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DRUG SAFETY

FDA Needs to Further Address Shortcomings in Its Postmarket Decision-making Process

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Highlights

Highlights of GAO-07-599T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

DRUG SAFETY

FDA Needs to Further Address Shortcomings in Its Postmarket Decision-making Process

Why GAO Did This Study

In 2004, several high-profile drug safety cases raised concerns about the Food and Drug Administration's (FDA) ability to manage postmarket drug safety issues. In some cases there were disagreements within FDA about how to address these issues.

GAO was asked to testify on the effectiveness of FDA's postmarket decision-making process. This testimony is based on *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, GAO-06-402 (March 31, 2006). The report focused on the complex interaction between two offices within FDA that are involved in postmarket drug safety activities: the Office of New Drugs (OND), and the Office of Drug Safety (ODS). OND's primary responsibility is to review new drug applications, but it is also involved in monitoring the safety of marketed drugs. ODS is focused primarily on postmarket drug safety issues. ODS is now called the Office of Surveillance and Epidemiology.

For its report, GAO reviewed FDA policies, interviewed FDA staff, and conducted case studies of four drugs with safety issues: Arava, Baycol, Bextra, and Propulsid. To gather information on FDA's initiatives since March 2006 to improve its decision-making process for this testimony, GAO interviewed FDA officials and reviewed FDA documents in February and March 2007.

www.gao.gov/cgi-bin/getrpt?GAO-07-599T.

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

What GAO Found

In its March 2006 report, GAO found that FDA lacked clear and effective processes for making decisions about, and providing management oversight of, postmarket drug safety issues. There was a lack of clarity about how decisions were made and about organizational roles, insufficient oversight by management, and data constraints. GAO observed that there was a lack of criteria for determining what safety actions to take and when to take them. Certain parts of ODS's role in the process were unclear, including ODS's participation in the meetings of scientific advisory committees organized by OND to discuss safety issues for specific drugs. In the case of Arava, for example, ODS staff were not allowed to present their analysis of postmarket safety at an advisory committee meeting held to review Arava's safety risks and benefits. Insufficient communication between ODS and OND hindered the decision-making process. ODS management did not systematically track information about ongoing postmarket safety issues, including the recommendations that ODS staff made for safety actions. GAO also found that FDA faced data constraints that contributed to the difficulty in making postmarket safety decisions. GAO found that there were weaknesses in the different types of data available to FDA, and FDA's access to data was constrained by both its authority to require certain studies and its limited resources.

During the course of GAO's work for its March 2006 report, FDA began a variety of initiatives to improve its postmarket drug safety decision-making process, including the establishment of the Drug Safety Oversight Board. FDA also commissioned the Institute of Medicine to examine the drug safety system, including FDA's oversight of postmarket drug safety. GAO recommended in its March 2006 report that FDA take four steps to improve its decision-making process for postmarket safety. GAO recommended that FDA revise and implement its draft policy on the decision-making process for major postmarket safety actions, improve its process to resolve disagreements over safety decisions, clarify ODS's role in scientific advisory committees, and systematically track postmarket drug safety issues. FDA has initiatives underway and under consideration that, if implemented, could address three of GAO's four recommendations. Because none of these initiatives was fully implemented as of March 2007, it was too early to evaluate their effectiveness. In the 2006 report GAO also suggested that Congress consider expanding FDA's authority to require drug sponsors to conduct postmarket studies, as needed, to collect additional data on drug safety concerns.

Mr. Chairman and Members of the Subcommittee,

I am pleased to be here today as you examine the Food and Drug Administration's (FDA) process for decision making regarding postmarket drug safety issues. In 2004, several high-profile drug safety cases raised concerns about FDA's ability to manage postmarket drug safety issues. Those cases showed that there were disagreements and potential delays within FDA about how to address serious safety problems. My remarks today are based on GAO's March 2006 report on FDA's postmarket decision-making process (*Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, GAO-06-402). I will also discuss a number of FDA initiatives to improve its decision-making process, including some that respond to the recommendations we made in that report.[1]

In carrying out the work for our report between December 2004 and March 2006, we focused on two offices within FDA's Center for Drug Evaluation and Research (CDER) that are involved in postmarket drug safety activities: the Office of New Drugs (OND) and the Office of Drug Safety (ODS).[2] While there is some overlap in the activities of OND and ODS, they have different organizational characteristics and perspectives on postmarket drug safety. OND is involved in postmarket drug safety activities as one aspect of its larger responsibility to review new drug applications, and it has the ultimate responsibility to take regulatory action concerning the postmarket safety of drugs. ODS is primarily focused on postmarket drug safety, which includes the review of reports of adverse reactions to drugs. ODS operates primarily in a consultant capacity to OND and does not have any independent decision-making responsibility.

For our report, we interviewed ODS, OND, and other CDER managers and staff, as well as drug safety experts from outside FDA. We also analyzed documents describing internal FDA policies and procedures. In order to obtain an in-depth understanding of FDA's policies and procedures, we conducted case studies of four drugs—Arava, Baycol, Bextra, and

[1]The report is available online at www.gao.gov/cgi-bin/getrpt?GAO-06-402.

[2]ODS was renamed the Office of Surveillance and Epidemiology in May 2006. For the purposes of this testimony, we are referring to this office by its former name.

Propulsid—that help to illustrate the decision-making process.[3] Each of these drugs presented significant postmarket safety issues that FDA acted upon in recent years, and they reflect differences in the type of adverse event or potential safety problem associated with each drug, the safety actions taken, and the OND and ODS staff involved. To follow up with FDA about its responses to our recommendations and its initiatives to improve its postmarket safety decision-making process, we interviewed four FDA managers, including CDER's Associate Director for Safety Policy and Communication, in February and March 2007. We did not evaluate the effectiveness of FDA's efforts to respond to our recommendations. All of our work was conducted in accordance with generally accepted government auditing standards.

In summary, we found that FDA lacked a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues. There was a lack of clarity about how decisions were made and about organizational roles, insufficient oversight by management, and data constraints. We observed that there was a lack of criteria for determining what safety actions to take and when to take them, which likely contributed to disagreements over decisions about postmarket safety. Certain parts of ODS's role in the process were unclear, including ODS's participation in scientific advisory committee meetings that were organized by OND to discuss specific drugs. Although ODS staff presented their analyses during some of these meetings, we found examples of the exclusion of ODS staff from making presentations at several meetings. For example, in 2003 ODS staff, who had recommended that Arava be removed from the market, were not allowed to discuss their analysis of Arava's postmarket safety data at a scientific advisory committee meeting. This meeting was held to review Arava's safety risks and benefits in the context of other similar drugs. Insufficient communication between ODS and OND's divisions was an ongoing concern and hindered the decision-making process. For example, ODS did not always know how OND had responded to ODS's safety analyses and recommendations. ODS management did not systematically track information about the recommendations its staff made and OND's response. This limited the ability of ODS management to provide effective oversight so that FDA could ensure that safety concerns were addressed

[3]FDA approved Arava to treat arthritis; Baycol to treat high cholesterol; Propulsid to treat nighttime heartburn; and Bextra to relieve pain. Baycol, Bextra, and Propulsid have since been withdrawn from the market (in August 2001, April 2005, and March 2000, respectively), and the warnings on Arava's label were strengthened.

and resolved in a timely manner. FDA faced data constraints that contributed to the difficulty in making postmarket safety decisions. In the absence of specific authority to require drug sponsors to conduct postmarket studies, FDA has often relied on drug sponsors voluntarily agreeing to conduct these studies. However, these studies have not consistently been completed. FDA was also limited in the resources it had available to obtain data from outside sources.

FDA has undertaken a variety of initiatives to improve its postmarket drug safety decision-making process. Prior to the completion of our report in March 2006, FDA commissioned the Institute of Medicine (IOM) to examine the drug safety system, including FDA's oversight of postmarket drug safety. FDA also established the Drug Safety Oversight Board in CDER and made other internal changes. Since March 2006, FDA has continued to address its oversight and decision-making shortcomings. In January 2007, FDA issued a detailed response to IOM's recommendations. In our 2006 report, we recommended that FDA revise and implement its draft policy on the decision-making process for major postmarket safety actions, improve its process to resolve disagreements over safety decisions, clarify ODS's role in scientific advisory committees, and systematically track postmarket drug safety issues. FDA has since begun to implement initiatives that we believe could address the goals of three of the four recommendations in our 2006 report. FDA has made revisions to, but not finalized, its draft policy on major postmarket drug safety decisions. FDA has not improved its process to resolve disagreements over safety decisions and the agency is developing but has not finalized guidance to clarify ODS's role in scientific advisory committees. FDA is in the process of implementing a tracking system. Although FDA's initiatives are positive steps, they are not yet fully implemented and it is too soon to evaluate their effectiveness.

Background

Because no drug is absolutely safe, FDA approves a drug for marketing when the agency judges that its known benefits outweigh its known risks. After a drug is on the market, FDA continues to assess its risks and benefits. FDA reviews reports of adverse drug reactions (adverse events)[4] related to the drug and information from clinical studies about the drug that are conducted by the drug's sponsor. FDA also reviews adverse events

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

from studies that follow the use of drugs in ongoing medical care (observational studies)[5] that are carried out by the drug's sponsor, FDA, or other researchers. If FDA has information that a drug on the market may pose a significant health risk to consumers, it weighs the effect of the adverse events against the benefit of the drug to determine what actions, if any, are warranted.

The decision-making process for postmarket drug safety is complex, involving input from a variety of FDA staff and organizational units and information sources, but the central focus of the process is the iterative interaction between OND and ODS. After a drug is on the market, OND staff receive information about safety issues in several ways. First, OND staff receive notification of adverse event reports for drugs to which they are assigned and they review the periodic adverse event reports that are submitted by drug sponsors.[6] Second, OND staff review safety information that is submitted to FDA when a sponsor seeks approval for a new use or formulation of a drug, and monitor completion of postmarket studies. When consulting with OND on a safety issue, ODS staff search for all relevant case reports of adverse events and assess them to determine whether or not the drug caused the adverse event and whether there are any common trends or risk factors. ODS staff might also use information from observational studies and drug use analyses to analyze the safety issue. When completed, ODS staff summarize their analysis in a written consult. According to FDA officials, OND staff within the review divisions usually decide what regulatory action should occur, if any, by considering the results of the safety analysis in the context of other factors such as the availability of other similar drugs and the severity of the condition the drug is designed to treat. Then, if necessary, OND staff make a decision about what action should be taken.

Several CDER staff, including staff from OND and ODS, told us that most of the time there is agreement within FDA about what safety actions should be taken. At other times, however, OND and ODS staff disagree

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

[6]Health care providers and patients can voluntarily submit adverse event reports to FDA. Adverse event reports become part of FDA's computerized database known as the Adverse Event Reporting System.

about whether the postmarket data are adequate to establish the existence of a safety problem or support a recommended regulatory action. In those cases, OND staff sometimes request additional analyses by ODS and sometimes there is involvement from other FDA organizations. In some cases, OND seeks the advice of FDA's scientific advisory committees, which are composed of experts and consumer representatives from outside FDA.[7] In 2002, FDA established the Drug Safety and Risk Management Advisory Committee, 1 of the 16 human-drug-related scientific advisory committees, to specifically advise FDA on drug safety and risk management issues. The recommendations of the advisory committees do not bind the agency to any decision.

FDA has the authority to withdraw the approval of a drug on the market for safety-related and other reasons, although it rarely does so.[8] In almost all cases of drug withdrawals for safety reasons, the drug's sponsor has voluntarily removed the drug from the market. For example, in 2001 Baycol's sponsor voluntarily withdrew the drug from the market after meeting with FDA to discuss reports of adverse events, including some reports of fatalities.[9] FDA does not have explicit authority to require that drug sponsors take other safety actions; however, when FDA identifies a potential problem, sponsors generally negotiate with FDA to develop a mutually agreeable remedy to avoid other regulatory action. Negotiations may result in revised drug labeling or restricted distribution. FDA has limited authority to require that sponsors conduct postmarket safety studies.

[7]These committees are either mandated by legislation or are established at the discretion of the Department of Health and Human Services.

[8]21 U.S.C. § 355(e). FDA may propose withdrawal when, for example, it determines through experience, tests, or other data that a drug is unsafe under the conditions of use approved in its application, there is a lack of substantial evidence that the drug will have the effect that it purports to have or that is suggested in its labeling, or required patent information is not timely filed. Prior to withdrawal, FDA would need to notify the affected parties and provide an opportunity for a hearing. Approval may be suspended immediately, prior to a hearing, if the Secretary of Health and Human Services finds that continued marketing of a particular drug constitutes an imminent hazard to the public health.

[9]At this meeting FDA communicated to the sponsor that it was considering proceeding with a withdrawal of the highest dose of Baycol because of its increased risk for a severe adverse event involving the breakdown of muscle fibers.

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

In our March 2006 report, we found that FDA's postmarket drug safety decision-making process was limited by a lack of clarity, insufficient oversight by management, and data constraints. We observed that there was a lack of established criteria for determining what safety actions to take and when, and aspects of ODS's role in the process were unclear. A lack of communication between ODS and OND's review divisions and limited oversight of postmarket drug safety issues by ODS management hindered the decision-making process. FDA's decisions regarding postmarket drug safety were also made more difficult by the constraints it faced in obtaining data.

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

While acknowledging the complexity of the postmarket drug safety decision-making process, we found through our interviews with OND and ODS staff and in our case studies that the process lacked clarity about how drug safety decisions were made and about the role of ODS. If FDA had established criteria for determining what safety actions to take and when, then some of the disagreements we observed in our case studies might have been resolved more quickly. In the absence of established criteria, several FDA officials told us that decisions about safety actions were often based on the case-by-case judgments of the individuals reviewing the data. For example, in the case of Bextra, ODS and OND staff disagreed about whether the degree of risk for serious skin reactions warranted a boxed warning, the most serious warning placed in the labeling of a prescription medication. Similarly, in the case of Propulsid, some staff, from both OND and ODS, supported proposing a withdrawal of approval because of the cardiovascular side effects of the drug while others believed label modifications were warranted.[10] Our observations were consistent with two previous internal FDA reports on the agency's internal deliberations regarding Propulsid and the diabetes drug Rezulin.[11] In those reviews FDA indicated that an absence of established criteria for determining what safety actions to take, and when to take them, posed a challenge for making postmarket drug safety decisions.

We also found that ODS's role in scientific advisory committee meetings was unclear. According to the OND Director, OND is responsible for setting the agenda for the advisory committee meetings, with the

[10]Propulsid's label was modified multiple times, including the addition of a boxed warning, to warn consumers and professionals about cardiovascular risks.

[11]Rezulin was removed from the market in 2000 because of its risk for liver toxicity.

exception of the Drug Safety and Risk Management Advisory Committee.[12] This includes who is to present and what issues will be discussed by the advisory committees. For the advisory committees (other than the Drug Safety and Risk Management Advisory Committee) it was unclear when ODS staff would participate. Although ODS staff presented their postmarket drug safety analyses during some advisory committee meetings, our case study of Arava provided an example of the exclusion of ODS staff. In March 2003, FDA's Arthritis Advisory Committee met to review the efficacy of Arava, and its safety in the context of all available drugs to treat rheumatoid arthritis.[13] The OND review division responsible for Arava presented its own analysis of postmarket drug safety data at the meeting, but did not allow the ODS staff—who had recommended that Arava be removed from the market—to present their analysis because it felt that ODS's review did not have scientific merit. Specifically, the OND review division felt that some of the cases in the ODS review did not meet the definition of acute liver failure, the safety issue on which the review was focused.[14]

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

A lack of communication between ODS and OND's review divisions and limited oversight of postmarket drug safety issues by ODS management also hindered the decision-making process. ODS and OND staff often described their relationship with each other as generally collaborative, with effective communication, but both ODS and OND staff told us that there had been communication problems on some occasions, and that this had been an ongoing concern. For example, according to some ODS staff, OND did not always adequately communicate the key question or point of interest to ODS when it requested a consult, and as ODS worked on the consult there was sometimes little interaction between the two offices. After a consult was completed and sent to OND, ODS staff reported that OND sometimes did not respond in a timely manner or at all. Several ODS staff characterized this as consults falling into a "black hole" or "abyss."

[12]ODS is responsible for setting the agenda for meetings of the Drug Safety and Risk Management Advisory Committee.

[13]The committee was asked to consider whether the data presented by the drug's sponsor supported improvement in physical function and whether the drug's labeling needed to be updated to add any additional warning about liver toxicity. Ultimately, the label was strengthened in 2003 to state that rare cases of severe liver injury, including cases of fatal outcomes, had been reported in Arava users.

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

OND's Director told us that OND staff probably do not "close the loop" in responding to ODS's consults, which includes explaining why certain ODS recommendations were not followed. In some cases CDER managers and OND staff criticized the methods used in ODS consults and told us that the consults were too lengthy and academic.

ODS management had not effectively overseen postmarket drug safety issues, and as a result, it was unclear how FDA could know that important safety concerns had been addressed and resolved in a timely manner. A former ODS Director told us that the small size of ODS's management team presented a challenge for effective oversight of postmarket drug safety issues. Another problem was the lack of systematic information on drug safety issues. According to the ODS Director, ODS maintained a database of consults that provided some information about the consults that ODS staff conducted, but it did not include information about whether ODS staff made recommendations for safety actions and how the safety issues were handled and resolved, such as whether recommended safety actions were implemented by OND.

Data Constraints Contributed to Difficulty in Making Postmarket Safety Decisions

Data constraints—such as weaknesses in data sources and FDA's limited ability to require certain studies and obtain additional data—contributed to FDA's difficulty in making postmarket drug safety decisions. OND and ODS used three different sources of data to make postmarket drug safety decisions. They included adverse event reports, clinical trial studies, and observational studies. While data from each source had weaknesses that contributed to the difficulty in making postmarket drug safety decisions, evidence from more than one source could have helped inform the postmarket decision-making process. The availability of these data sources was constrained, however, because of FDA's limited authority to require drug sponsors to conduct postmarket studies and its resources.

While decisions about postmarket drug safety were often based on adverse event reports, FDA could not establish the true frequency of adverse events in the population with data from adverse event reports. The inability to calculate the true frequency made it hard to establish the magnitude of a safety problem, and comparisons of risks across similar

drugs were difficult.[15] In addition, it would have been difficult to attribute adverse events to particular drugs when there was a relatively high incidence rate in the population for the medical condition. It was also difficult to attribute adverse events to the use of particular drugs because data from adverse event reports may have been confounded by other factors, such as other drug exposures.

FDA can also use available data from clinical trials and observational studies to support postmarket drug safety decisions. Although each source presents weaknesses that constrained the usefulness of the data provided, having data from more than one source can help improve FDA's decision-making ability. Clinical trials, in particular randomized clinical trials, are considered the "gold standard" for assessing evidence about efficacy and safety because they are considered the strongest method by which one can determine whether new drugs work.[16] However, clinical trials also have weaknesses. Clinical trials typically have too few enrolled patients to detect serious adverse events associated with a drug that occur relatively infrequently in the population being studied. They are usually carried out on homogenous populations of patients that often do not reflect the types of patients who will actually take the drugs. For example, they do not often include those who have other medical problems or take other medications. In addition, clinical trials are often too short in duration to identify adverse events that may occur only after long use of the drug. This is particularly important for drugs used to treat chronic conditions where patients are taking the medications for the long term. Observational studies, which use data obtained from population-based sources, can provide FDA with information about the population effect and risk associated with the use of a particular drug. For example, in the case of Propulsid, an observational study showed that a 1998 labeling change warning about contraindications did not significantly decrease the percentage of users in one population who should not have been prescribed this drug. Because they are not controlled experiments,

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

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

however, there is the possibility that the results can be biased or confounded by other factors.

We found that FDA's access to postmarket clinical trial and observational data was limited by its authority and available resources. FDA does not have broad authority to require that a drug sponsor conduct an observational study or clinical trial for the purpose of investigating a specific postmarket safety concern. One senior FDA official and several outside drug safety experts told us that FDA needs greater authority to require such studies. Long-term clinical trials may be needed to answer safety questions about risks associated with the long-term use of drugs. For example, during a February 2005 scientific advisory committee meeting, some FDA staff and committee members indicated that there was a need for better information on the long-term use of anti-inflammatory drugs and discussed how a long-term trial might be designed to study the cardiovascular risks associated with the use of these drugs.[17]

Lacking specific authority to require drug sponsors to conduct postmarket studies, FDA has often relied on drug sponsors voluntarily agreeing to conduct these studies. But the postmarket studies that drug sponsors agreed to conduct have not consistently been completed. One study estimated that the completion rate of postmarket studies, including those that sponsors had voluntarily agreed to conduct, rose from 17 percent in the mid-1980s to 24 percent between 1991 and 2003.[18] FDA has little leverage to ensure that these studies are carried out.

In terms of resource limitations, several FDA staff (including CDER managers) and outside drug safety experts told us that in the past ODS has not had enough resources for cooperative agreements to support its postmarket drug surveillance program. Under the cooperative agreement program, FDA collaborated with outside researchers in order to access a wide range of population-based data and conduct research on drug safety. Annual funding for this program was less than $1 million from fiscal year

[17]This was a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

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

2002 through fiscal year 2005. In 2006, FDA awarded four contracts for a total cost of $1.6 million per year to replace the cooperative agreements.

FDA's Initiatives to Improve Postmarket Drug Safety Decision Making

Prior to the completion of our March 2006 report, FDA began several initiatives to improve its postmarket drug safety decision-making process. Most prominently, FDA commissioned the Institute of Medicine (IOM) to convene a committee of experts to assess the current system for evaluating postmarket drug safety, including FDA's oversight of postmarket safety and its processes. IOM issued its report in September 2006.[19] FDA also had underway several organizational changes that we discussed in our 2006 report. For example, FDA established the Drug Safety Oversight Board to help provide oversight and advice to the CDER Director on the management of important safety issues. The board is involved with ensuring that broader safety issues, such as ongoing delays in changing a label, are effectively resolved. FDA also drafted a policy that was designed to ensure that all major postmarket safety recommendations—including those that involve disagreements—would be discussed by involved OND and ODS managers, beginning at the division level.[20] The draft policy states that decisions about major postmarket safety recommendations would be documented. FDA implemented a pilot program for dispute resolution that is designed for individual CDER staff to have their views heard when they disagree with a decision—including the failure to take a drug safety action—that could have a significant negative effect on public health. In that program, the CDER Director would decide whether the process should be initiated, appoint the chair for a panel to review the case, and make the final decision on how the dispute should be resolved. Because the CDER Director is involved in determining whether the process will begin and makes the final decision, the pilot program did not offer employees an independent forum for resolving disputes. FDA also began to explore ways to access additional data sources that it can obtain under its current authority, such as data on

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

[20]The draft policy is entitled "Process for Decision-Making Regarding Major Postmarketing Safety-Related Actions."

Medicare beneficiaries' experience with prescription drugs covered under the prescription drug benefit.[21]

Since our report, FDA has made efforts to improve its postmarket safety decision-making and oversight process. In its written response to the IOM recommendations, FDA agreed with the goals of many of the recommendations made by GAO and IOM.[22] In that response, FDA stated that it would take steps to improve the "culture of safety" in CDER, reduce tension between pre-approval and post-approval staff, clarify the roles and responsibilities of pre- and postmarket staff, and improve methods for resolving scientific disagreements.

FDA has also begun several initiatives since our March 2006 report that we believe could address three of our four recommendations. Because none of these initiatives was fully implemented as of March 2007, it was too early to evaluate their effectiveness.

- To make the postmarket safety decision-making process clearer and more effective, we recommended that FDA revise and implement its draft policy on major postmarket drug safety decisions. CDER has made revisions to the draft policy, but has not yet finalized and implemented it. CDER's Associate Director for Safety Policy and Communication told us that the draft policy provides guidance for making major postmarket safety decisions, including identifying the decision-making officials for safety actions and ensuring that the views of involved FDA staff are documented. According to the Associate Director, the revised draft does not now discuss decisions for more limited safety actions, such as adding a boxed warning to a drug's label.[23] As a result, fewer postmarket safety recommendations would be required to be discussed by involved OND and ODS managers than envisioned in the draft policy we reviewed for our 2006 report. Separately, FDA has instituted some procedures that are consistent with the goals of the draft policy. For example, ODS staff now participate in regular, bimonthly safety meetings with each of the review divisions in OND.

[21]In October 2006, the Centers for Medicare & Medicaid Services published a proposed rule that would, when finalized, facilitate access by FDA and others to information about prescription drugs covered by Medicare. See 71 *Fed. Reg.* 61445 (Oct. 18, 2006).

[22]HHS, 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* (Rockville, Md.: January 2007).

[23]The original draft policy included the market withdrawal of a drug, restrictions on a drug's distribution, and boxed warnings as major postmarket drug safety decisions.

- To help resolve disagreements over safety decisions, we recommended that FDA improve CDER's dispute resolution process by revising the pilot program to increase its independence. FDA had not revised its pilot dispute resolution program as of March 2007, and FDA officials told us that the existing program had not been used by any CDER staff member.

- To make the postmarket safety decision-making process clearer, we recommended that FDA clarify ODS's role in FDA's scientific advisory committee meetings involving postmarket drug safety issues. According to an FDA official, the agency intends to, but had not yet, drafted a policy that will describe what safety information should be presented and how such information should be presented at scientific advisory committee meetings. The policy is also expected to clarify ODS's role in planning for, and participating in, meetings of FDA's scientific advisory committees.

- To help ensure that safety concerns were addressed and resolved in a timely manner, we recommended that FDA establish a mechanism for systematically tracking ODS's recommendations and subsequent safety actions. As of March 2007, FDA was in the process of implementing the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) to track such information on postmarket drug safety issues. Among many other uses, DAARTS will track ODS's safety recommendations and the responses to them. CDER's Associate Director for Safety Policy and Communication told us that DAARTS would be fully operational by the end of April 2007.

We also suggested in our report that Congress consider expanding FDA's authority to require drug sponsors to conduct postmarket studies in order to ensure that the agency has the necessary information, such as clinical trial and observational data, to make postmarket decisions.

Mr. Chairman, this concludes my prepared remarks. I would be pleased to respond to any questions that you or other members of the Subcommittee may have.

For further information regarding this testimony, please contact Marcia Crosse at (202) 512-7119 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. Martin T. Gahart, Assistant Director; Pamela Dooley; and Cathleen Hamann made key contributions to this statement.

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