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GAO

Report to Congressional Requesters

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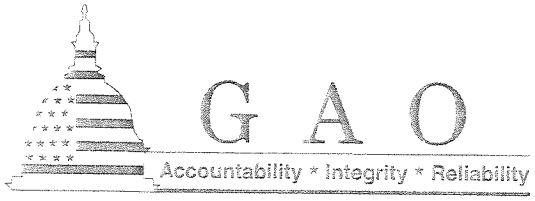
DRUG SAFETY

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



GAO-06-402

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Highlights

Highlights of GAO-06-402, a report to the Chairman, Committee on Finance, United States Senate and the Chairman, Committee on Energy and Commerce, House of Representatives

DRUG SAFETY

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

Why GAO Did This Study

In 2004, several high-profile drug safety cases raised concerns about the Food and Drug Administration's (FDA) ability to manage postmarket drug safety issues. In some cases there have been disagreements within FDA about how to address safety issues. In this report GAO (1) describes FDA's organizational structure and process for postmarket drug safety decision making, (2) assesses the effectiveness of FDA's postmarket drug safety decision-making process, and (3) assesses the steps FDA is taking to improve postmarket drug safety decision making. GAO conducted an organizational review and case studies of four drugs with safety issues: Arava, Baycol, Bextra, and Propulsid.

What GAO Recommends

To improve the decision-making process for postmarket drug safety, GAO suggests that the Congress consider expanding FDA's authority to require drug sponsors to conduct postmarket studies when needed. GAO also recommends that FDA systematically track postmarket drug safety issues, revise and implement its draft policy on major postmarket safety decisions, improve the dispute resolution process, and clarify ODS's role in scientific advisory committees. In its comments on a draft of this report, FDA stated that GAO's conclusions were reasonable. FDA did not comment on GAO's recommendations.

www.gao.gov/cgi-bin/getrpt?GAO-06-402.

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

What GAO Found

Two organizationally distinct FDA offices, the Office of New Drugs (OND) and the Office of Drug Safety (ODS), are involved in postmarket drug safety activities. OND, which holds responsibility for approving drugs, is involved in safety activities throughout the life cycle of a drug, and it has the decision-making responsibility to take regulatory actions concerning the postmarket safety of drugs. OND works closely with ODS to help it make postmarket decisions. ODS, with a primary focus on postmarket safety, serves primarily as a consultant to OND and does not have independent decision-making responsibility. ODS has been reorganized several times over the years. There has been high turnover of ODS directors in the past 10 years, with eight different directors of the office and its predecessors. In the four drug case studies GAO examined, GAO observed that the postmarket safety decision-making process was complex and iterative.

FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints. GAO observed that there is a lack of criteria for determining what safety actions to take and when to take them. Certain parts of ODS's role in the process are unclear, including ODS's participation in FDA's scientific advisory committee meetings organized by OND. Insufficient communication between ODS and OND has been an ongoing concern and has hindered the decision-making process. ODS does not track information about ongoing postmarket safety issues, including the recommendations that ODS staff make for safety actions. FDA faces data constraints in making postmarket safety decisions. There are weaknesses in the different types of data available to FDA, and FDA lacks authority to require certain studies and has resource limitations for obtaining data.

Some of FDA's initiatives, such as the establishment of a Drug Safety Oversight Board, a draft policy on major postmarket decision making, and the identification of new data sources, may improve the postmarket safety decision-making process, but will not address all gaps. FDA's newly created Drug Safety Oversight Board may help provide oversight of important, high-level safety decisions, but it does not address the lack of systematic tracking of ongoing safety issues. Other initiatives, such as FDA's draft policy on major postmarket decisions and regular meetings between OND divisions and ODS, may help improve the clarity and effectiveness of the process, but they are not fully implemented. FDA has not clarified ODS's role in certain scientific advisory committee meetings. FDA's dispute resolution processes for disagreements about postmarket safety decisions have not been used. FDA is taking steps to identify additional data sources, but data constraints remain.

U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
http://finance.senate.gov

Opening Statement of U.S. Senator Chuck Grassley of Iowa
Chairman, Senate Committee on Finance
Hearing – FDA Merck and Vioxx: Putting Patient Safety First?
Thursday, November 18, 2004

Good morning. We're here today because Congress has a Constitutional duty to conduct oversight of the executive branch of government. Congressional oversight can expose wrongdoing in the federal bureaucracy and in the private sector. Congressional oversight can shed disinfecting sunlight. It can result in accountability and necessary reforms for the public good. Today's hearing will consider allegations of mismanagement by the Food and Drug Administration and the Merck pharmaceutical company regarding the safety of the painkiller Vioxx.

On September 30th of this year, Merck withdrew Vioxx from the worldwide market. A blockbuster drug became a blockbuster disaster. Before September 30th, Vioxx was the subject of controversy in the scientific community behind closed doors. Today we will look out in the open at the decisions made about Vioxx. Depending on the perspective you take, Vioxx either changed lives for the better or ended lives prematurely.

Historically the Food and Drug Administration has met its charge to protect the health and safety of the American people. Those who work at the agency are by and large committed to doing no harm. Even so, the FDA has also stood watch over failures when it comes to drug safety.

Likewise, the pharmaceutical industry in the United States has achieved extraordinary advancements in medicine. Drug makers have helped to save lives and improve the quality of life of people around the world. They've profited by doing so. At the same time, the industry has contributed to the skyrocketing costs of health care and settled billions of dollars in false claims against the government, including both civil and criminal actions.

Merck & Co. has a reputation for excellence in research and development. Yet today Merck is faced with one of the worst drug disasters in history. Merck acknowledged that Vioxx carried with it serious cardiovascular risks when it withdrew the drug from the market. During today's hearing we'll hear about the red flags that were raised about those risks in the years before and the years after Vioxx was approved by the FDA.

The Finance Committee has jurisdiction over the Medicare and Medicaid programs.

Accordingly, the committee has a responsibility to the more than 80 million Americans who receive health care coverage — including prescription drugs — under these programs. Of the 20 million Americans who reportedly took Vioxx, an untold number are Medicare and Medicaid beneficiaries. I asked the Office of the Inspector General for the Department of Health and Human Services how much the federal government reimbursed Merck for Vioxx. I was told that the Medicaid program paid in excess of $1 billion for Vioxx while Vioxx was on the market. I've also seen a June 4, 1999 Merck document titled "IN IT TO WIN IT" that said: "As of yesterday, Vioxx became reimbursable on Medicaid in 42 states with the other 8 states close behind." The Medicaid market was clearly going to be a money maker for Merck, and Medicaid has paid Merck well for Vioxx.

Last year Vioxx sales totalled $2.5 billion. Merck's marketing effort included $160 million for direct-to-consumer advertising. It's been said that in the history of pharmaceutical advertising, Vioxx was one of the most directly-marketed-to-consumers prescription drugs ever. In addition to targeting consumers directly, Merck reportedly spent more than that marketing Vioxx to directly to physicians. There's nothing wrong with either of these efforts. Such marketing is part of the system, but today's hearing will consider whether Merck followed the letter and spirit of the law with its marketing of Vioxx.

The witnesses here today will help tell the Vioxx story. That story will continue to unfold in the months ahead. It will affect public confidence. When the FDA approves a drug, it's considered a "Good Housekeeping Seal of Approval." However, what's come to light about Vioxx since September 30th makes people wonder if the FDA has lost its way when it comes to making sure drugs are safe. Today's witnesses will describe how danger signals were ignored. They'll offer perspective on how appropriate action wasn't taken. We'll see that the FDA failed to heed the words of its own scientists.

It also looks like the FDA allowed itself to be manipulated by Merck on labeling changes that became necessary after a review by Merck that's known as the VIGOR trial. The VIGOR trial found that heart attacks were five times higher for Vioxx patients than for patients on another drug. Even so, nearly two years passed before any label change was made by the FDA. Merck completed the VIGOR trial in March 2000. It gave the findings to the FDA in June 2000. The trial was the subject of an advisory board meeting in February 2001. But it was April 11, 2002 before the Vioxx label was actually changed. During these 22 months, Merck aggressively marketed Vioxx, knowing that consumers and doctors were largely unaware of the cardiovascular risks found in the VIGOR trial.

One of my concerns is that the FDA has a relationship with drug companies that is too cozy. That's exactly the opposite of what it should be. The health and safety of the public must be the FDA's first and only concern. I'm interested in changes inside the FDA that result in greater transparency and openness at the Food and Drug Administration. One reform that may be needed is an independent office of drug safety. It doesn't make sense from an accountability standpoint to have the office that reviews the safety of drugs that are already on the market to be under the thumb of the office that put the drugs on the market in the first place.

The bottom line is, consumers should not have to second guess the safety of what's in their medicine cabinets. The public should feel confident that when the FDA approves a drug, you can bank on it being safe, and if a drug isn't safe, the FDA will take it off the market.

We have three panels of witnesses today. The first witness is Dr. David Graham. He is an epidemiologist for the FDA. Dr. Graham recently completed a study involving Vioxx and he'll discuss his findings. Dr. Graham will also describe the environment where he works in the FDA's Office of Drug Safety. It's this office that's responsible monitoring the effect of a drug once it's on the market.

Our next witness is Dr. Gurkipal Singh. Dr. Singh will testify by video conference from California where he is recovering from a heart attack. Dr. Singh is an Adjunct Professor of Medicine at Stanford University. He is a former consultant to Merck on Vioxx. Dr. Singh will describe how he was threatened by Merck in that capacity because of his concerns about Vioxx. Dr. Singh will also explain how drugs like Vioxx work, the information that was available about the cardiac safety of Vioxx, and the labeling changes made to Vioxx. The committee will also hear testimony from Dr. Bruce Psaty. Dr. Psaty is an epidemiologist, a practicing physician and a drug safety expert. He will discuss the studies about Vioxx, the risks and benefits of such drugs, and how similar drug disasters can be prevented. After these three witnesses, we will hear from Dr. Sandra Kweder of the Food and Drug Administration, and Mr. Raymond Gilmartin, the Chief Executive Officer of Merck & Co.

The record for this hearing will remain open for 10 days. Committee members should submit remarks and questions for the record no later than November 29. In addition, a number of documents will be discussed today. They have been made available to the committee members, their staffs and the hearing witnesses. Many of these documents have been provided to the committee by Merck and other parties to litigation involving Vioxx. As a result, they may be considered confidential in the context of those court proceedings. I ask that committee members, their staffs and the hearing witnesses not leave the room with their bound copies of these documents during this hearing today. Committee staff will collect the exhibits from each witness, committee member and from all committee staff at the close of the hearing.

I look forward to the opening remarks of the Ranking Member of the Finance Committee, my colleague, Senator Baucus.

Before the testimony begins, I will to respond to comments issued last night by the FDA's acting administrator, Dr. Crawford, about Dr. Graham, our first witness. News reports today say the FDA is calling Dr. Graham a "a maverick who did not follow Agency protocols."

Today's hearing includes a lot of testimony about scientific findings. It's not about protocols or administrative "he said, she saids." Dr. Graham completed an FDA-sponsored three-year study under FDA guidance and with Drs. Campen, Levy, Shoor, Ray, Cheetham, Spence and Hui. Dr. Graham's immediate supervisor said the paper that formed the basis of the study was "... an excellent study and analysis of a complex topic." So the clarifications provided last night by Dr. Crawford appear intended intimidate a witness on the eve of hearing. I want to hear about Dr. Graham's study today. In fact, just seven days ago — on November 9th — Dr.

Crawford met with Dr. Graham and acknowledged that there was a culture problem at the FDA and a problem with drug safety. Dr. Crawford even asked Dr. Graham to consider helping with an "internal FDA drug safety program and develop(ing) recommendations for improvements…." So Dr. Crawford knows there's a problem and would better serve the FDA by spending time on the problem rather than going after congressional witnesses who helped identify the problem in the first place.