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FDA considers new rules to speed up confirmatory trials of drugs granted accelerated approval

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Since 1992, the U.S. Food and Drug Administration has granted accelerated approval to 47 new indications for 35 cancer drugs and in more than half the cases—26 indications—further trials have confirmed the benefits of the drugs. But the agency has concerns about the length of time some drugs have remained on the market without confirmation of their benefits, according to a review article published online March 25 in the *Journal of the National Cancer Institute.* New requirements and fines are possible solutions say the authors, from FDA's Office of Oncology Drug Products.

John R. Johnson, M.D., and colleagues reviewed the FDA's experience with the accelerated approval process from its beginning in 1992 to July 2010. Among the 26 indications that eventually received regular approval, the median time between accelerated approval and regular approval was 3.9 years and the average time was 4.7 years. These represent "substantial time savings in terms of earlier availability of drugs to patients," the authors write.

However, three indications have been withdrawn from the market or placed under very restricted patient distribution because subsequent trials did not confirm a benefit. Two were on the market for 10 years before being withdrawn. Fourteen accelerated approvals still do not have completed confirmatory trials; one of these drugs has been on the market for 10.5 years, and three have been marketed for more than 5 years. And

among the indications that have converted from accelerated approval to regular approval, five took longer than 7 years to complete confirmatory trials, with one taking 12.6 years and another 9.7 years.

"Because of the possibility that confirmatory trials will not confirm clinical benefit, indications that have received accelerated approval should not be on the market for unacceptably prolonged intervals in the absence of completed confirmatory trials," the authors write.

They suggest that one solution to this problem is for the FDA to require that a confirmatory trial be in progress before granting accelerated approval. Another is to make use of the Food, Drug and Cosmetic Act of 2007, which gave the FDA authority to fine companies up to $10 million for lack of due diligence in completing confirmatory trials. "The FDA believes that this will be an effective new tool," the authors conclude.

In an accompanying editorial, Susan S. Ellenberg, Ph.D., of the University of Pennsylvania School of Medicine in Philadelphia, notes that analyses such as this one are essential in improving the regulatory process. She discusses several questions that are not fully addressed by the current review, the most important of which is the extent to which accelerated approval actually speeds the availability of products.

Ellenberg argues that the time to complete a study that was aimed at regular approval from the start would likely be shorter than the time to do first a study for accelerated approval and then a second, confirmatory study. "Thus the time to availability of a new drug, although undoubtedly shorter with accelerated approval as an option, may not be as impressive as Johnson et al. suggest."

The editorialist adds that the FDA's new regulatory science initiative announced last fall "should support more in-depth analyses of regulatory data that could provide valuable insights regarding optimization of

regulatory approaches."

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