in authority, formal role, and resources between

OND and OSE constituted a major obstacle to a healthy organizational culture in CDER. Furthermore, IOM reported that FDA's challenges are reflective of how premarket and postmarket functions have been divided historically. OSE generally takes a population-based perspective in their drug safety work by utilizing adverse event reporting and observational studies, while OND generally takes a clinical perspective that focuses primarily on randomized clinical trials. They reported that OND staff often view the observational data used by OSE as "soft" and unconvincing, while OSE staff view these data as informative and carrying great weight. IOM noted that the imbalance in roles and responsibilities denoted a subservience of the safety function and a devaluation of OSE's discipline and approach by agency management.

We also identified several specific limitations to FDA's postmarket decision-making process. Several years prior to the release of our 2006 report, FDA started drafting a policy intended to clarify the role of staff, including those from OSE, in the decision-making process. However, the policy had not been finalized and implemented by the time our 2006 report was issued. In addition, we reported that the role of OSE staff in planning for and participating in advisory committee meetings, other than those involving DSaRM, was not clear. We also found that the DPO program had not been used and may not have been viewed as sufficiently independent because it did not offer employees a forum for resolving disputes that was independent of the CDER Director. We reported, for example, that the CDER Director would help decide whether a dispute warranted review and would also make the final decision about how the dispute would be resolved.

We also found that OSE management had not effectively overseen postmarket drug safety and lacked systematic information on this process. Specifically, although OSE maintained a database of consult requests it received from OND, the database did not include information about whether OSE staff had made recommendations to OND regarding safety actions. It also did not include information on how the safety issues were resolved, including whether OSE's recommended safety actions were implemented by OND. In addition, in 2006, OIG found weaknesses in the extent to which FDA tracked another element of postmarket drug safety, the progression of postmarketing studies that FDA had requested drug sponsors to complete. OIG found that FDA could not readily identify

whether or how timely these studies were progressing toward completion.[23]

We also found in 2006 that FDA faced constraints in its access to data that allow it to monitor the safety of marketed drugs. For example, FDA staff and external drug safety experts told us that OSE did not have enough funding to support the purchase of data for postmarket drug surveillance. Similarly, IOM found that funding for purchasing data was severely limited and had changed little in over 20 years. IOM also found that FDA devoted limited resources for staff training and supportive technology that was needed to fully utilize purchased data. Furthermore, IOM concluded that AERS was outdated and inefficient and the agency had given little attention to using systematic methods for screening AERS for adverse events.

We made multiple recommendations to FDA in 2006 that were intended to improve its oversight of postmarket drug safety. We recommended that FDA

• revise and implement its draft policy on major postmarket drug safety decisions,

• clarify OSE's role in FDA's scientific advisory committee meetings involving postmarket drug safety issues,

• improve CDER's dispute resolution process by revising the DPO program to increase its independence, and

• establish a mechanism for systematically tracking OSE's recommendations and subsequent safety actions.

(See app. I for a summary of FDA actions taken in response to these recommendations.)

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[23]HHS Office of Inspector General, *FDA's Monitoring of Postmarketing Study Commitments* (June 2006), downloaded from http://www.oig.hhs.gov/oei/reports/oei-01-04-00390.pdf (accessed Aug. 6, 2008).

Changes to FDA's Postmarket Drug Safety Authority and Funding

The Food and Drug Administration Amendments Act of 2007 (FDAAA) provided the agency with additional responsibilities intended to improve its oversight of postmarket drug safety.[24] For example, FDAAA provided FDA with new authority to require drug sponsors to complete postmarketing studies to identify a serious risk or assess a known serious risk.[25] Prior to the enactment of FDAAA, FDA only had the authority in limited circumstances to require drug sponsors to conduct a postmarket drug safety study;[26] outside of these circumstances, the agency could request that drug sponsors voluntarily agree to conduct such studies. FDAAA also provided FDA with new authority to require drug sponsors to complete risk management plans. Previously, FDA issued guidance to drug sponsors to assist in the development of voluntary risk management plans. FDA may now require drug sponsors to implement a risk management plan through specific approaches, known as a Risk Evaluation and Mitigation Strategy (REMS).[27] FDAAA also provided the agency with authority to impose civil monetary penalties on drug sponsors who violate these requirements.[28]

FDAAA also requires FDA to conduct several other postmarket drug safety activities. For example:

- FDA must, in collaboration with public, academic, and private entities, develop a postmarket risk identification and analysis system that can be used to analyze safety data from multiple sources.[29]

- FDA is required to screen AERS biweekly and publish quarterly reports of new safety information or potential signals of serious risks associated with the use of a drug.[30]

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[24]Pub. L. No. 110-85, 121 Stat. 823.

[25]21 U.S.C. § 355(o).

[26]Prior to FDAAA, FDA had the authority in limited situations to require that sponsors commit to conducting postmarketing studies as a condition of approval. See 21 U.S.C. § 356(b)(2). For example, in certain 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. 21 C.F.R. § 314.610(b)(1)(2009).

[27]21 U.S.C. § 355-1.

[28]21 U.S.C. § 333(f)(4).

[29]21 U.S.C. § 355(k)(3).

[30]21 U.S.C. § 355(k)(5).

- FDA is required to use DSaRM to seek input on certain activities, such as elements of REMS and the analysis of drug safety data.[31]

In addition to increasing FDA's authorities, FDAAA also reauthorized the Prescription Drug User Fee Act of 1992 (PDUFA).[32] Originally, PDUFA authorized FDA to collect user fees[33] from drug sponsors in order to support the review of drug applications and it established performance goals, such as time frames for the review of applications. The increase in attention to timely drug approval decisions led to greater awareness of the need for FDA to strengthen its monitoring of postmarket drug safety, which was reflected in the 2002 reauthorization of PDUFA.[34] The most recent authorization of PDUFA, in September 2007 as part of FDAAA, expanded the postmarket drug safety activities for which FDA is authorized to apply user fees.[35] For example, the law identified the development of adverse event data collection systems as an activity that could be funded through user fees. In addition to amounts authorized to be used for all user fee activities, both premarket and postmarket, the PDUFA reauthorization identified specific annual fee revenues to be used for postmarket drug safety activities. In total, FDA reported that it plans to increase its allocation of annual user fees to support postmarket drug safety from about $54 million in fiscal year 2008 to about $102 million in fiscal year 2012.[36]

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[31]21 U.S.C. § 355-1(f)(5).

[32]See Pub. L. No. 110-85, §§ 101-109, 121 Stat. 823, 825-42.

[33]Under PDUFA, FDA receives user fees from the pharmaceutical industry as part of its annual appropriation for salaries and expenses. To delineate the source of the appropriated funds in this report, we use the terms "user fee funding" to describe amounts derived from user fee collections, and "fiscal year appropriations" to describe amounts derived from the General Fund of the Treasury. Both user fee funding and fiscal year appropriations are made available through the annual appropriations process.

[34]See Pub. L. No. 107-188, §§ 501-509, 116 Stat. 594, 687-94.

[35]See 21 U.S.C. § 379g(6)(F).

[36]FDA, Prescription Drug User Fee Act (PDUFA) IV Drug Safety Five-Year Plan, December 2008, http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM119244.pdf, (accessed July 16, 2009). According to FDA, these user fee funds were allocated to CDER, the Center for Biologics Evaluation and Research, and other components of the agency.

Overall premarket and postmarket funding for OSE and OND increased since fiscal year 2006.[37] From fiscal year 2006 through fiscal year 2008, OSE funding increased from about $31 million to about $71 million. During that same period, OND funding increased from about $115 million to $144 million. For both OSE and OND, much of the increase occurred in fiscal year 2008 and can be attributed to increased user fees. (See fig. 1.) Additionally, across all of CDER, funding for postmarket drug safety increased from about $54 million in fiscal year 2006 to $139 million in fiscal year 2008. Of the $139 million in fiscal year 2008, about $84 million was from fiscal year appropriations and $55 million was from user fees.

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[37]FDA was not able to provide OSE and OND funding specifically for postmarket drug safety. However, based on a fiscal year 2004 study, it estimated that OSE devoted about 91 percent of its work time to postmarket drug safety, while OND devoted about 11 percent.

Figure 1: OSE and OND Funding, Fiscal Years 2004 through 2009

OSE funding

Dollars (in millions)

OND funding

Dollars (in millions)
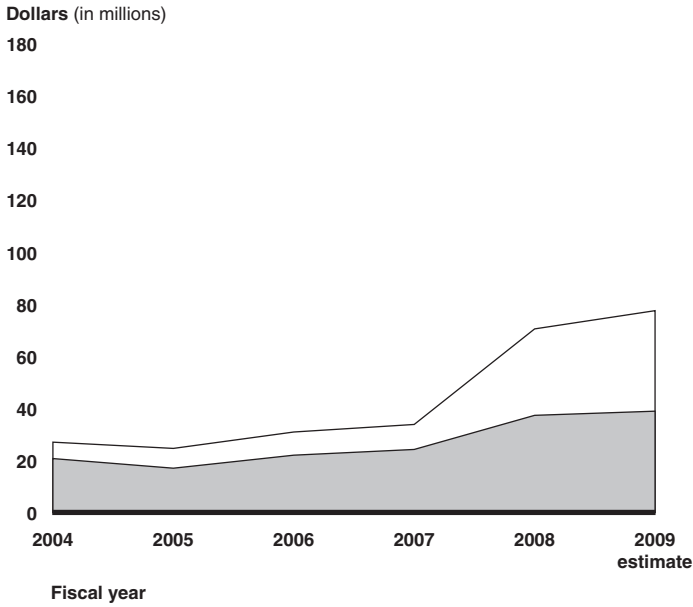
Fiscal year
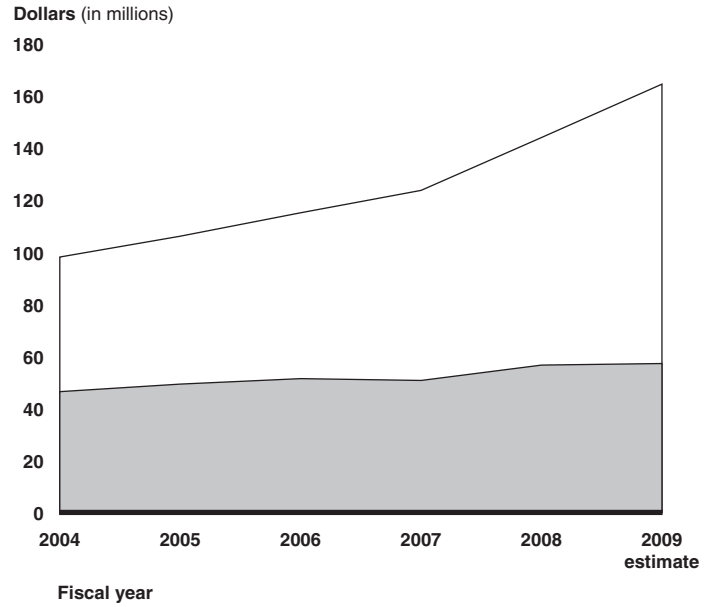
Fiscal year

☐ User fees

▨ Fiscal year appropriations

Source: GAO analysis of FDA data.

Note: Under PDUFA, FDA receives user fees from the pharmaceutical industry as part of its annual appropriation for salaries and expenses. We use the terms "user fee funding" to describe amounts derived from user fee collections and "fiscal year appropriations" to describe amounts derived from the General Fund of the Treasury to delineate the source of the appropriated funds. Both user fee funding and fiscal year appropriations are made available through the annual appropriations process.

FDA Has Begun to Formalize Its Postmarket Decision-Making Process and Recently Implemented Oversight Initiatives, but Challenges Remain

FDA has begun to implement a new process and initiatives intended to clarify roles related to postmarket safety decision making, but faces a variety of challenges. Several initiatives have not been fully implemented and the agency has not increased the independence of its dispute resolution program.

FDA Has Begun to Formalize OND and OSE's Decision-Making Process for Postmarket Drug Safety, but a Time Frame for Implementing Key Elements Has Yet to Be Established

To enhance postmarket drug safety, FDA has begun to formalize interactions between OND and OSE, although some key elements of this new process have not been implemented. In the past, FDA has not afforded the same focus and attention to postmarket drug safety as it has to the drug approval process. For example, an agency official said that, unlike for the premarket process, roles and responsibilities for the postmarket process have not been clearly defined. Therefore, in January 2008, the agency began to establish a new framework for drug safety—which it calls the Safety First Initiative—that is intended to provide this structure. Under the initiative, the agency has adopted a multidisciplinary approach based on the principles the agency refers to as Equal Voice, which are intended to ensure that all necessary parties contribute to decision making. In addition, OSE and OND signed a memorandum of agreement (MOA) in June 2008 that states FDA's intent for the two offices to contribute equally in determining regulatory actions related to drug safety.[38] However, in most cases, OND retains the authority to decide whether to take regulatory action. According to FDA, OND retains these authorities because, for most decisions related to postmarket drug safety, OND staff have the broadest expertise in evaluating and managing clinical risks and benefits of drugs.

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[38]The MOA expired in June 2009 and a new agreement is in effect through June 2010. FDA officials said the agency plans to reevaluate the MOA each year to determine if it is still necessary.

However, as part of the MOA, FDA has transferred authority for one regulatory responsibility related to premarket drug safety from OND to OSE and plans to transfer authority for two postmarket responsibilities, but has not set a time frame for doing so. The MOA describes the agency's intent to transfer to OSE the authority to make final decisions for those activities in which the office has expertise. Initially, these include three drug safety activities that reside with OND: (1) review of proprietary drug names submitted by sponsors, (2) review of protocols and findings of observational epidemiologic studies, and (3) review of protocols and studies that assess medication error risks. In April 2009, OSE was transferred authority for the first regulatory responsibility, the premarket review of proprietary drug names, which gives OSE final decision-making authority for the activity and allows the office to communicate directly with the drug sponsor and issue letters approving or rejecting drug names. An OND official said that the transfer of authority for this responsibility has been beneficial because proprietary name review was not an area in which OND had much expertise. An OSE official said that, since the transfer, decisions have been more consistent and the decision letters issued to drug sponsors have been more transparent. Agency officials said they selected proprietary name reviews as the first authority to transfer to OSE because the process is well defined and self contained, and it will give OSE experience leading a significant drug safety activity while building its expertise to assume authority for the additional responsibilities named in the MOA. Officials said the agency intends to transfer authority for the two postmarket drug safety responsibilities to OSE, but it has not set a time frame for doing so. Agency officials added that coordinating some elements of the remaining responsibilities will be more complex and OSE still needs to increase its staff to assume these additional responsibilities.

FDA has established multiple opportunities for staff from different disciplines to discuss drug safety issues. As part of the MOA, postmarket safety issues would be managed by an interdisciplinary team process that is similar to FDA's process for managing drug approvals. FDA issued an interim policy describing these safety issue teams in May 2009. Teams would be created as needed and include the OSE, OND, and other staff necessary to evaluate a given safety issue and make a decision about any needed regulatory actions. As part of this process, the teams would establish target dates for evaluating the safety issue and later monitor the implementation of any regulatory actions. FDA officials said that teams have been formed in the past to discuss safety issues, but this new policy formalizes existing team-based review practices to provide consistency in resolving safety issues. Officials said that they began training staff on the

new policy in July 2009, but they could not provide an estimate of the number of teams that have been formed. In addition, FDA established routine joint safety meetings between OND divisions and their OSE counterparts. In contrast to the safety issue teams, which are established to manage a specific issue, the joint safety meetings focus on broader scientific matters and status updates of joint interest to both OND and OSE. The agency also continues to hold meetings of its Drug Safety Oversight Board. FDA indicated that the board serves as a forum to discuss emerging and often controversial drug safety issues. The board recently expanded its membership to include representatives from additional federal agencies, including the Department of Defense and HHS's Indian Health Service. According to FDA, board members from other federal agencies allow FDA to hear perspectives on how its drug safety decisions affect federal healthcare systems.

OSE and OND employees in our small group interviews generally identified positive outcomes from FDA's initiatives, although most OSE employees indicated that OND still has more authority in the postmarket decision-making process. Many of the OND and OSE employees who participated in our small group interviews told us that the more formalized process for managing safety issues has helped improve interactions between the two offices since our last report. For example, several OSE employees said that they now consistently receive a response from OND about their consults and recommendations, even if they are not always followed, and these reports no longer fall into a "black hole," as we reported in 2006. Employees also described increased communication between the two offices, which some said improved tracking of safety issues but others said slowed the decision-making process. With regard to OSE's influence in the postmarket decision-making process, 75 percent (39 of 52) of OND and OSE employees who completed our DCI indicated that OSE's influence has increased since 2006. However, OND and OSE employees differed in whether they thought OSE currently serves as an equal partner in decision making. Of the OND employees who completed our DCI, 64 percent (14 of 22) indicated that OSE now serves as an equal partner. In contrast, 57 percent (17 of 30) of OSE employees indicated that OND's perspective still carries more weight, although 60 percent (18 of 30) indicated that they thought OSE would serve as an equal partner once the new initiatives were fully implemented.

Despite changes to FDA's postmarket decision-making process, OND and OSE employees report that differences still exist in how the two offices view information used to make decisions. For example, one OSE employee said that OND staff trust the results of randomized clinical trials

over the epidemiologic data used by OSE, and another OSE employee said that OND is generally more resistant to accepting drug safety recommendations based on epidemiologic data. Some OND employees also said that physicians are better at identifying the direct clinical impact of a drug than other types of staff, such as epidemiologists, who may be more skilled in data analysis. OSE is taking steps to address these differences. For example, an official said that OSE has provided training to OND staff on the methods it uses to do its work. In addition, officials told us that OSE plans to increase clinical expertise by hiring additional medical reviewers to assist it with the review of adverse event reports.

FDA Recently Implemented Initiatives to Facilitate Oversight of Postmarket Safety Issues, although There Have Been Implementation Challenges

FDA implemented both staffing and tracking initiatives intended to improve oversight of postmarket drug safety issues. In January 2008, OND created two new safety management positions within each of its 17 review divisions to reduce variability in how the divisions oversee postmarket drug safety.[39] In addition to coordinating interactions between the offices, employees in these new management positions are to provide leadership and to ensure that adequate OND resources and attention are focused on safety issues. They also track postmarket safety activities which may reduce the burden on individual medical reviewers, who are also responsible for reviewing and recommending whether to approve drug applications. Several OND medical reviewers indicated during the small group interviews that the OND safety management positions have helped to track and coordinate management of postmarket safety issues. For example, one medical reviewer noted that medical reviewers have competing premarket deadlines related to PDUFA and it is helpful to have safety staff who do not have these deadlines and can focus on postmarket drug safety.

In addition, OSE reorganized its existing safety project manager positions into a single group in October 2006 to oversee the management of safety issues across OSE divisions. These safety project manager positions serve as OSE counterparts to the OND management positions and are responsible for, among other things, coordinating meetings with OND and

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[39]Each OND division now has a Deputy Director for Safety and a Safety Regulatory Project Manager; one division has two Safety Regulatory Project Managers. As of July 2009, 3 of the 17 Deputy Director for Safety positions and 11 of 18 Safety Regulatory Project Manager positions were filled in an acting capacity; the remaining positions had permanent staff. OND has also created an Associate Director for Safety that has responsibility for coordinating the activities of the safety positions across review divisions.

monitoring OSE activities. These project manager positions were each previously assigned to a specific OSE division. An OSE official said this reorganization was intended to provide OND staff with a single point of contact within OSE, rather than having separate contacts for each OSE division. Since the reorganization, the total number of safety project manager positions in this group has expanded from 9 to 25. However, several OSE employees in our small group interviews cited challenges related to their interactions with those holding these OSE safety project manager positions. Some said individuals in these positions still seem to be learning their new roles and responsibilities. An employee also said that turnover among the safety project manager positions has made it difficult for the individuals holding those positions to gain experience. As of July 2009, 20 of the 25 OSE safety project manager positions were filled, but an official stated that turnover has been a problem and only one of the individuals has been in that position since October 2006. The official said that the expansion of responsibilities resulting from the reorganization was challenging for some of the individuals and noted that a lack of training and clear policies and procedures for these new positions may have contributed to the high turnover. The official said OSE is hoping to improve retention by implementing training and other support systems for these staff.

FDA is also implementing a new tracking system to assist OSE and OND staff in overseeing identified safety issues, although the system has limitations. In January 2007, in response to our 2006 recommendation, FDA began to incorporate a safety module within its Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) to track the agency's management of and response to significant safety issues identified with the use of marketed drugs.[40] FDA requires that each significant safety issue identified by OND and OSE be tracked within DARRTS by creating a "tracked safety issue" file. As of July 14, 2009, there were 394 active issues. DARRTS is used, among other things, to generate a workplan and assign responsibilities for managing these issues, as well as to provide updates on the status of these issues. Officials told us that while the system contains documents describing specific recommendations and safety actions, it does not, as we recommended, allow FDA to systematically track how issues were resolved and whether OSE's

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[40]DARRTS is intended to help CDER staff manage the drug review process by serving as a central repository for information and allowing staff to upload communications and other documentation, generate reports, and create status updates. The agency is releasing DARRTS in stages. The first version was released in January 2006.

recommendations were implemented. For example, an FDA official told us that DARRTS cannot provide the agency with a summary of the recommendations for safety actions that OSE has made to OND or how the safety issues were ultimately resolved. FDA indicated that, due to limited resources, it does not plan to incorporate this capability into DARRTS in the next year or two. In addition, FDA has identified certain limitations with the system, such as problems of completeness and accuracy and the need for a mechanism to notify relevant staff when a new tracked safety issue is created. According to FDA, some of the identified problems have been corrected while others will be addressed at a later date. An official said that the agency expects that future problems will be minimized by improved preimplementation testing. For example, the official noted that the July 2009 update of DARRTS, which allows the system to be used for monitoring both postmarket studies and risk management plans, was more rigorously tested by users prior to its implementation.

FDA is also utilizing contractors to improve oversight of specific new authorities created by FDAAA. We and others have identified problems in the agency's tracking of required and requested postmarketing studies, such as OND reviewers not meeting their goals for reviewing in a timely manner the annual status reports submitted by drug sponsors.[41] In 2008, FDA hired a contractor to monitor and provide support for postmarketing studies, including the review of these annual status reports.[42] FDA officials said that this contract has been very productive because it allows the review of the annual status reports to be completed, which is very time consuming, while allowing the agency to move ahead in its oversight of the new postmarketing studies it is requiring under its FDAAA authority. The

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[41]GAO, *New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints*, GAO-09-866 (Washington, D.C.: Sept. 23, 2009). See also, Booz Allen Hamilton, *Postmarketing Commitments Study Final Report*, a report prepared at the request of FDA, January 2008, http://www.fda.gov/ForIndustry/ UserFees/Prescription DrugUserFee/ucm119856.htm (accessed July 23, 2009).

[42]The contractor is annually reviewing the annual status reports associated with postmarketing studies that were requested prior to the enactment of FDAAA—what the agency defines as its "backlog." The review of these reports is required by FDAAA. Pub. L. No. 110-85, § 921, 121 Stat. 823, 962 (codified at 21 U.S.C. § 355(k)(5)). The contractor is also reviewing the annual reports submitted by drug sponsors for those postmarket studies that have been required or requested since FDAAA. See, for example, Booz Allen Hamilton, *Deliverable 2-8: Final Report on the PMR/PMC Backlog Review*, a report prepared at the request of FDA, April 10, 2009, http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Post-marketingPhaseIVCommitments/ucm180982.htm (accessed Oct. 20, 2009).

agency is also hiring a contractor to help oversee the required risk management plans.

FDA Is Revising Its Program for Resolving Scientific Disputes but the Changes Have Not Sufficiently Addressed the Independence of the Process

FDA is revising CDER's program for resolving scientific disputes raised by individual employees, but the changes do not sufficiently address our prior recommendation for improving the independence of the process. Beginning in 2007, FDA conducted a review of each of its centers' dispute resolution processes, including CDER's DPO program.[43] As a result of this review, FDA developed a list of mandatory elements for all centers to implement during fiscal year 2008 and a list of voluntary best practices for scientific dispute resolution activities. For example, FDA now requires that employees of each center who file a DPO have the option to appeal to FDA's Office of the Commissioner for a review to determine if the center followed its own dispute resolution process correctly.[44] CDER indicated that its DPO policy is being revised to reflect this "process review" and other new agencywide requirements, but noted that CDER plans to make few other changes. As of October 2009, the revised policy had not been finalized.

While CDER continues to make changes to its DPO policy, the planned changes do not address a weakness we identified in our 2006 report—that the program it established to resolve scientific disputes may not be viewed as independent as a result of the CDER Director's extensive involvement. According to a July 2009 draft of the revised policy, as was the case in 2006, the Ombudsman, whom the policy designates as the focal point for overseeing the resolution of disputes, would consult with the CDER Director before deciding whether a dispute warrants review. An agency official told us that this consultation is important because the Ombudsman does not have the same scientific expertise as the CDER Director. The official acknowledged that, while the Ombudsman is included as a way to improve the independence of the DPO program, this position does not meet the standards of independence established by the Coalition of

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[43]FDA has five centers: CDER, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Food Safety and Applied Nutrition, and the Center for Veterinary Medicine.

[44]The process review would also include an assessment of whether the center considered all relevant evidence bearing on the scientific question at issue and whether the initiator of the dispute was provided an opportunity to express his or her concerns at all appropriate levels. As examples of other requirements, FDA requires center dispute resolution policies to include antiretaliation language and an 'opt-up' to the center director if a dispute is of sufficient immediacy and scale of impact to public health.

Federal Ombudsmen.[45] In addition, according to the draft DPO policy, the CDER Director would still appoint the chair of the ad hoc review panel and decide how the dispute should be resolved, in consideration of the panel's recommendation. The draft DPO policy includes the required option of a process review by the Office of the Commissioner, which would not involve the center director or other center staff in decision making. However, this review is limited to determining whether CDER followed its own processes correctly, and it does not consider the scientific merits of the dispute. As a result, CDER's revised DPO program still may not be viewed as sufficiently independent for resolving disputes.

As of July 2009, CDER's DPO program had not been used to resolve a difference of opinion. The Ombudsman attributed the lack of use to the CDER Ombudsman's Office's management of disputes so that they never reach the level of a formal DPO.[46] FDA also indicated that the DPO program is narrowly focused on individual disagreements that employees have been unable to resolve within their supervisory chain; if agreement has not been reached between scientific disciplines, the principles of Equal Voice are intended to help different disciplines express differences of opinion. OND and OSE employees who completed our DCI reported a variety of reasons for why they chose not to file a formal DPO. Of the 52 OND and OSE employees who completed our DCI, 36 indicated that they had not had a difference of opinion that would have qualified for filing a dispute. However, 13 of the employees did report having a difference of opinion where they thought that FDA's action or lack of action had the potential to have a significant negative impact on public health.[47] When asked why they did not use CDER's program to resolve this difference, these employees most frequently indicated that they preferred to express

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[45]The standards state that several factors are important to assessing independence, such as whether anyone affected by the ombudsman's actions can control or limit the ombudsman's performance or reduce the ombudsman's budget or resources. Coalition of Federal Ombudsmen (CFO) and Federal Interagency ADR Working Group Steering Committee, *A Guide For Federal Employee Ombuds: A Supplement to and Annotation of the Standards For The Establishment And Operations Of Ombuds Offices Issued By The American Bar Association*, May 9, 2006, http://www.adr.gov/pdf/final_ombuds.pdf, (accessed July 27, 2009*)*.

[46]An agency official told us that CDER asked staff in 2007 for input on why the program had not been used, but only a few staff responded. The official said that CDER interpreted the low response rate to mean that staff did not feel strongly about the program, so, at that time, no changes were made to the program.

[47]The remaining 3 employees out of the 52 who completed the DCI indicated that they had no opinion about the issue (2) or did not provide an answer (1).

the opinion in written documentation (7) or were not aware of the program (6).[48] In addition, 3 of these 13 employees noted concerns about the fairness of the DPO program as one reason for why they did not utilize it. None of the 13 employees indicated that they preferred the option of discussing the differing opinion informally with the Ombudsman.[49]

FDA Plans to Implement New Adverse Event Systems and Is Increasing Access to External Sources of Drug Safety Data

FDA plans to improve its identification of drug safety issues by developing new adverse event systems to collect and store adverse event reports and by increasing access to external sources of data. However, the adverse event systems and a new network of external data providers have not yet been implemented.

FDA Is Developing New Systems to Improve Collection and Analysis of Drug Adverse Event Reports, but Implementation Is Not Expected Until 2010

FDA is developing two new adverse event systems to help it identify drug safety problems—one to improve the collection and processing of adverse event reports and another to store reports and provide FDA staff with improved tools for analyzing them. FDA's complete adverse event system for human drugs will not be implemented until the end of 2010.

Adverse Event Collection and Processing

The new adverse event report collection and processing system, MedWatchPlus, is intended to increase the accuracy and timeliness of reports accessible to FDA staff and is scheduled to be implemented for human drugs by summer 2010.[50] The current MedWatch Web site collects

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[48]Under 21 C.F.R. § 10.70, an agency employee working on a matter may record individual views on that matter in a written memorandum, which is to be placed in the file.

[49]Employees completing the DCI were able to select more than one reason why they did not use CDER's program to resolve differences of opinion.

[50]MedWatchPlus will be implemented in stages. The first version is scheduled to be complete by fall 2009, but will only be able to accept adverse event reports for food and veterinary drugs. In spring 2011, FDA plans to release a version that will be able to accept adverse event reports for medical devices and other remaining products.

adverse event reports about prescription drugs by providing forms that patients and healthcare providers can submit online or download and send to FDA in paper form.[51] Drug manufacturers may also use this system to download forms, although they may elect to submit electronically through an alternative system, the Electronic Submissions Gateway (ESG).[52] Although reports submitted through ESG go directly into CDER's database of adverse events, AERS, paper reports, and reports submitted using the MedWatch online form must be processed and manually entered into AERS before they are available to FDA staff. FDA estimates that reports submitted on paper may take from 2 weeks to 2 months from the time of receipt to be entered into AERS where they can be analyzed by FDA staff. The new MedWatchPlus system will allow online reports to be processed automatically and transferred directly into the agency's adverse event system,[53] reducing the need to process and enter reports manually. According to FDA, automatic processing will cut down on errors related to data entry and should allow for more timely availability of reports for analysis. FDA estimates that electronic submissions are generally available in AERS within 2 days of their receipt.

FDA expects that MedWatchPlus will enable the agency to increase the electronic submission rate of reports, increase the number of reports accessible to FDA staff for analysis, and improve report quality. In fiscal year 2008, 61 percent of reports from manufacturers were submitted electronically. In August 2009, FDA issued notice of a proposed rule that would require manufacturers to submit adverse event reports electronically,[54] which would mean that manufacturers who do not currently submit reports electronically would either use ESG or would

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[51]FDA also provides a toll-free telephone number that can be used to submit adverse event reports.

[52]ESG is an FDA system that enables the electronic submission of regulatory information, such as adverse event reports, for review. Manufacturers that choose not to utilize ESG must submit paper forms, which may be obtained through MedWatch.

[53]MedWatchPlus will process each report by assigning a unique identifier, translating the report into accepted medical terminology using standard medical dictionaries, prioritizing the report based on factors such as the seriousness of the adverse event, and routing the report to the correct center within FDA.

[54]See 74 *Fed. Reg.* 42,184 (Aug. 21, 2009). This proposed rule amends previous requirements for the submission of postmarket safety reports, see 21 C.F.R. §§ 310.305, 314.80, 314.98, and 600.80 (2009). The rule will be available for comment until November 19, 2009, after which FDA may issue the final rule. FDA has proposed that the new requirements would go into effect 1 year after the publication of the final rule.

need to use the MedWatchPlus online form.[55] Increasing the electronic submission rate should allow for more reports to be available to FDA staff. Currently, FDA does not routinely enter all paper reports from manufacturers into AERS,[56] which an official said is because of the cost to the agency. However, all reports from manufacturers submitted electronically through MedWatchPlus will be automatically entered into AERS, which should reduce costs and allow for more reports to be available for analysis.[57] FDA also expects to increase the number of electronic submissions from patients and healthcare providers by making the system easier to use. As part of MedWatchPlus, FDA will use an interactive questionnaire that will guide submitters through a series of questions, which FDA expects will increase the accuracy and completeness of reports. For example, submitter errors, such as inaccurate drug names, create a burden for FDA.[58] Through MedWatchPlus, the submitter will be provided with a menu of choices for the name of the drug. The questionnaire will also audit the information received and prompt for missing information.

[55]According to FDA, it is mostly larger manufacturers that have invested in the data exchange systems needed to use ESG. The agency expects that MedWatchPlus will provide smaller manufacturers with a more cost effective means of reporting adverse events electronically.

[56]FDA enters all adverse event reports sent directly to it from patients and healthcare providers. The agency also enters all electronic reports from manufacturers, as well as all paper reports from manufacturers concerning new molecular entities for the first 3 years after approval. New molecular entities are potentially innovative drugs containing active chemical substances that have never been approved for marketing in the United States in any form. For all other paper reports from manufacturers, FDA only enters reports for serious adverse events. In fiscal year 2008, 93,085 paper reports from manufacturers of adverse events not classified as serious, which comprised almost 18 percent of all reports received by FDA, were not entered into AERS.

[57]According to FDA, paper reports cost approximately $35 per report to process, whereas electronic submissions cost approximately $12 per report to process.

[58]In a 2008 report, IOM noted that submitters may use multiple different names for the same drug due to the use of the trade name rather than the generic name, inclusion of dosage information in the drug name, or misspellings. IOM reported that a manual review of the AERS database identified 300,000 different drug names that reviewers determined actually represented only about 3,000 standard generic names. S. Robinson, R. Pool, and R. Giffin, Institute of Medicine of the National Academies, Forum on Drug Discovery, Development, and Translation, *Emerging Safety Science: Workshop Summary* (Washington, D.C.: National Academies Press, Apr. 9, 2008).

Adverse Event Storage and Analysis

FDA is also developing a new database to store adverse event reports once they have been submitted that should offer integrated data analysis features to facilitate the identification of safety issues. The new database, the FDA Adverse Event Reporting System (FAERS), is expected to receive reports from MedWatchPlus and other FDA applications for all FDA-regulated products and store them in a single location.[59] In addition to avoiding redundancy among the center databases, FDA has stated that a consolidated database would benefit drug safety, for example, by facilitating the sharing of adverse event reports across centers for combination products.[60] FAERS will replace AERS and is intended to address some current AERS limitations that affect how OSE staff do their work. FDA officials told us that OSE staff view the current version of AERS as a giant "filing cabinet," which lacks integrated software for data mining and signal management that could help them to monitor drug safety more effectively.[61] FDA officials said that, currently, to use the software, staff have to periodically extract the data from AERS and transfer them to another system for analysis, which means that analyses cannot be conducted in real time. In contrast, FDA plans to include integrated signal management and data mining software in FAERS, which will make these features easier to use and allow for analyses of safety signals closer to real time.

FDA officials said that the agency plans to address other adverse event report quality problems by including new features in FAERS. For example, an adverse event reviewer told us that AERS lacks a dedicated data field (such as a checkbox) to indicate whether a female patient described in an adverse event report is pregnant. As a result, reviewers must manually review the narrative of reports for women aged 15 to 45 to determine whether the patient was pregnant. FDA officials said that FDA plans to include a dedicated data field to indicate whether a report identified the patient as pregnant in FAERS. An adverse event reviewer also identified the lack of a link between an adverse event report and FDA-approved label

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[59]Currently, FDA maintains multiple databases for storing adverse event data. For example, AERS is used by CDER to store drug reports, while another center uses a separate database to store medical device reports.

[60]Combination products are comprised of two or more regulated components, for example, a drug-device combination product. According to FDA, sharing information about such products is currently difficult to do in a timely manner.

[61]Data mining software allows OSE staff to more easily identify patterns in the reports to find new safety signals. Signal management software allows OSE staff to monitor safety signals over time and create alerts.

information as a problem because it hinders staff in determining whether the adverse event is new or has already been identified and included in the drug's label. FDA officials said that linkage to label information is a goal for inclusion in FAERS, but it is complex and the agency does not have a time frame for its inclusion.

FAERS development has experienced delays, but FDA expects that it will be partially implemented by the end of 2010. FDA began developing an update to AERS in 2004. However, according to a 2006 report by an FDA contractor, deficiencies in FDA's procurement practices and the agency's decision to expand the project's scope to develop an agencywide database for all FDA-regulated products resulted in delays.[62] The contractor reported that these obstacles in development resulted in a 4- to 5-year delay and an estimated $25 million in additional development costs. Currently, FDA indicated that it is prioritizing FAERS requirements to determine what features and capabilities are possible for the first version of FAERS. FDA plans to complete the first version of FAERS, for drugs and biologics, by the end of 2010. However, this version will not include fully integrated data mining and signal management software. FDA does not have an estimated time frame for when these features will be fully integrated.

FDA Increased Funding for External Data Acquisition and Is Beginning to Access Data from Federal Sources

FDA increased funding for acquiring the external data that it uses to examine drug safety issues from about $5 million in fiscal year 2007, to about $28 million in fiscal year 2008.[63] FDA recently added additional funds to existing contracts with four private companies that conduct drug safety studies using their own databases of electronic health information. Since FDA initially awarded about $5.4 million in total to these companies in fiscal year 2005, these contracts have yielded five completed epidemiologic studies on drug safety, including a study on how antidepressant use in pregnancy affects the health of newborns. In fiscal year 2008, FDA added about $9 million in total to the four contracts. However, FDA officials said that under the current contracts it is difficult to expand funding in response to the agency's needs and they will be

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[62]Breckenridge Institute, *Independent Verification and Validation of AERS II Requirements Process* (Breckenridge, Colo.: 2006).

[63]Most of the increase, about $22 million, came from user fee funding resulting from the reauthorization of PDUFA.

changing to a different contract type when these contracts end in 2010.[64] They said the new contract type will make it easier to add funds as the need arises for additional epidemiologic studies to examine previously unknown drug safety issues.

FDA has also used the increased data acquisition funds for contracts with private companies that allow FDA staff direct access to data that can be used to conduct drug safety studies internally. These contracts provide the agency with access to drug utilization data, which are useful to FDA for, among other things, providing an estimate of how many people have been exposed to a drug, which provides context for adverse event analyses. These contracts allow FDA to download the data onto the agency's servers where staff can access the data to conduct drug safety studies. In 2008, FDA awarded contracts valued collectively at over $14 million for a base year and 3 option years.[65] The three new contracts replaced an existing contract with a single vendor and, according to an FDA official, represent an approximate tripling of funding for access to drug utilization data. The official also said that contracts with three vendors allow shortcomings in one data set to be compensated by information from another. For example, one contractor has mail order pharmacy claims data, which are not available from the other two contractors.

In addition to funding contracts with private companies, FDA is in the early stages of forming partnerships with the Department of Veterans Affairs (VA), the Department of Defense (DOD), and the Centers for Medicare & Medicaid Services (CMS) to access their databases of electronic health information for drug safety research. FDA signed memoranda of understanding with VA and DOD in 2007 to enable these agencies to share information necessary to evaluate drug safety with FDA. FDA allocated about $3.6 million to fund these agreements in 2008, which among other things, provided funding for research projects, such as a study of the relationship between the use of smoking cessation drugs and suicidal behavior, and funding for staff to support such studies.[66] In

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[64]The new contracts will be indefinite delivery contracts, which do not procure or specify a firm quantity of services (other than a minimum or maximum quantity) and which provide for the issuance of orders for the performance of tasks during the period of the contract.

[65]FDA officials explained that the contracts are structured with multiple option years so that FDA has adequate time to learn to use the databases, but can choose to switch vendors as new technologies emerge.

[66]FDA allocated an additional $4.3 million for VA and DOD in fiscal year 2009.

addition, FDA signed an interagency agreement with CMS in August 2008 to access both Medicaid and Medicare data. As part of this agreement, FDA transferred $1 million to CMS in part to fund a project to create a Medicaid database amenable to research on drug safety.[67] FDA is also working on several pilot projects using Medicare prescription drug data. These data on Medicare beneficiaries provide the agency with access to new information on the elderly and disabled—groups that are generally underrepresented in traditional clinical trials that FDA uses to assess safety prior to approval. FDA officials said that partnering with federal agencies is beneficial because they have large databases of electronic health information that may be accessed more cheaply than contracting with private entities.

FDA Is in the Early Stages of Developing a Network of External Data Providers Intended to Enhance Its Drug Safety Surveillance

FDA is also taking steps to improve identification of safety issues by creating a network of external drug safety data providers, but the agency is in the early stages of developing it. The FDAAA-mandated surveillance system, known as the Sentinel System, will be a network of databases of electronic health information that can be utilized for safety signal evaluation for drugs and other marketed medical products. FDA officials said one of the purposes of the Sentinel System will be to provide the agency with an active surveillance tool that will be capable of generating safety signals that are not identifiable through AERS. For example, AERS relies on patients and doctors to submit adverse event reports, but if they do not recognize an event as being potentially drug-related, they may not file an adverse event report. In addition, FDA expects that the Sentinel System will build on the current data contracts the agency uses to conduct formal epidemiologic studies, which are generally used to confirm safety signals after they have been identified, by allowing researchers to specify potential safety problems in advance and monitor for these problems in near real time. The Sentinel System is in the early stages of development and as of June 2009 there were no established milestones.[68] Thus far, FDA

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[67]Currently, each state Medicaid program stores its data files in separate state databases, which makes it difficult to conduct drug safety studies. This project will combine these databases into a single, unified Medicaid database. An FDA official said the agency planned to continue funding this project in 2009 and has allocated an additional $1 million.

[68]In June 2009, we recommended that FDA develop a plan for completing Sentinel, including the establishment of milestones. We also recommended that FDA implement appropriate security and privacy safeguards as Sentinel is developed. GAO, *Privacy and Security: Food and Drug Administration Faces Challenges in Establishing Protections for Its Postmarket Risk Analysis System*, GAO-09-355 (Washington, D.C.: June 1, 2009).

has established a senior management team, conducted a series of meetings with stakeholders, and created a working group of federal agencies that are developing complimentary initiatives. FDA officials said they have not finalized funding or staffing plans for the system. In addition, many other key decisions have yet to be made, including: sources of data, an information technology infrastructure, and methods of analysis. In 2008, FDA awarded eight contracts to investigate these and other issues. Seven of the reports from these contracts have been completed and FDA expects that the remaining report will be completed by the end of 2009.

Although Staff Has Recently Increased, FDA Faces Challenges Meeting Its Expanding Postmarket Safety Workload

FDA's workload related to postmarket drug safety has increased as a result of new authorities and other factors. While the agency received increased funding and is hiring staff to conduct postmarket drug safety activities, it faces difficulties in recruiting the additional staff and external experts needed to meet its increasing responsibilities.

FDA Reports That New Postmarket Drug Safety Responsibilities Have Increased Its Workload and That It Is Challenged by Competing Priorities

FDA reports that new postmarket drug safety responsibilities and other factors have led to an increased workload for which FDA has identified a need for increased staff.[69] Of the OSE and OND staff that completed our DCI, 77 percent (40 of 52) indicated that their workload had increased or greatly increased since 2006. In addition, 60 percent (31 of 52) of the employees said that they either were not able to meet their postmarket drug safety responsibilities during an average workweek or were only able to meet these responsibilities by working overtime. Many employees told us during our small group interviews that one source of this increased workload has been the new postmarket drug safety responsibilities added by FDAAA. FDA officials said that requiring a drug sponsor to conduct

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[69]Similarly, in June 2009, we reported that FDA's workload had grown due to an increase in the agency's statutory responsibilities and a growing number of medical products subject to FDA oversight. We also reported that an increased reliance on user fee funding has limited the agency's ability to fulfill its oversight responsibilities in some other areas. GAO, *Food and Drug Administration: FDA Faces Challenges Meeting Its Growing Medical Product Responsibilities and Should Develop Complete Estimates of Its Resource Needs*, GAO-09-581 (Washington, D.C.: June 19, 2009).

postmarketing studies is more time consuming for FDA staff than the past process of requesting such studies. For example, to require a study, officials said the agency needs to document its rationale in a legally enforceable contract with a sponsor that may describe specific elements of the study design. The agency also works with sponsors to establish milestones for the completion of these studies. In addition, officials said the process of overseeing the development and implementation of a drug sponsor's required risk management plan has led to additional meetings between OND and OSE, as well as additional interactions with drug sponsors to review the proposal and discuss even minor modifications to it. FDA officials said that the new FDAAA authorities are especially time consuming because the agency is still developing processes for how to conduct this new work. Officials said that proposals for requiring postmarketing studies and REMS are being reviewed by others within FDA to ensure consistency in the application of the authorities. FDA officials expect that some of this additional workload will decrease as the process becomes more routine.

OND medical reviewers described challenges meeting their premarket and postmarket responsibilities. Several reviewers noted that their primary focus is on completing premarket work within PDUFA time frames, and issues related to postmarket safety receive lesser priority. Two medical reviewers said that important identified safety issues would take priority over meeting PDUFA deadlines, but other reviewers told us that their workload prevents them from conducting reviews that would allow them to identify new postmarket safety issues. For example, reviewers said they are unable to fully review the Periodic Safety Update Reports submitted by drug sponsors, which are comprehensive reports containing information on serious and nonserious adverse events.[70] According to some OND reviewers, medical reviewers do not have the time to fully analyze these

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[70]FDA defines adverse events as serious when they result in death, are life-threatening, require inpatient hospitalization or prolongation of hospitalization, cause significant disability/incapacity, or cause a birth defect. Other events may also qualify as serious if they require medical or surgical intervention to prevent one of these outcomes from occurring. See 21 C.F.R. § 314.80(a) (2009). FDA defines nonserious adverse events as any events that do not qualify as serious. However, an FDA medical reviewer advised us that events categorized as nonserious may include events that would constitute an important safety signal. For example, the reviewer said that a medical event that is significant enough to send a patient to the emergency room may not be considered serious in the regulatory sense, if the patient is treated and released without being admitted to the hospital. FDA officials said that, as a result, staff need to consider both serious and nonserious adverse event reports when monitoring the safety of drugs.

reports to look for potential safety issues.[71] OSE staff told us that workload demands prevent them from reviewing these reports. Given that nonserious adverse events may not be entered into AERS, failure to fully review Periodic Safety Update Reports may result in FDA missing safety signals for nonserious adverse events.

OSE also reported that competing demands impact its ability to meet its postmarket responsibilities, such as its new premarket responsibilities for reviewing proposed proprietary drug names within PDUFA deadlines and communicating its decisions to drug sponsors. The staff involved in these reviews estimated that approximately 90 percent of their time is spent on such premarket activities, which leaves little time to spend on their other postmarket drug safety responsibilities, such as analyzing reports of medication errors. For example, an FDA employee told us that they do monitor AERS to identify safety signals, but they do not have time to complete follow-up reviews of these signals. Although employees agreed that the most important safety issues do get resolved, one employee said that follow-up reviews are often lower priority than fulfilling premarket responsibilities.[72] In addition, other OSE staff identified competing demands that hampered their ability to conduct postmarket safety work. For example, OSE adverse event reviewers told us that consult requests from OND consumed the majority of their time, leaving them less time to conduct self-initiated safety analyses of adverse event data. According to FDA, each OSE adverse event reviewer receives an average of about 44 adverse events reports per day,[73] and reviewers told us that given competing priorities, they are not able to review them all.

A contractor reviewing OSE's increasing workload found that additional staff will be needed in order to fulfill the new responsibilities related to FDAAA and the MOA. According to the contractor's December 2008

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[71]OND is officially responsible for reviewing these reports. OND medical reviewers described several other challenges that impeded their review, including a lack of sufficient epidemiologic expertise and available guidance. They also said that these reports are of poor quality and do not provide the total numbers of adverse events reported by the sponsor since the drug was approved, which limits their usefulness in identifying potential trends in the data.

[72]One employee said that there are safety issues identified in 2006 for which they still have not been able to complete follow-up reviews.

[73]Adverse event reviewers told us that the number of reports they receive varies considerably based on the drugs in each adverse event reviewer's portfolio, and can be as high as 200 reports per day.

report, OSE would need an estimated total of 453 full-time equivalent employees by 2011 to meet its increased workload, more than double OSE's current staffing.[74] While the contractor identified workload increases throughout OSE, it found that the greatest increases would be related to the review of risk management plans and postmarket safety data, such as adverse events.

FDA Has Hired Some New Staff, but May Face Obstacles Recruiting Additional Staff to Manage Its Increased Workload

OSE and OND officials described fiscal year 2008 as a very successful hiring year, due in part to specific hiring initiatives. FDA indicated that since the start of fiscal year 2008, OND increased its staff from 736 to 928 and OSE increased its staff from 114 to 193.[75] The staff hired included OND medical reviewers who conduct premarket and postmarket reviews and OSE staff with postmarket drug safety responsibilities, such as epidemiologists and risk management experts. Agency officials attributed this success to specific hiring initiatives. For example, officials told us that both OSE and OND used a summer 2008 job fair and direct-hire authority to hire staff more quickly.[76] While the agency has had direct-hire authority for medical reviewers since 2003, FDA indicated that it temporarily obtained direct-hire authority from April 2008 through September 2008 for epidemiologists. The OSE and OND Directors said that they hired candidates within weeks under the authority, rather than the 3 to 6 months it can typically take to announce positions, screen applications, conduct interviews, and hire individuals. The OSE Director told us that without the authority, interested candidates have sometimes accepted employment

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[74]Leadership Performance Solutions, *Office of Surveillance and Epidemiology Workload Analysis Report*, a report prepared at the request of FDA (Silver Spring, Md.: December 2008). The contractor acknowledged that its estimates were not statistically valid because it used agency estimates to analyze OSE's future workload. The contractor noted that OSE did not have a consistent, systematic process for collecting workload data and recommended that the office implement an ongoing process for estimating staffing needs. In a 2009 report, we also found that FDA lacks reliable data on workload and accomplishments, and we recommended that FDA develop an evidence-based estimate of the resources need to fulfill all of its responsibilities. GAO-09-581.

[75]FDA provided staff counts as of September 22, 2009. According to FDA officials, the fiscal year 2009 staffing ceiling for OND was 930, while for OSE it was 211.

[76]Direct-hire authority, given by the Office of Personnel Management, allows agencies to expedite the hiring of qualified applicants for critically needed positions by eliminating the need to comply with certain elements of the federal hiring process. See 5 C.F.R. §§ 337.201-337.206 (2009).

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offers elsewhere before FDA could extend its own offer.[77] In addition, an official said that CDER's ability to offer hiring bonuses, relocation reimbursement, and student loan repayment contributed to its hiring success during fiscal year 2008.[78]

Although OSE significantly increased its staff in fiscal year 2008, hiring and staffing challenges could make it difficult for the office to meet the workload generated by its new postmarket drug safety responsibilities. While the contractor estimated that OSE would need 453 full-time equivalent employees by 2011, the OSE Director did not know if the agency planned to increase OSE's fiscal year 2009 staff ceiling of 211 in fiscal year 2010. However, officials said that recruiting the right people with the desired drug safety expertise is difficult. For example, an OSE official said that it is hard to find candidates who have experience with the specific epidemiologic activities conducted by FDA, and the agency therefore looks for candidates with epidemiologic skills who can then be trained by the agency once they are hired. Officials indicated that while the new hires can bring up-to-date skills, their lack of experience means that it can take up to 3 years before newly hired employees can work independently. In addition, an official said it is difficult for OSE to compete with drug companies, who can offer higher compensation, for the same pool of talent. Given the estimated workload increases identified in the FDA contractor's December 2008 review, OSE may be challenged to hire staff quickly enough to meet its increasing workload.

FDA Faces Technological and Staffing Challenges That Limit Its Capacity to Conduct a Growing Number of Postmarket Safety Studies

FDA officials said that they lack adequate computational capacity and enough staff to make full use of external sources of data for drug safety studies, and FDA expects the number of such studies to grow. OSE has increased funding for acquiring external data and a recent workload planning report prepared by an FDA contractor indicates that OSE intends to triple the number of epidemiological studies it conducts using such data from 13 in 2008 to 39 in 2011. An OSE official told us that currently, most of the epidemiologic studies are conducted by contractors, but that OSE would like to conduct more studies internally. The official said that internal studies afford FDA more control over the analyses, as well as

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[77]According to FDA, the agency no longer plans to request new direct-hire authority for epidemiologists from the Office of Personnel Management.

[78]The official said the incentives it offered new hires were made available by FDA from savings realized from unfilled vacancies. These incentives are no longer available.

provide increased professional opportunities to OSE staff, which may lead to greater staff retention. However, the official said that conducting more internal studies would require greater computational capacity and more staff.[79] OSE officials told us, for example, that the current technological infrastructure limits staff to running a single analysis at a time and that the computer servers in CDER "routinely crash" when dealing with large data sets. OSE officials also said that they lack programmers who are needed to extract data from databases and prepare data sets for analysis. OSE officials said that the office has faced difficulties hiring programmers because the position descriptions that it would use to hire these programmers are currently only available to the agency's Office of Information Management, which has meant that such staff may not be hired by OSE.[80] They indicated that, without enough programmers, this work is shifted to epidemiologists, who must then spend more time on each study and have less time to devote to developing and carrying out additional studies.

CDER is developing a computational science center that is intended to address some of these challenges, but this center is in the early stages of development. FDA indicated that the center is intended to support both pre- and postmarket quantitative analyses of the safety, efficacy, and quality of drugs.[81] FDA officials said it should address current problems by providing increased computational capacity and more staff, including programmers and data managers that can be utilized by OSE. However, they said that the center is currently in the developmental stages, and that there is no time frame for its completion.[82] In the interim, OSE is using short-term fixes, such as increasing the memory capacity of existing servers. OSE officials noted that OSE may also contract out some

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[79]According to FDA, studies completed by external contractors also consume agency resources. An FDA official said that each external epidemiologic study conducted by a contractor should have an OSE lead epidemiologist assigned to it to help plan the study, as well as a programmer to extract the data from the contractor's database.

[80]Agency officials said that OSE could still hire staff with programming expertise under the office's existing position descriptions. While OSE officials said that they have managed to hire an employee with programming expertise to support ongoing drug safety studies under the epidemiologist position description, they said that it is extremely rare to find a programmer who meets all of the qualification requirements for an epidemiologist position.

[81]According to FDA, the center will be a virtual organization that draws on expertise from across CDER and it will not be housed in a single location or set of offices.

[82]According to FDA, a contractor has developed a strategic plan for the completion of the center for activities to be taken through the end of fiscal year 2013.

programming work, although they described challenges associated with contracting out this type of work. The officials said that each drug safety study can take 1 to 2 years to complete and receiving programming support on a task-by-task basis requires OSE to spend time reeducating new programmers each time there is a new task. In contrast, an OSE official said that having programmers within CDER could allow them to gain expertise on the kind of work OSE does.

FDA Has Encountered Difficulties Filling Vacancies for Its Increasingly Utilized Committee of External Drug Safety Experts

FDA increasingly utilized external drug safety experts serving on DSaRM to participate in advisory committee meetings to discuss identified safety issues of specific products, but the agency faces challenges recruiting new members. From 2002 through 2006, DSaRM met 9 times in 5 years—5 times on its own as a committee and 4 times as part of joint meetings with other advisory committees. DSaRM met more frequently from January 2007 through December 2008, meeting 9 times—once on its own and 8 times as part of joint meetings. Most DSaRM meetings, and all 9 of the meetings in 2007 and 2008, have been held to discuss drug-specific issues. In addition to attending joint advisory committee meetings, individual DSaRM members served temporarily to supplement expertise during 12 meetings of other CDER advisory committees that occurred from 2007 through 2008.[83] While several DSaRM members acknowledged the important expertise in drug safety that they can bring to discussions with other advisory committees, some members told us that the small number of meetings involving only DSaRM has resulted in a lack of cohesion among committee members. In addition, some members noted that meeting as a single committee would allow them to discuss broad principles of drug safety, rather than specific drug products, and to examine lessons learned across meetings. One member noted that without meeting as a single group on broad safety issues, the committee is unable to take advantage of the cumulative learning that comes with a coherent process. An FDA official said that the agency recognizes that temporarily serving on other advisory committees has been a burden for DSaRM members. The official said that, therefore, the agency has been expanding

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[83]In a January 2007 response to IOM's drug safety report, FDA indicated that it would increase involvement of epidemiology expertise in advisory committee meetings, including by utilizing DSaRM members. FDA, *The Future of Drug Safety - Promoting and Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report*, January 2007, http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrug SafetyInformationforPatientsandProviders/UCM171627.pdf (accessed July 22, 2009).

a pool of consultants that can instead provide temporary drug safety expertise at these other advisory committee meetings.[84]

Despite the increased demand for DSaRM's drug safety expertise, the agency has been challenged to fill all of the committee's vacancies. For the past few years DSaRM has had between 6 and 9 of its 14 slots vacant. In contrast, from 2003 through 2006, DSaRM had no more than one vacancy.[85] A few of the DSaRM members that we interviewed told us that additional members are needed to reduce the existing members' workload. The OSE Director said that a more intensive effort to recruit members to the committee began in 2008, but it has been difficult to find qualified individuals who have no financial conflicts of interest.[86] Recruiting new members will be especially important because 3 members' terms expired on May 31, 2009. An official said that the agency appointed 3 new members to the committee on July 1, 2009. While this gives the committee a total of 8 members, 3 of these members' terms expire on May 31, 2010. An official said the agency is reviewing approximately 43 candidates for potential conflicts of interest, with the goal of filling the DSaRM vacancies as soon as possible.

The number of vacancies may present challenges to FDA's implementation of new FDAAA requirements for seeking advice from DSaRM on risk management plans and the analysis of drug safety data. FDA indicated that it plans to convene DSaRM in accordance with the FDAAA requirements, although officials said that the agency has not yet done so and the requirements will result in FDA using DSaRM differently than in the past. An official said that the agency is therefore in the process of determining how to best involve the committee in these new activities. Some of the

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[84]Consultant pools are lists of individuals who FDA has determined have expertise that may be needed in the future for a specific advisory committee meeting. FDA officials also told us that consultants may be former FDA advisory committee members. GAO, *FDA Advisory Committees: Process for Recruiting Members and Evaluating Potential Conflicts of Interest*, GAO-08-640 (Washington, D.C.: Sept. 30, 2008).

[85]Although DSaRM was created in 2002 and held one meeting in that year, members were not appointed to the committee until 2003. The 2002 meeting was attended by nine temporary members, most of whom would be appointed as full members in 2003.

[86]See 5 U.S.C. app. 2 § 5(b)(2). FDA advisory committees are subject to the Federal Advisory Committee Act, which requires that committee memberships also be fairly balanced in terms of views presented and the functions to be performed by the advisory committee. FDA is also experiencing similar recruitment difficulties for recruiting members of other committees as well. See GAO-08-640.

DSaRM members with whom we spoke noted that the FDAAA provisions appear to relate to broader drug safety issues than the committee has generally considered. One member noted that the committee would not be able to fulfill the new FDAAA requirements at product-specific meetings; rather, the complete committee would probably have to meet on its own. If the agency continues to have a large number of vacancies with DSaRM, it could be difficult for the committee to fulfill these additional duties while also participating in discussions of specific drug products.

Conclusions

FDA's oversight of postmarket drug safety has been a long-standing concern, with various groups reporting problems for more than 30 years. Our 2006 report on this topic cited the need for FDA to improve its decision-making process for postmarket drug safety. To enhance this process, FDA has recently begun to take steps that respond to our concerns, as well as those expressed by others. However, many of its initiatives are new and are in the early stages of development and implementation. For example, the agency's efforts to begin formalizing its decision-making process, hire more staff, and establish dedicated safety positions within OND are an encouraging start. As FDA has gone about planning to improve its postmarket oversight, it has also needed to respond to changes brought about by FDAAA, which resulted in increased responsibilities for postmarket drug safety. FDA employees have since cited several instances in which increases in their workload and competing premarket demands and other priorities have prevented them from fully carrying out their postmarket drug safety responsibilities. We recognize that with a growing workload, come additional challenges. The agency's initiatives will require time and resources before they can make a significant impact on previously identified problems. While we view FDA's plans as positive, it is not yet clear if or when FDA's decision-making process will be substantially improved as a result of its efforts.

As one of its efforts to enhance postmarket decision making, the agency plans to transfer additional authorities from OND to OSE. Transferring these authorities could help FDA better align decision-making responsibilities with the division of expertise between the two offices. However, the agency has set no time frames for their transfer and has stated that OSE needs increased experience and resources before the office is able to assume the new authorities. FDAAA provided the agency with greater flexibility to allocate funds to postmarket drug safety. Therefore, as FDA considers this transfer, it is important that it take advantage of this flexibility to align its resources in such a way that it strike an appropriate balance between its competing premarket and

postmarket priorities and ensure postmarket safety receives sufficient attention. Establishing a time frame for this transfer and adequately preparing OSE to assume these authorities are important next steps to ensuring appropriate oversight of postmarket drug safety.

Recommendation

To address weaknesses in FDA's oversight of postmarket drug safety, we recommend that the Commissioner of FDA develop a comprehensive plan for transferring the additional regulatory authorities from OND to OSE that includes time frames for the transfer and steps to ensure resources are properly aligned to allow OSE to assume these responsibilities.

Agency Comments and Our Evaluation

We provided a draft of this report to HHS for review. HHS provided comments from FDA, which agreed with our recommendation. FDA's comments are reprinted in appendix II. FDA also provided technical comments, which we incorporated as appropriate.

Regarding our recommendation, FDA agreed that developing a comprehensive plan to prepare OSE for the transfer of additional regulatory authorities is desirable. However, it noted that the details of such a plan, including time lines, remain dependent upon available funding and the agency's ability to recruit and retain the necessary staff to assume additional responsibilities. While we agree that both funding and staff are important to the successful transfer of these regulatory authorities, we believe that FDA has the flexibility to align its resources in such a way as to ensure that postmarket drug safety receives appropriate attention. Furthermore, we believe that the development of a comprehensive plan and time line is an important step towards ensuring that necessary funding levels and staffing needs are identified and secured.

In addition to commenting on our recommendation, FDA addressed several other issues. First, it emphasized that, since our 2006 report was issued, it has undertaken a comprehensive set of activities to improve its postmarket drug safety program. We agree that FDA has begun to take some important steps to improve its decision-making process, but as we noted earlier, we believe that it is too early to judge the effectiveness of these steps. Second, FDA stressed that postmarket drug safety decisions are often complex and frequently require the involvement of staff from a number of scientific disciplines. The agency noted that for each of the many regulatory decisions that need to be made, a decision maker must have the delegated responsibility and authority to make these decisions. It indicated, for example, that in most cases OND has the broadest expertise

to make decisions about postmarket drug safety. We understand that, while multiple areas of expertise are brought to bear in assessing safety issues, there may need to be a single office responsible for making final decisions. We added language in the report to clarify FDA's position on OND expertise in postmarket decision making. Third, it also noted that we implied that OND and OSE are the only significant participants in drug safety decision making. We understand that, depending on the safety issue, a variety of FDA offices and scientific disciplines may be involved in decision making and our draft report acknowledged this. However, our work appropriately focused on OND and OSE because of the key roles they play in postmarket decision making and because of the concerns that were raised about the relationship between these two offices in our 2006 report. Finally, FDA said that our report omitted the contribution its Drug Safety Oversight Board has made to postmarket decision making. We recognize that this board plays a role in postmarket safety, as discussed in our 2006 report. The focus of our current report was to describe new initiatives underway at FDA. However, we have added information about the board to our report in response to FDA's comments.

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the Commissioner of FDA and appropriate congressional committees. The report also will be available at no charge on the GAO Web site at http://www.gao.gov. If you or your staff have any questions about this report, please contact me at (202) 512-7114 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 III.

Sincerely yours,

Marcia Crosse
Director, Health Care

Appendix I: Status of FDA Actions Related to Our 2006 Recommendations

In our 2006 report,[1] we made recommendations to the Food and Drug Administration (FDA) that were intended to improve its oversight of the postmarket drug safety decision-making process. Specifically, we recommended that FDA:

1. revise and implement its draft policy on major postmarket drug safety decisions,

2. clarify the Office of Surveillance and Epidemiology's (OSE) role in FDA's scientific advisory committee meetings involving postmarket drug safety issues,

3. improve the Center for Drug Evaluation and Research's (CDER) dispute resolution process by revising the pilot program for resolving differing professional opinions (DPO) to increase its independence,[2] and

4. establish a mechanism for systematically tracking OSE's recommendations and subsequent safety actions.

Regarding the draft policy on major postmarket drug safety decision making, according to FDA, the agency no longer plans to complete it. This policy was intended to ensure that all major postmarket safety recommendations be discussed by the relevant officials and present a process for making recommendations and resolving disagreements. An official said that, in light of the multidisciplinary approach it has established through the Safety First Initiative and principles of Equal Voice, FDA's postmarket decision-making process has changed, and as a result, the process described in the draft policy was no longer relevant. The official said that the agency determined that it was not necessary to issue a separate policy on major postmarket drug safety decision making.

Regarding the clarification of OSE's role at scientific advisory committee meetings, an FDA official told us that instead of developing such a policy,

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[1]GAO, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, GAO-06-402 (Washington, D.C.: Mar. 31, 2006).

[2]In our prior report, we referred to multiple FDA processes for resolving scientific disputes as "dispute resolution processes," including what FDA terms as its DPO program. See GAO-06-402. For the purposes of this report, we use the term "dispute resolution" to refer to the broad category of processes involved in resolving scientific disputes, including the review of the dispute by the supervisory chain and DPO program.

the agency added language to the manual for the agency staff responsible for managing the advisory committees. The manual instructs these staff to ask the OND division coordinating an advisory committee meeting involving drug safety issues whether OSE should be involved in the meeting. This manual does not specifically address the role of presentations by OSE staff in those advisory committee meetings. However, an FDA official we spoke with was not aware of any recent instances in which OSE employees were excluded from presenting at an advisory committee meeting. Of the 30 OSE employees who completed our data collection instrument, 15 indicated that they had no opinion about the extent to which CDER has become more or less accepting of employees expressing dissenting views at advisory committee meetings. However, of the remaining 15 employees, 10 indicated that CDER has been more accepting of such presentations since 2006.

Regarding CDER's DPO program, FDA initiated an agencywide review of its dispute resolution process that instituted new requirements for each center to follow. CDER indicated that it is making few changes to its DPO policy, which an official told us already incorporated most of the new elements resulting from the agencywide review. However, according to a July 2009 draft of that policy, the planned changes do not address our recommendation to increase the program's independence. A CDER official indicated that, under the revised policy, the Ombudsman would still consult with the CDER Director before deciding whether a dispute warrants formal review. In addition, the CDER Director is still the final decision maker regarding how the dispute should be resolved.

Regarding the implementation of a mechanism for systematically tracking OSE's recommendations and subsequent safety actions, FDA is in the process of implementing the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS). In January 2007, in response to our 2006 recommendation, FDA began to incorporate a safety module within DARRTS to track the agency's response to significant safety issues identified with the use of marketed drugs. For each significant safety issue, FDA creates a "tracked safety issue" within DARRTS that allows staff, among other things, to generate a workplan and assign responsibilities for managing these issues, as well as update their status. While the system contains documents describing specific recommendations and safety actions, an official told us that it does not, as we recommended, allow FDA to systematically track how issues were resolved and whether OSE's recommendations were implemented.

Appendix II: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

OCT 19 2009

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street N.W.
Washington, DC 20548

Dear Ms. Cross:

Enclosed are comments on the U.S. Government Accountability Office's (GAO) report entitled: DRUG SAFETY: FDA Has Begun Efforts to Enhance Postmarket Safety but Additional Actions Are Needed (GAO-10-68).

The Department appreciates the opportunity to review this report before its publication.

Sincerely,

Andrea Palm
Acting Assistant Secretary for Legislation

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Date: October 19, 2009

To: Acting Assistant Secretary for Legislation

From: Principal Deputy Commissioner of Food and Drugs

Subject: FDA's General Comments to GAO's Draft Report Entitled, *Drug Safety: FDA
            Has Begun Efforts to Enhance Postmarket Safety but Additional Actions Are
            Needed (GAO-10-68)*

FDA is providing the attached general comments to the U.S. Government Accountability
Office's draft report entitled, *Drug Safety: FDA Has Begun Efforts to Enhance
Postmarket Safety but Additional Actions Are Needed (GAO-10-68)*.

FDA appreciates the opportunity to review and comment on this draft report before it is
published.

Joshua M. Sharfstein, M.D.
Principal Deputy Commissioner of Food and Drugs

Attachment

**FDA's General Comments to the United States Government Accountability Office's
Draft Report Entitled,** *Drug Safety: FDA Has Begun Efforts to Enhance Postmarket
Safety but Additional Actions are Needed (GAO-10-68)*

The Food and Drug Administration (FDA) welcomes the opportunity to comment on the
Government Accountability Office's (GAO) findings in the draft report and respond to
the single recommendation made by GAO to FDA.

The safety of drugs throughout their lifecycle has always been a key focus of FDA's
mission to protect and promote the public health. Since the GAO issued its last report on
postmarket drug safety in 2006, the FDA has undertaken a comprehensive set of activities
to improve our postmarket drug safety program, and much progress has been made.
These efforts are now incorporated into the *Safety First* initiative.

One major area of focus for FDA since the previous GAO report study has been
enhancing the processes for decision-making in the Center for Drug Evaluation and
Research (CDER), including making decisions about the safety of marketed drugs, as
examined in this report. While the GAO report has noted FDA's progress in this area, it
seems to focus on two Offices in CDER, the Office of New Drugs (OND) and the Office
of Surveillance and Epidemiology (OSE), as the only two significant participants in
postmarket drug safety decision-making. Postmarket drug safety decisions are often very
complex and frequently require much broader involvement than described by GAO,
including substantial input from a number of scientific disciplines working closely
together as a multidisciplinary team.

Ensuring the continued availability of drugs for which the benefits continue to outweigh
the risks demands that CDER reach institutional decisions efficiently within legislative,
regulatory and practical time limits. For each of the many regulatory decisions that must
be made, someone must be designated as the decision-maker, having the delegated
responsibility and authority to make the decision. In many cases, this is the signatory
authority. For most decisions related to new drug approvals and postmarket drug safety,
the delegated authority rests with OND, where staff with the broadest expertise and
experience in evaluating and managing the clinical risks and benefits for drug products
resides. For other types of regulatory decisions, the authority resides in other
organizational units where the most expertise about the issues exists. For example, as
mentioned in the report, authority for regulatory decision-making for proprietary names
was transferred to OSE because most of the expertise for issues related to regulation of
proprietary name exists in that organization. Similar transfer of regulatory authority
occurred some years ago, when signatory authority for manufacturing supplements was
moved from OND to the Office of New Drug Quality Assessment.

The GAO report emphasizes which organizational unit within the Center is assigned
regulatory (or signatory) authority for postmarket decisions. Under its *Equal Voice*
initiative, the focus of CDER's efforts over the past two years has been to assure that,
regardless of where the signatory authority resides, regulatory decisions are made only
after all appropriate expertise is brought to bear.

**FDA's General Comments to the United States Government Accountability Office's
Draft Report Entitled, *Drug Safety: FDA Has Begun Efforts to Enhance Postmarket
Safety but Additional Actions are Needed (GAO-10-68)***

Within this framework, the Center forms multidisciplinary teams to best inform the
ultimate decisions. Within those teams, each discipline is expected to have an "equal
voice" in representing the expertise they bring to bear on the issue. The designated
decision-maker is expected to carefully consider the input of all relevant disciplines
before reaching what he/she considers to be the best decision based on law, the
regulations, the science, the precedents, and public health concerns. If one of the
disciplines believes an action to be taken is so flawed (i.e., having a significant adverse
impact on public health and safety, to be counter to law or regulation, or to be counter to
existing precedent without adequate justification for deviation) that the action must be
revisited, that discipline can elevate the decision through the management ranks to the
Center Director.

One notable omission from the GAO's report is the contribution of the Drug Safety
Oversight Board (DSB) to postmarket decision-making. FDA established the DSB in
2005 to strengthen its internal management of complex drug safety issues and to provide
a forum to discuss these issues as well as emerging, and often controversial, drug safety
issues. The DSB provides advice and recommendations to the CDER Director on how
CDER should handle these important drug safety issues. In 2009, the DSB continued to
provide an ongoing forum for healthy debate within CDER, to anticipate and embrace
new methods for evaluating drug safety, and to incorporate the best ideas from its Federal
partners. Over the past year, the Board has added additional members and now has
representation from five agencies within the Department of Health and Human Services
(AHRQ, CDC, FDA, NIH, IHS), as well as representatives from the Department of
Veteran Affairs and the Department of Defense. In addition, the Board routinely invites
guest experts to participate in the meetings to help sort through complex drug safety
issues.

Response to GAO's Recommendation

**GAO recommended that FDA develop a comprehensive plan to prepare OSE for the
transfer of regulatory authorities from OND.**

FDA has acknowledged and explicitly stated in the Memorandum of Agreement between
OSE and OND that additional transfer of regulatory authorities and responsibilities would
occur once OSE has the resources and experience to accept such transfer. FDA agrees
that developing a comprehensive plan to prepare OSE for the transfer of additional
regulatory authorities is desirable. The details of such a plan, including timelines, remain
dependent upon available appropriated and PDUFA funding as well as the Agency's
ability to recruit and retain the necessary staff to assume additional responsibilities.

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Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

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