Accelerated Drug Approval: FDA May Get Tougher; Companies Cite Hurdles

By Merrill Goozner

The U.S. Food and Drug Administration’s Oncology Drugs Advisory Committee (ODAC), at its February meeting, urged the agency to raise its standards for granting experimental cancer drugs accelerated approval on the basis of surrogate markers. ODAC also called on drug developers to conduct more tests more rapidly to determine whether drugs given accelerated approval actually extend life.

The 16-member committee concluded that single-arm trials, which were used to justify more than half the accelerated approvals since the program’s inception in 1992, should be accepted only for rare cancers or when the evidence of efficacy from a single-arm trial was overwhelmingly positive (this happened with imatinib[Gleevec] for Philadelphia chromosome-positive chronic myeloid leukemia). The committee also reached a consensus—no votes took place at the meeting—that the FDA should require at least two controlled trials as final proof of efficacy and recommended that those trials should be under way when accelerated approval is granted.

“There will be exceptions to that for rare diseases and perhaps some other niche areas where there is a very high positive signal in the accelerated approval trial,” said Wyndham Wilson, M.D., Ph.D., chief of the lymphoma therapeutics section of the National Cancer Institute’s Center for Cancer Research, who chaired the committee. “There may be some overriding reason for not doing two [trials], but two ought to be the standard.”

Written Guidance Coming

Richard Pazdur, M.D., director of the office of oncology drugs products at FDA, said after the meeting that the agency is leaning toward specifying the tougher standards for accelerated approvals in the form of written guidance for drug developers. “This will require planning on the part of the sponsor,” he said. “What we’re asking for is a comprehensive drug development plan … These [confirmatory] studies should be discussed with the agency long before the new-drug application is even submitted.”

The original accelerated approval regulations were issued in 1992. Four years later, President Bill Clinton responded to escalating industry and patient advocacy group pressure by allowing tumor shrinkage to serve as a surrogate endpoint for accelerated approval of cancer-fighting drugs. The president’s communication said that the frequency and duration of the tumor response needed to outweigh the toxicity and other risks before accelerated approval could be given, as well as that trials would be necessary.

But the FDA never adopted specific rules for drug developers to follow after drugs gained early access to the market. The result has been many delays in the initiation and completion of confirmatory trials. Just 27 (55%) of the 49 indications for 37 oncology products granted accelerated approval have completed postmarketing trials verifying benefit, according to the agency, and eight of those took 6 years or more to complete. Seven (14.3%) have been approved within the past 2 years, whereas five (10.2%) failed to confirm benefit. The rest are involved in clinical tests, some of which have dragged on for a decade. The Food and Drug Administration Amendments Act of 2007 gave the FDA the power to impose financial penalties of up to $10 million on companies that fail to complete confirmatory trials in a timely manner, although the law left defining what constituted excessive delays to the agency.
“This would not be a problem if all confirmatory trials verified the benefit,” Pazdur said, “but as expected, drugs have failed to confirm clinical benefit.” The agency’s goal is to minimize how long ineffective cancer drugs—about 10% of those granted accelerated approval so far—remain on the market.

**Five That Failed**

Five drugs have either failed confirmatory trials or have been withdrawn for specific indications, including four that have made headlines as major advances in targeted therapy. Most recently, the FDA asked Genentech, now a unit of Roche, to withdraw its application for bevacizumab (Avastin) for HER-2-negative metastatic breast cancer. Bevacizumab received accelerated approval for that indication in 2006, but after four confirmatory trials showed that the drug failed to extend patients’ lives, the agency, in December, initiated proceedings to withdraw approval for it. The company is challenging the FDA’s decision.

Celecoxib (Celebrex) has been marketed as a colon cancer prevention drug for 11 years—the longest an accelerated-approval drug has gone without proof of benefit. Granted approval because of evidence that the drug reduced colon polyps, Pfizer took until 2008 to start a trial in 200 pediatric patients with familial adenomatous polyposis (the CHIP trial) to see whether reducing polyps reduced cancer incidence. Last June, the company agreed to voluntarily withdraw the indication from the drug’s label. The CHIP trial won’t be completed before 2019.

Several companies cited extenuating circumstances for the long delays in completing their phase III confirmatory trial commitments. Amgen’s panitumumab (Vectibix) for metastatic colorectal cancer received accelerated approval in September 2006. Its pivotal confirmatory trial began 1 year earlier. It was the second approved monoclonal antibody, the other being cetuximab (Erbitux), that targets epidermal growth factor receptor—expressing cancer cells. The 243-patient trial that led to accelerated approval had extended median progression-free survival time by a little over a month, but it did not increase overall survival time.

By late 2007, however, retrospective analyses of clinical trials involving both cetuximab and panitumumab showed that epidermal growth factor receptor–expressing colorectal cancer cells with the KRAS mutation did not respond to monoclonal antibodies. That finding transformed the clinical landscape for treating metastatic disease and undermined the already under-way phase III randomized trial in 593 patients, which added panitumumab to the FOLFIRI (folinic acid, fluorouracil, and irinotecan) chemotherapy regimen.

The results from that trial showed only a minor improvement in progression-free survival time and no statistically significant increase in overall survival time. The results were clouded because the study had no validated test for identifying patients with the KRAS mutation during enrollment, according to Paul Eisenberg, M.D., chief medical officer for regulatory affairs at Amgen.

Although the labels for panitumumab and cetuximab have changed to limit their use in patients without the KRAS mutation, Amgen still hasn’t proved efficacy for its drug. The company is negotiating with the FDA over launching two more trials. One is using panitumumab as third-line therapy in metastatic colorectal cancer patients who are KRAS mutationfree and have never received monoclonal antibody therapy, whereas the other is in a head-to-head trial against cetuximab in the same population. The company admitted at the ODAC meeting that the results of the first trial, supposedly blinded, could have been confounded because the drugs leave a telltale skin rash, clearly indicating who was getting the drug and who was not.

After presenting their data, Amgen officials argued that the clinical benefits from postponing progression were meaningful and warranted more time for confirmatory trials. That brings up more issues for regulators: “How many bites of the apple do you get to take after a trial has failed?” Pazdur asked. “That is an issue that has to be addressed.” Committee chairman Wilson added, “If the benefit is one month . . . reasonable people could conclude there’s no advantage.”

Other companies cited the rarity of the cancer being treated and the complexity of treatment for the difficulties in meeting their commitments to complete phase III trials. Nelarabine (Arronon) was approved for patients with T-cell lymphoblastic leukemia who have failed at least two chemotherapy regimens. The entire U.S. patient population, many of them children, is just 1,600 people per year, and fewer than 300 have a second relapse.

Working with the Children’s Oncology Group, GlaxoSmithKline has pledged to enroll 1,380 patients in a 10-year trial testing different methotrexate regimens with or without nelarabine. The trial is recruiting patients at 68 centers in six countries. “It is a complicated study, but when you look at the numbers of patients contributing to the methotrexate question or the nelarabine question, it will be about 80% of all patients,” said Stuart S. Winter, M.D., chief of pediatric hematology–oncology at the University of New Mexico Children’s Hospital. “I think we’ll be able to determine whether nelarabine really contributed to therapy,” said Winter, for whom Glaxo paid travel expenses to the FDA meeting.

With such a prolonged timeline, advisory committee members wanted to know whether the trial organizers had identified interim endpoints that would signal that the drug wasn’t working. “We have a couple of futility endpoints that the data monitoring safety committee looks at twice a year,” Winter said. “It has not been an issue so far.”

**European Approach**

The European Medicines Agency in 2006 adopted comparable regulations for what it calls conditional marketing authorization of drugs that show positive benefits for
life-threatening diseases. There’s one major difference in Europe, however. The approval must be renewed each year, and the companies must annually reassure the agency that the confirmatory studies remain feasible and are under way. “We find this a very effective tool,” said Hilda Boone, the European agency’s liaison to the FDA. “The possibility for the agency to see the latest available information and the status of clinical trials is very helpful in discussions about how we can move forward.”

Members of the advisory panel complained that the language of the U.S. statute impeded public understanding of the tentative nature of the approval. “The word provisional has always made more sense to me than the word accelerated,” said Silvana Martino, D.O., director of the breast cancer program at the Angeles Clinic and Research Institute in Santa Monica, Calif.

The marginal effectiveness of many new cancer drugs lay behind the committee’s endorsement of multiple confirmatory trials for drugs that were given accelerated approval on the basis of surrogate markers. “Unfortunately, most of our new drugs have little treatment effect and will require at least two [trials] to show robustness,” said William Kelly, D.O., professor of medical oncology and urology at Thomas Jefferson University.

Martino agreed: “When you have a really good drug, the biology repeats itself over and over. It’s when you have a marginal drug that you get opposing results.”