Accelerated Approval Seen as Triumph and Roadblock for Cancer Drugs

The U.S. Food and Drug Administration’s accelerated drug approval process gives cancer patients faster access to the oncology drug pipeline and the chance to receive new and promising drugs.

That is the bright side of a process that has been part of the drug approval landscape for more than a decade. However, some observers suggest that there may be a dark side as well, one that could actually harm cancer patients.

The accelerated approval process came about in 1992 as a way to speed to market drugs for life-threatening diseases. Through this mechanism, drugs are approved on the basis of preliminary evidence that uses a surrogate marker to show a clinical benefit—in most cases, a surrogate for survival. For example, Gleevec (imatinib mesylate) was given accelerated approval in May 2001 based on data from three studies that used hematologic and cytogenetic response as a surrogate endpoint.

What is considered by many to be the fundamental flaw in the regulation is that once a pharmaceutical company has an accelerated approval in hand, the incentive to seek full approval with a pivotal phase III trial diminishes.

Seeking Full Approval

In a review of the process in this issue of the Journal (p. 1500), scientists at the FDA, led by Ramzi Dagher, M.D., of the Center for Drug Evaluation and Research, report that 22 applications involving anticancer drugs or biologics were approved between 1992 and 2004. Fifteen received accelerated approval based on studies that were either uncontrolled or compared two dose levels and did not use an active comparator. The remaining seven were approved on the basis of one or more randomized trials.

Only six of the 22 approved biologics or drugs—capecitabine, dexrazoxane, docetaxel, imatinib mesylate, irinotecan, and oxaliplatin—have had at least one indication converted to full, regular approval.

“That’s what I [mean] by ‘hurry up and wait,’” said Richard Schilsky, M.D., professor of hematology/oncology at the University of Chicago. “We ‘hurry up’ to get these drugs on the market and into the patients based on a surrogate marker, such as response rate, but then we have to ‘wait’ for the definitive studies that these drugs actually make a difference in outcome.”

There are also practical obstacles to carrying out another clinical trial of a drug already on the market. If a drug is available on the pharmacist’s shelf and is being reimbursed by insurance, subsequent double-blind, placebo-controlled studies of similar drugs may be impossible to perform because patients will not want to enter a trial in which they may not receive the newest treatment.

“We could have the situation [in which] patients would refuse to enter a clinical trial because they would want to be certain they were receiving [the new drug],” regardless of the fact that a definitive study showing that the drug has a clinical benefit might not have been done—and might never be carried out, said Harmon Eyre, M.D., chief medical officer of the American Cancer Society in Atlanta.

“I don’t believe that the average patients—not the average oncologist—can distinguish between an FDA-approved drug that has been approved through the accelerated process and an FDA-approved drug that has been given full approval,” Schilsky added.

Suggested Reform

The concern about how these types of approvals may affect subsequent clinical trials led Schilsky to suggest that the system might require a little tweaking.

The ideal situation, he said, would be an integrated approach: The pharmaceutical company would begin a phase III trial of the new agent and build into that trial an interim evaluation, which would occur only after the trial had completed accrual. If a benefit appeared likely at the time of the interim analysis, then accelerated approval could be granted on the basis of surrogate markers. If at the end of the trial, the drug showed a survival or clinical benefit, then full approval could be obtained.

Schilsky said that this system would ensure that researchers would be able to recruit patients for a well-designed trial and be more likely to ensure that the pharmaceutical company would have evidence-based outcomes that could determine the role of the new medicine in oncology.

FDA officials like that type of planning as well. Robert Temple, M.D., associate director for medical policy at the Center for Drug Evaluation and Research, said the FDA is leaning toward granting accelerated approvals now for oncology drugs much the same way that accelerated approvals are granted for drugs used to fight human immunodeficiency virus (HIV) infection.

With HIV drugs, accelerated approvals can be awarded in clinical trials after a 6-month interim analysis that shows the surrogate marker of reduced viral load has been maintained. In those trials, which continue for 48 weeks or 96 weeks beyond the interim analysis, the patients have already been enrolled, so there is confidence that a full efficacy trial will be completed.

“Clearly the manufacturer is required to pursue [clinical efficacy] trials with due diligence,” Temple said. “If we were to conclude that they are not being pursued, there is no doubt that we could remove this drug [from the market]. ...
The whole process is credible only if you eventually get the data.”

However, Schilsky pointed out that there has never been a case in which an oncology drug that has been approved—either through the accelerated process or through the full approval process—has been withdrawn by the FDA. “Once the drug it is in the marketplace, it is out there,” he said.

Not only is the drug “out there” for use in its approved indication, it is also available for oncologists to use in other cancers, making it difficult to test the drug in a controlled manner for an alternate indication. For example, “people are now using Iressa [gefitinib] in all sorts of lung cancer patients,” Schilsky said, “even though it was approved as a second-line treatment.” (Iressa was approved under the accelerated program in May 2003 and has not yet received full approval.) “I think the accelerated approval of Iressa has made it extremely difficult to do the definitive clinical trials that need to be done with that drug to really determine how to use it,” he said.

For targeted drugs such as Iressa, just how they will be used is an issue, particularly in light of their high cost and the fact that many add, at most, months onto a cancer patient’s life. “The country cannot afford these expensive biologic drugs in the treatment of metastatic cancer in order to gain a few months of survival,” said Eyre. But, “the country can afford the use of these drugs if they are used in conjunction with other chemotherapy agents to improve the cure rate in metastatic diseases such as colon cancer. If accelerated approval helps us to get to that target, I think it will be very helpful. On the other hand, once a drug gets approved, it can slow down the recruitment and execution of more definite studies. In that case it can be disadvantageous,” he said.

Like Temple and Schilsky, Eyre believes that it may be time to rethink the accelerated approval process because of the potential problems and also the changing technology. “I think that the FDA’s decision to approve drugs on an accelerated basis may have unlocked Pandora’s box, and to get things under control again, the FDA is going to have to take a global re-look at how it approves cancer drugs,” he said.

**Better Surrogate Markers**

As researchers focus more on developing surrogate markers for clinical outcomes such as survival, the debate will continue as to how the FDA will incorporate them into drug approvals. “The FDA approves drugs [for heart disease] on the basis of whether the drug lowers blood pressure or lowers cholesterol. It doesn’t wait to see whether lowering blood pressure or not lowering blood pressure will kill you. We don’t have the luxury of these intermediate tests in cancer,” Eyre said.

However, Schilsky noted that current statutes require that anticancer drugs prove efficacy with hard outcomes. “We have to validate that these intermediate tests are accurate,” Eyre agreed, “but I can see that in 10 years a molecular marker will be discovered for most if not all common cancers. Ten years might not be enough time, or it might prove to be conservative. We are in a transition point. There is not an easy answer.”

“It is a double-edge sword,” said Schilsky. “Certainly I would not argue that we want to delay getting potentially useful drugs out to the American public, and the accelerated approval mechanism is a good way to [get them out]. But the public has to recognize that there are limitations to it that, in some ways, potentially slow down the development of the definitive data that really demonstrate safety and effectiveness.”

—Edward Susman