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# NEW DRUG APPROVAL

## FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints

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Highlights

Highlights of GAO-09-866, a report to the Ranking Member, Committee on Finance, U.S. Senate

### Why GAO Did This Study

Before approving a drug, the Food and Drug Administration (FDA) assesses a drug's effectiveness. This assessment may be based on evidence showing that a drug has a positive impact on a surrogate endpoint—a laboratory measure, such as blood pressure—instead of more direct clinical evidence, like preventing strokes. After approval, FDA often requires or requests a drug sponsor to further study the drug. Concerns have been raised about FDA's reliance on surrogate endpoints and its oversight of postmarketing studies. This report provides information on (1) all drug applications approved based on surrogate endpoints in FDA's accelerated approval process, (2) a subset of applications for potentially innovative drugs approved based on surrogate endpoints under FDA's traditional process, and (3) FDA's oversight of postmarketing studies. GAO identified drugs approved based on surrogate endpoints, obtained the status of related postmarketing studies, and reviewed FDA's oversight of a sample of 35 studies it required under its accelerated approval process, selected to include studies which were at varying levels of completion.

### What GAO Recommends

GAO recommends that FDA clarify the conditions under which it would utilize its authority to expedite the withdrawal of drugs under its accelerated approval process. FDA disagreed with the need to develop such clarifying guidance. GAO believes doing so would enhance FDA's oversight.

View GAO-09-866 or key components.
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### What GAO Found

FDA approved 90 applications for drugs based on surrogate endpoints through its accelerated approval process from the creation of the process in 1992 through November 20, 2008, and about two-thirds of postmarketing studies have been closed. FDA created the accelerated approval process to expedite the approval of drugs which are designed to treat serious or life-threatening illnesses and are expected to provide meaningful therapeutic benefits compared to existing treatments. Under this process, 79 of the 90 applications were approved for drugs to treat cancer, HIV/AIDS, and inhalation anthrax. Because of the need to expedite approval, FDA approves drugs under this process based on surrogate endpoints which are not yet proven substitutes for clinical endpoints, but does require that drug sponsors complete postmarketing studies to confirm the drug's clinical benefit. FDA had required drug sponsors to conduct 144 postmarketing confirmatory studies associated with these 90 applications, and as of December 19, 2008, classified 64 percent as closed—meaning that drug sponsors had met FDA's requirements for these studies or FDA determined the studies were no longer needed or feasible. However, several of the remaining studies have been classified by FDA as open for an extended period.

FDA approved 69 applications on the basis of surrogate endpoints for new molecular entities (NME)—potentially innovative drugs containing active chemical substances that have never been approved for marketing in the United States in any form—through its traditional approval process from January 1998 through June 30, 2008. These 69 NME drugs accounted for about one-third of the 204 applications for NME drugs which FDA approved through its traditional process during this period, many for drugs to treat cancer, heart disease, and diabetes. Unlike surrogate endpoints used in the accelerated process, FDA considers those used in the traditional process as valid substitutes for demonstrating the clinical benefit of drugs, and thus does not require sponsors to complete postmarketing confirmatory studies. However, FDA requested that sponsors complete 175 postmarketing studies to obtain other information on many of these NME drugs, and as of February 13, 2009, FDA classified about one-half as closed.

Weaknesses in FDA's monitoring and enforcement process hamper its ability to effectively oversee postmarketing studies. FDA has not routinely been reviewing sponsors' annual submissions on the status of studies in a timely manner. It has little in the way of readily accessible, comprehensive data to monitor studies' progression and does not consider such oversight a priority. FDA is implementing initiatives to improve its oversight, but it is too early to tell if they will be effective. Although FDA has authority to expedite the withdrawal of a drug from the market if a sponsor does not complete a required confirmatory study with due diligence, or if a study fails to confirm a drug's clinical benefit, it has not specified the conditions that would prompt it to do so. It has never exercised its authority, even when such study requirements have gone unfulfilled for nearly 13 years.