

Expediting the availability of drugs for US patients with cancer

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In the US, to obtain marketing approval for a New Drug Application (NDA), an applicant must demonstrate that the drug is safe, and provide substantial evidence from adequate and well-controlled investigations that the drug is effective.^{1–3} The studies must allow a valid comparison of participants receiving the drug with participants from a control group, and must provide a quantitative assessment of the drug's effect. Guidance from the US FDA, published in the 1980s, indicated that efficacy should be demonstrated by a prolongation of life, by an improvement in quality of life, or by an established surrogate outcome measure for at least one of these effects.^{4,5} The safety requirement for the NDA is derived from the Federal Food, Drug, and Cosmetic Act of 1938, and a 1962 amendment to the Act codifies the efficacy requirement.

In the early 1990s, the FDA finalized its accelerated approval regulations,⁴ which are intended to encourage the development and expeditious approval of drugs for serious or life-threatening diseases. These regulations allow for the approval of a drug on the basis of a surrogate end point that is reasonably likely (based on epidemiologic, therapeutic, pathophysiologic, or other evidence⁴) to predict clinical benefit. These surrogates are explicitly less well-established than those commonly used in pivotal trials for regular approval, such as blood pressure or cholesterol level. Since the inception of the accelerated approval regulations, over 35 oncology drugs have been approved in the US via this regulatory mechanism.^{3,6}

An accelerated approval is subject to the requirement that the pharmaceutical company continues to study the drug, in order to verify and describe its clinical benefit, after obtaining marketing approval. Preferably, these studies would be underway at the time the accelerated approval is granted. A postapproval study is not necessarily required in the same indication investigated in the accelerated approval trials. For example, for a product that was approved to treat patients with a refractory malignancy,

additional information from the same patient population may not be as useful as information from previously untreated patients who participate in randomized controlled studies. A dialogue between the pharmaceutical company and the FDA during the conduct of such confirmatory studies should be ongoing, with strategies in place for alternative studies to be conducted if those originally proposed fail to demonstrate clinical benefit. If the postmarketing studies fail to demonstrate clinical benefit, or if the applicant does not demonstrate "due diligence" in performing these trials, the drug may be removed from the market.⁶

In oncology, accelerated approval is commonly based on objective response rates in single-arm studies in patients with refractory disease. This approach may expedite drug availability to patients with life-threatening disease, as single-arm studies are completed and analyzed more rapidly than large, randomized controlled trials. However, single-arm trials do not allow for an assessment of time-to-event end points (e.g. progression-free survival or overall survival) as they lack a comparator arm. In addition, single-arm studies do not assess the potential benefit of adding the drug to standard therapy, and they may not be sufficient to completely evaluate the drug's toxicity profile. An alternative to the single-arm trial in patients with refractory disease is a randomized controlled trial that could support accelerated approval based on an interim analysis of one or more surrogate end points (e.g. response rate or time-to-progression). At the completion of the randomized trial, an established clinical benefit, such as survival, would be evaluated. Randomization allows for the evaluation of time-to-event end points and a more comprehensive evaluation of the drug's toxicity profile than single-arm studies.^{7,8}

Regardless of whether a company is seeking regular approval based on the demonstration of clinical benefit, or accelerated approval based on a surrogate end point that is reasonably likely to

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predict clinical benefit, substantial evidence of safety and efficacy must be demonstrated for a drug to receive FDA approval for an intended indication. Before the pivotal study is conducted, the FDA will evaluate the proposed study population, randomization and blinding, comparators, efficacy end points, and prespecified analysis plans. Ordinarily, claimed benefits indicated by nonprespecified subgroups and post-hoc analyses do not constitute substantial evidence to support marketing approval. Rather, they are considered exploratory, hypothesis-generating analyses that potentially justify further controlled trials.^{5,9,10}

The FDA has long recognized the need to facilitate access to experimental drugs for serious and life-threatening diseases to patients who lack satisfactory alternative therapies, and methods for providing access have been in place since before the availability of accelerated approval. In 1977, the so-called "Group C" access mechanism was established to meet this need, by agreement between the FDA and the National Cancer Institute. The program requirements were that the drugs should have shown evidence of relative and reproducible efficacy in a specific tumor type, and could be administered by properly trained physicians without the need for specialized supportive care facilities. Over 20 "Group C" unapproved drugs were distributed by the National Institutes of Health under these National Cancer Institute protocols. Drugs distributed under this program included cisplatin, paclitaxel, fludarabine, asparaginase and azacitidine.

In 1987, the FDA revised the Investigational New Drug (IND) regulations to formalize the use of unapproved drugs for treatment.¹¹ Broad access was provided to these drugs under the so-called "treatment IND" for seriously ill patients, while the investigational drug was being evaluated in ongoing or completed trials. In addition, large, open-label safety studies have been used to provide unapproved drugs in the latter stages of development to seriously ill patients. Gemcitabine for pancreatic cancer, docetaxel for breast cancer, temozolomide for malignant gliomas, trastuzumab for breast cancer, imatinib for chronic myeloid leukemia, oxaliplatin for colorectal cancer, gefitinib for non-small cell lung cancer, and pemetrexed for malignant mesothelioma, were all made available in large, open studies. These trials provided unapproved drugs to many thousands of patients. These protocols were generally implemented near the time of

closure of the key trials that supported marketing approval, and did not affect the timing of such approval being granted.¹²

The FDA currently has several pathways to provide access to unapproved drugs for patients with serious diseases who lack therapeutic alternatives. Access for a specified patient is available through a "single patient IND" or as an "exception" to an existing clinical trial. In addition, the treatment IND mechanism is used to provide access to large groups of patients. In each case where an investigational drug could be used before marketing approval, the pharmaceutical company must agree to release the drug.^{12,13}

The FDA is currently revising its regulations to make the expanded access mechanisms more transparent and equitable. The proposed new regulations, published on 14 December 2006,¹⁴ clarify that the goal of expanded access is treatment rather than data development. The proposed regulations describe three types of INDs for obtaining access, based on the amount of evidence to support the use of a drug and the size of the population to be treated. These INDs are the single patient IND (including emergency use), intermediate-sized patient population IND (intended to bridge the gap between the individual patient IND and treatment IND), and the treatment IND for large populations. The goal of these regulations is to provide access to as many patients as possible, as equitably as possible, without impeding the development and marketing approval of potentially life-saving therapies.

Under the proposed rule, all types of expanded access uses must fulfill the following requirements. First, the FDA must determine that the patient(s) to be treated has a serious or immediately life-threatening disease or condition, and that no comparable or satisfactory alternative therapy to diagnose, monitor or treat the condition exists. Second, the potential patient benefit must justify the potential risks of treatment use, and the potential risks must not be unreasonable in the context of the disease or condition to be treated. Third, the investigational drug for the requested use must not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval, or otherwise compromise the potential development of the expanded use. The proposed rule also describes the required content of IND submissions for expanded access uses and clarifies the responsibilities of companies and investigators.

Competing interests

The authors declared no competing interests.

The FDA received a great deal of commentary and discussion on the proposed rule after the publication in December 2006. Comments were received from the general public (including patients and advocacy groups), pharmaceutical and biotechnology companies, and health-care organizations. Internal review and consideration of the submitted comments revealed that the majority were supportive of the proposed rule and the goal of expanded access. The FDA is actively working toward publishing these rules in the next few months.

Although these procedures allow access to promising drugs, the safest and most effective way for the American public to access therapy is to use approved drugs. Hence, the FDA is committed to collaborating with stakeholders to expedite the development and review of promising therapies for serious and life-threatening diseases.^{13,15–17} The results of this policy are reflected in the approval data of the Office of Oncology Drug Products (part of the FDA's Center for Drug Evaluation and Research) from July 2005 (at its inception) to the end of 2007. During this 18-month period, 53 new indications were approved, including 18 new molecular entities for hematology and oncology use. Of these 53 new indications, 10 received accelerated approval, 38 received regular approval, and 5 previously accelerated approvals were converted to regular approval following successful completion of trials confirming their clinical benefit. Furthermore, 39 (74%) of these applications were priority reviews, indicating a review time after the receipt of the application of 6 months or less. During this same time period, only five hematology and oncology drugs did not achieve approval. End points used for approval included overall survival, progression-free survival, response rates, and novel end points, such as asparagine depletion and reduction in iron level. These data are evidence of the FDA's regulatory flexibility, and readiness to implement a variety of regulatory mechanisms in order to ensure timely approval of safe and effective drugs for patients with cancer.

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