July 2010

NEW DRUG APPROVAL

FDA's Consideration of Evidence from Certain Clinical Trials

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Highlights

Highlights of GAO-10-798, a report to congressional requesters

Why GAO Did This Study

Before approving a new drug, the Food and Drug Administration (FDA)—an agency of the Department of Health and Human Services (HHS)—assesses a drug's effectiveness. To do so, it examines information contained in a new drug application (NDA), including data from clinical trials in humans. Several types of trials may be used to gather this evidence. For example, superiority trials may show that a new drug is more effective than an active control—a drug known to be effective. Non-inferiority trials aim to demonstrate that the difference between the effectiveness of a new drug and an active control is small—small enough to show that the new drug is also effective. Drugs approved on this basis may provide important benefits, such as improved safety.

Because non-inferiority trials are difficult to design and interpret, they have received attention within the research community and FDA. FDA has issued guidance on these trials. GAO was asked to examine FDA's use of non-inferiority trial evidence. This report (1) identifies NDAs for new molecular entities—potentially innovative new drugs not FDA-approved in any form—that included evidence from non-inferiority trials, (2) examines the characteristics of these trials, and (3) describes FDA's guidance on these trials. GAO reviewed NDAs submitted to FDA between fiscal year 2002 (the first full year that FDA documentation was available electronically) and fiscal year 2009 (the last full year of submissions), examined FDA's guidance, and interviewed agency officials.

View GAO-10-798 or key components.
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What GAO Found

Evidence from non-inferiority trials was included in about one-quarter, or 43, of the 175 NDAs for new molecular entities that were submitted to FDA for review from fiscal years 2002 through 2009. Many of these applications were for antimicrobial drugs, such as those treating bacterial, viral, and fungal infections. As of December 31, 2009, FDA approved 18 of the 43 NDAs on the basis of evidence from non-inferiority trials. Of the remaining 25 NDAs, FDA approved 11 based on other evidence, such as proof that the new drug was more effective than a placebo (no treatment), and decided not to approve 14.

The non-inferiority trials included in these NDAs varied with respect to their characteristics. FDA generally requires sponsors to provide evidence of a drug's effectiveness as shown in more than one trial. For the 18 NDAs that were approved based on evidence from non-inferiority trials, the number of non-inferiority trials used to provide primary support for approval ranged from one to four, with an average of 2 such trials per NDA. Half of these applications included non-inferiority trials that tested the effectiveness of the new drug against more than one active control. The non-inferiority margins—the maximum clinically acceptable extent to which the new drug can be less effective than the active control and still show evidence of an effect—ranged from 5 to 20 percent among trials that supported approval. Among the other 25, FDA identified nine NDAs that included poorly designed non-inferiority trials which did not provide primary evidence for approval. Some of these problems included an inappropriate selection of an active control and an improper calculation of a non-inferiority margin. FDA notified sponsors of its concerns with the poorly designed trials prior to the sponsors' submissions of all NDAs that included such trials.

In March 2010 FDA issued draft guidance which focused solely on the use of non-inferiority trials. This guidance presents detailed and comprehensive recommendations on how non-inferiority trials may be used to provide evidence of a drug's effectiveness. For example, it provides advice on how to select an active control and how to set the non-inferiority margin, as well as how to interpret the trials. This guidance offers broad, generally applicable recommendations to supplement indication-specific guidance documents that FDA had previously issued. These indication-specific guidance documents include FDA's advice on many issues related to the development of drugs for particular indications, some of which are related to the use of non-inferiority trials. GAO's review of FDA's guidance showed that the agency has become more conservative in allowing evidence from non-inferiority trials to demonstrate a drug's effectiveness. First, FDA has limited the indications for which these trials may be used. Second, the agency has also become more rigorous in its review of evidence from non-inferiority trials.

We sent a draft of this report to HHS for review. HHS provided us with technical comments, which we incorporated as appropriate.