GAO Responses to Questions from the Honorable Bart Stupak, Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce

1. What is the most important reform that Food and Drug Administration (FDA) should undertake to address drug safety?

Our work has identified three important reforms that are needed to improve FDA's postmarket decision-making and oversight process. First, FDA should increase its resources for access to data sources to help monitor postmarket drug safety and inform its decision-making process. Several FDA staff, including managers within the Center for Drug Evaluation and Research (CDER) and outside drug safety experts, told us in the past that FDA has not had enough resources to support its postmarket drug surveillance program. We found that annual funding for FDA's program to access a wide range of population-based data and conduct research on postmarket drug safety is currently $1.6 million per year. Second, FDA needs stronger oversight of postmarket safety issues, including a mechanism for tracking postmarket safety recommendations and subsequent actions. In 2006 we reported that FDA management had not effectively overseen postmarket drug safety issues, in part, because FDA lacked systematic information on drug safety concerns. As a result, it was unclear how FDA could know that important safety concerns had been addressed and resolved in a timely manner. Third, Congress should consider expanding FDA's authority to require drug sponsors to conduct postmarket studies, such as clinical trials or observational studies, as needed. FDA lacks specific authority to require drug sponsors to conduct postmarket studies. While FDA has often relied on drug sponsors voluntarily agreeing to conduct postmarket studies, the postmarket studies that drug sponsors agree to conduct have not been consistently completed.

2. How has FDA addressed the major problems with drug safety the Government Accountability Office (GAO) identified a year ago?

FDA has only partially addressed the problems we identified in our 2006 report. When we interviewed FDA officials in February and March 2007, they told us that FDA has initiatives underway and under consideration that, if implemented, could address three of the four recommendations we made in our report. Because none of these initiatives is fully implemented, it is too early to evaluate their effectiveness. First, 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. Second, 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 has not revised its pilot dispute resolution program. Third, to make the postmarket safety decision-making process clearer, we recommended that FDA clarify the Office of Drug Safety's (ODS) role in FDA's scientific advisory committee meetings involving postmarket drug safety issues. (ODS is

now called the Office of Surveillance and Epidemiology). The agency intends to, but has not yet, drafted a policy to describe ODS's role in scientific advisory committee meetings. Fourth, 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. FDA is in the process of implementing a system to track information on postmarket drug safety issues.

3. Has the dispute resolution process instituted by FDA been used yet?

In November 2004 FDA implemented a program for dispute resolution that is designed for individual CDER staff to have their views heard when they disagree with a decision that could have a significant negative effect on public health, such as a proposed safety action or the failure to take a safety action. An FDA official told us in March 2007 that the program had not been used by any CDER staff member.

4. What are your concerns about the independence of the dispute resolution process?

According to the dispute resolution pilot program, the CDER director is involved in determining whether the dispute resolution process should be initiated. If it is decided that the process will proceed, the CDER director is responsible for appointing the chair for a panel to review the case. The panel would then make a recommendation to the CDER director, who would then decide how the dispute should be resolved. Because the CDER director is involved in deciding whether the process should be initiated, appoints the chair of the panel, and is the final adjudicator, the pilot program does not offer employees an independent forum for resolving disputes.

5. What additional authority should Congress grant FDA to improve its drug safety programs?

In order to ensure that FDA has the necessary information to make postmarket decisions, we recommended in our 2006 report that Congress should consider expanding FDA's authority to require drug sponsors to conduct postmarket studies, such as clinical trials and observational studies, as needed.

6. Did your GAO team learn of any cases where Office of Drug Safety (ODS) personnel were excluded from advisory committee meetings by Office of New Drugs (OND) personnel?

In our 2006 report we described two examples where ODS personnel were excluded from advisory committee meetings. In March 2003, FDA's Arthritis Advisory Committee met to review the efficacy and safety of the drug Arava in the context of all available drugs to

treat rheumatoid arthritis. 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 some of the cases in the ODS review did not meet the definition of acute liver failure, the safety issue under consideration. As another example, in February 2004 an ODS epidemiologist was not allowed to present his analysis of safety data at a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee that was held to discuss reports of suicidal thoughts and actions in children with major depressive disorder for various antidepressant drugs. OND believed that the ODS staff member's analysis, which showed a relationship between the use of antidepressants and suicidal thoughts and behaviors in children, was too preliminary to be presented in detail. The ODS epidemiologist had recommended an interim plan to discourage the use of all but one antidepressant in the treatment of pediatric major depressive disorders.

7. Did FDA ever define the role of ODS in advisory committee meetings involving postmarket safety issues?

We recommended in our report that FDA clarify ODS's role in its scientific advisory committee meetings involving postmarket drug safety issues. An FDA official told us in March 2007 that the agency intends to, but has not yet, drafted a policy to describe ODS's role in scientific advisory committee meetings.

8. In your case study reviews, was there any pattern of OND resistance to instituting labeling changes or other safety measures?

For our 2006 report we conducted case studies of four drugs—Arava, Baycol, Bextra, and Propulsid—to illustrate FDA's current decision-making process. Our case studies provide examples of disagreements over the evidence that was required to warrant certain safety actions, such as a labeling change. For example, in March 2004 ODS staff recommended that Bextra, an anti-inflammatory drug, carry a boxed warning on its label about its risk of serious skin reactions. The ODS staff based their recommendation on the finding that Bextra's risk for serious skin reactions was significantly higher than that for other similar drugs. The OND review division responsible for Bextra did not initially agree that a boxed warning was warranted, but agreed about five months later after ODS conducted another analysis. We believe that if FDA had established criteria for determining what safety actions to take and when, then some of the disagreements might have been resolved more quickly. Without established criteria, decisions about safety actions are often based on case-by-case judgments of the individuals reviewing the postmarket safety data.