The modification of Food and Drug Administration (FDA) investigational new drug regulations to provide for “accelerated approval” of promising new drugs was put in place in 1992 (1), motivated largely by the emergence of HIV/AIDS. The increasing rigor of FDA review, beginning with the 1962 passage of the Kefauver–Harris amendments to the Federal Food, Drug and Cosmetic Act, and the resulting changes to the FDA regulations regarding evaluation of investigational drugs, were perceived as intolerable obstacles to making potentially life-saving therapy available in the most rapid way possible to those suffering from a deadly disease with very limited therapeutic options. Accelerated approval was to be based on positive results for surrogate endpoints that were considered likely predictors of clinical benefit, as typically measured for oncological drugs by an improvement in survival. The application of this less restrictive pathway to drug approval was quickly used in other medical areas; among the first eight drugs to receive accelerated approval, four were for HIV/AIDS indications, two were for cancer treatment (one was for Kaposi sarcoma, an AIDS-related malignancy), one was for multiple sclerosis, and one was for bacterial infection.

The article by Johnson et al. (2) in this issue of the Journal updates the FDA experience with accelerated approval of oncological drugs and biologics that first appeared in 2004 (3). Over 18 years, from the initiation of the accelerated approval process in 1992 through 2010, 35 products for 47 indications have been approved in accelerated fashion; 20 of these products have so far received regular approval for one or more indications. In only three cases has a product that received accelerated approval clearly failed to have clinical benefit confirmed (although it appeared that for one of these—gefitinib—the drug was, in fact, effective in a small subset of patients with certain tumor characteristics). The final status of many products that have received accelerated approval is as yet undefined because the clinical trials that were mounted to confirm clinical benefit of these products have either not yet been completed or remain under FDA review.

Of the 47 accelerated approvals, 28 were based on single-arm trials and 19 were based on randomized trials. The proportion based on randomized trials has increased somewhat in recent years. Since 2005, half of accelerated approvals for oncology drugs were based on data from randomized trials; before 2005, the proportion was about 2:1 in favor of single-arm studies. Most of the accelerated approvals for a first-line or adjuvant treatment indication have been based on data from randomized studies. Only imatinib gained approval for first-line indications (for gastrointestinal stromal tumor and pediatric Philadelphia chromosome–positive chronic myeloid leukemia) based on data from single-arm studies.

An important question related to accelerated approvals for oncology products that is not fully addressed by these data is the extent to which accelerated approval actually speeds the availability of products that offer an important advance in cancer treatment. In 2009, Richey et al. (4) challenged the assumption that accelerated approval actually did accelerate the availability of new oncology drugs. They based their argument on comparisons of time from investigational new drug application to accelerated vs regular approval of oncology drugs approved between 1995 and 2008. In response, Lanthier et al. (5) from the FDA noted that products for which accelerated approval is not considered an option might be different in many ways from products with perceived potential for accelerated approval, and these differences may have major effects on the time needed to evaluate the product, so that such comparisons are not very meaningful. Although this is certainly a valid point, the time saving estimated by Johnson et al. (2) is equally questionable. They point to the median and mean times between accelerated and regular approvals (for those drugs receiving the latter) of 4–5 years and interpret this number as the time saved in making these new drugs available. However, this surely overstates the case. The time to complete a study aimed at achieving regular approval from the start would likely be far shorter than the time under the current scenario to complete an initial study to achieve accelerated approval plus the time to conduct a confirmatory study aimed at regular approval, unless (perhaps) the confirmatory study was a continuation of the initial 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. (2) suggest.

Other issues of interest also cannot be addressed from the data provided by Johnson et al. (2). For example, one cannot tell from the tables how many of the accelerated approvals based on randomized trials (table 1) and ultimately converted to regular approval (table 3) were converted based on continued follow-up of the trial on which the accelerated approval was based. The FDA argues for this strategy as the most efficient and the most reliable approach. One would like to know often this strategy is actually used, and how the time between accelerated and regular approval for this strategy compares with the time for other strategies.

Johnson et al. (2) do not address the obstacles—real or perceived—that may dissuade drug manufacturers from initiating randomized trials designed to assess a survival or other clinical benefit but with the potential for supporting accelerated approval on the basis of a surrogate endpoint (eg, progression-free survival or response rate). One likely obstacle is the anticipated difficulty in completing a study when preliminary data on surrogate endpoints suggest that...
the treatment under study is superior to the control treatment. Individuals receiving control treatment in such a trial may wish to cross over to the potentially superior treatment. If that treatment is already marketed for other indications (as would often be the case), there would be no way to prevent such crossovers, which have the potential to substantially diminish the observable differences in the outcomes needed for regular approval (e.g., survival). Drug manufacturers may find it less complicated to mount an independent study [possibly in a population with less advanced disease, as the Johnson et al. (2) suggest] to support regular approval.

The accelerated approval process has been criticized on a variety of grounds. Many have noted the risks associated with making toxic drugs available rapidly on the basis of surrogate endpoints that may not translate into real clinical benefit (6–8). Others deplore the delays in completing the required studies to demonstrate a survival advantage or other established clinical benefit following an accelerated approval (9), a problem that Johnson et al. (2) acknowledge. Still others, such as Richey et al. (4), are concerned that the process has been insufficiently accelerated.

The FDA is routinely castigated for proceeding too cautiously and slowly, and at the same time, for rushing drugs to market too rapidly without adequate study. What some might consider a happy medium will inevitably leave many other scientists, clinicians, and consumers dissatisfied. The recent decision by the FDA to remove the breast cancer indication from the label of bevacizumab when clinical trials following the drug’s accelerated approval in 2008 did not confirm any survival advantage in this population is an excellent example: the FDA has received both great praise and harsh criticism for this decision. There is always room to improve regulatory processes and analyses such as the one conducted by Johnson et al. (2) are an essential step in identifying and implementing such improvements. The FDA’s new regulatory science initiative announced in the fall of 2010 (10) should support more in-depth analyses of regulatory data that could provide valuable insights regarding optimization of regulatory approaches.

References

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