Oncology Drug Review Process

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Abstract
The U.S. Food and Drug Administration facilitates the development of drugs intended to treat cancer and other serious or life-threatening diseases. This article describes the new drug application (NDA) process, endpoints used in oncologic trials, and recent initiatives to expedite the review of drugs used to treat serious and life-threatening diseases. The Food and Drug Administration can grant either regular or accelerated marketing approval for oncology drugs. Regular approval is based on endpoints demonstrating that the drug provides a clinical benefit, such as longer life, enhanced quality of life, or a favorable effect on an established surrogate for longer or better life, such as long-term complete responses. Accelerated approval is based on a surrogate endpoint that is less well established but is reasonably likely to predict a longer or better life and can be granted for drugs that are intended to treat a serious or life-threatening illness and that provide meaningful therapeutic benefit to patients over existing therapies. The Agency classifies an NDA as either a priority or a standard application. Drugs that receive priority review are agents that appear to represent significant improvements over existing therapies. A priority NDA is reviewed by the Agency within 6 months; a standard review is accomplished within 10 months. The Agency communicates with sponsors throughout the drug development process, suggesting appropriate trial designs and meaningful endpoints. (JNCCN 2003; 1:109–113).

The U.S. Food and Drug Administration’s (FDA) mission is to ensure that safe and effective drugs are available to the American public. Before a new drug application (NDA) receives marketing approval, the Agency carefully considers all submitted scientific evidence, as well as evaluating what needed information is missing, to determine whether the data meet the legal requirements for approval. To facilitate drug development for serious and life-threatening medical conditions, the FDA has implemented several special programs and policies that promote frequent interaction with pharmaceutical companies during drug development and allow approval in some cases based on surrogate endpoints rather than on documented clinical benefit.

NDA Review Process
The NDA review and approval process is designed to ensure that safe and effective drugs are available. NDA approval is actually the approval of a marketing application and occurs after the Agency has carefully considered the submitted study reports, data, and a proposed product label for a drug’s use for a specific indication. The approval is for 1 or more specific indications rather than for the drug itself. The final product label/package insert describes the approved indication, dose regimen, clinical efficacy data, and potential adverse reactions. Once an NDA is approved, the pharmaceutical company may advertise and promote the drug’s use as long as it is consistent with the approved labeling.

To be approved, an application must provide substantial evidence of effectiveness (as represented in the labeling) derived from adequate and well-controlled studies. The data must demonstrate that the drug is safe for its intended use, a requirement usually translated as evidence that the demonstrated benefits of the drug outweigh its risks to the patient. This risk–benefit analysis is critical in decisions regarding oncology drugs because conventional anticancer drugs are toxic and have relatively modest therapeutic benefits compared with other therapeutic classes. The application must define the appropriate patient population and provide adequate...
Agency Review Programs and Policies

The agency has several special programs and policies to facilitate the drug-development process for serious or life-threatening diseases such as cancer. These include Accelerated Approval,1,2 the Fast Track Program and Rolling NDA Submission,3 Priority Review,4 and Special Protocol Assessment.5

Full Approval

Full approval of an application is based on the demonstration of clinical benefit, such as increases in survival time or, in selected cases, improvement in disease-related symptoms. A reduction of tumor size may not be evidence of clinical benefit, especially in asymptomatic patients.

The Legislative Branch of the U.S. Government and the FDA have worked together to facilitate the development of drugs to treat serious and life-threatening diseases. In 1992, the agency published the final rule governing accelerated approval. The FDA Modernization Act (FDAMA) of 1997 designated certain drugs as “fast track products.” This designation allows these drugs to undergo expedited study and approval. FDAMA also directed the Agency to meet with sponsors for the purpose of agreeing on the design and size of clinical trials intended to form the primary basis of an efficacy claim in a marketing application. These initiatives are discussed further in the following sections.

Accelerated Approval

Accelerated approval is granted for new drugs to treat serious or life-threatening diseases when the new drug appears to provide benefits over available therapy.6 Accelerated approval can also be granted on a surrogate endpoint “reasonably likely to predict clinical benefit.” A frequently used surrogate endpoint for clinical benefit in the treatment of solid tumors is the response rate (RR).

Pharmaceutical sponsors whose applications are granted accelerated approval are obligated to perform postapproval clinical trials to demonstrate that the drug does provide clinical benefit.7 These trials do not necessarily have to be performed in the identical indication. Oncology drug applications receiving accelerated approval based on a surrogate endpoint in patients with refractory disease may subsequently demonstrate clinical benefit in patients with an earlier stage of disease. Frequently, oncology drug trials for accelerated approval are performed as single-arm trials, and these drugs typically demonstrate RRs in patients with refractory disease. The demonstration of efficacy in that population will fulfill an unmet medical need. Although the use of single-arm trials is beneficial in terms of lower costs and fewer patients required, they also carry distinct disadvantages. Compared with active comparator randomized trials, single-arm trials do not permit comparisons of endpoints such as time to progression or survival or of safety issues such as toxicity.

Fast-Track and Rolling NDA Submissions

The Fast Track Program, responding to a provision of the FDAMA, facilitates both the development and review of potentially important drugs. To be eligible for the Fast Track Program, drugs must treat a serious or life-threatening disease and demonstrate the potential to address an unmet medical need. The development plan must be designed to determine whether the drug does, in fact, represent an advance over existing therapy.8 After an oncology drug is designated as a fast-track drug, the oncology division of the FDA schedules meetings with the sponsor throughout the development process. Fast-track designation provides sponsors with the option of a rolling NDA submission. With this provision, completed sections of the application (e.g., chemistry and manufacturing and control, clinical) may be submitted to the Agency before the entire completed application submission. Fast-track designation also includes the same surrogate endpoint provision as accelerated approval.

Priority Reviews

The Agency classifies an NDA as receiving either a priority or a standard review based on an estimate of its therapeutic, preventative, or diagnostic value.9 To receive a priority review, the NDA drug should represent a significant improvement over existing therapy or treat a condition that is currently lacking treatment. The time goal for reviewing a priority review application is 6 months or less. The review time goal for a standard review of an NDA is 10 months.

Special Protocol Assessment

FDAMA directed the Agency to meet with sponsors for the purpose of agreeing on the design and size of clinical trials intended to form the primary basis of an
efficacy claim in a marketing application. The Guidance for Industry: Special Protocol Assessment describes a procedure wherein the Agency will review certain submitted protocols within 45 days of receipt. Eligible protocols include carcinogenicity studies, drug stability studies, and clinical phase 3 trials. If the Agency agrees with the protocol, under the special assessment procedure, the FDA will not alter its previous agreement on the issues of design, execution, or analyses unless previously unrecognized public health concerns emerge.

**NDA Approval Issues**

In 1962, the Federal Food, Drug, and Cosmetic Act added an amendment that required drug manufacturers to establish the drug’s effectiveness. The FDA’s legal standard for the demonstration of effectiveness was termed “substantial evidence.” Substantial evidence was defined as “evidence consisting of adequate and well-controlled investigations, including clinical investigations.” The Agency has interpreted this phrase to mean that at least two adequate and well-controlled trials are necessary to demonstrate a new drug’s effectiveness. FDAMA permits the Agency to consider an application containing one adequate and well-controlled trial with supporting data. This situation occurs when effectiveness is demonstrated in a single study of a new use and this effectiveness is independently substantiated in related study data. Types of supporting data include documentation of effectiveness in other related clinical situations, such as these:

- another biologically similar cancer;
- effectiveness in adult tumors that allows extrapolation to children who have the same cancer;
- use as monotherapy when the drug has already been approved for use in combination;
- a new dosing regimen;
- an earlier disease stage.

Single trials may be used to support effectiveness claims without independent substantiation from another controlled trial if the trial has one or more of the following characteristics: the efficacy results must be statistically persuasive; trials must be large and multicenter, ensuring that the results can be generalized to treatment centers across the United States; and trial results should have consistency across patient subsets, ensuring that the trial results are applicable to the oncology patient population. A single trial with multiple endpoints has considerable credibility when positive results are seen in beneficial but different endpoints.

**Endpoints for Approval**

Clinical benefit endpoints for approval vary depending on disease, stage, previous treatment, and available therapies. Endpoints that have been used for approval are detailed in the following sections.

**Survival**

Survival is defined as the time from randomization to death. Survival is an unambiguous, objective endpoint not subject to investigator interpretation or bias even in unblinded studies. The disadvantages of using survival as a trial endpoint include the need for a somewhat larger patient population and a longer observation period compared with other endpoints. Most important, however, is the confounding potential of subsequent therapies on drug’s true effect on survival. Subsequent therapies are administered after progression, and the confounding effect can be especially strong if crossover to test treatment occurs. This confounding situation can be problematic if the test drug is already marketed.

**Time to Progression**

Time to progression (TTP) is defined as the time from randomization to evidence (usually radiologic) of progression. TTP can be a subjective endpoint when based on results from serial radiologic scans. Unless the trial has a central blinded adjudication committee reviewing all films, radiographs may be inconsistently interpreted. The timing, frequency, and symmetry of radiographic studies in randomized trials are important in trial designs using this endpoint. Compared with survival as an endpoint, the use of TTP has the advantages of requiring smaller patient numbers and shorter observation times. The endpoint is not obscured by the subsequent therapy. Other disadvantages include the expense associated with performing serial scans to completely assess all disease sites.

**Time to Treatment Failure**

The time to treatment failure (TTF) is a hybrid endpoint that combines measures of effectiveness and safety. TTF is defined as the time from randomization to documentation of progressive disease or death,
withdrawal because of adverse events (toxicity), loss to follow-up, patient refusal, or initiation of a new therapy. Because TTF is a hybrid endpoint of efficacy and safety, possible trade-offs between efficacy and toxicity may occur. Potentially progressive selection of less toxic therapies with lessening efficacy over the course of several trials may result in the eventual approval of nontoxic placebos. Therefore, TTF has not been accepted as a regulatory endpoint.

Response Rate
RR is an endpoint in which the treatment is entirely responsible for the measured endpoint (reduced tumor size) and in which there is essentially no response without treatment. RR can be an acceptable endpoint for approval in a single-arm study. In fact, RR is the only interpretable endpoint in a single-arm trial, unlike TTP or survival for which the effect in a treated group must be compared with a randomized control. The Agency has adopted both the World Health Organization criteria and the National Cancer Institute’s Response Evaluation Criteria in Solid Tumors to define RR. The determination of RR is comprised of complete responses and partial responses. Stable disease is not part of RR and is more appropriately reflected in the TTP endpoint. Response criteria should be prospectively identified and are usually ascertained through timed evaluations.

Drug approval for selected hematologic diseases (e.g., hairy cell leukemia) have been based on durable complete RRs. In many hematologic malignancies, a durable complete response is correlated with reduced need for antibiotics and blood products and potentially improved survival, thus representing clinical benefit to the patient. Durable partial and complete RRs have been used in the approval of hormonal agents for the treatment of recurrent breast cancer, based on randomized clinical trials with an active comparator.

Symptom Palliation and Patient Reported Outcomes
Clinical trials showing improvement in symptoms demonstrate clinical benefit. Given the subjective nature of the endpoint, these trials need to be double blinded. In some cases, a blinded evaluator may be necessary as the treatment effects unmask patients and observers. These trials may be most successful when simple assessment instruments are used.

Health-related quality of life (HRQOL) tools have frequently been incorporated into clinical trials. The major advantage of using HRQOL tools is that they can provide the patient’s perspective on treatment; however, the accurate assessment of HRQOL can be difficult. Few clinical trials in oncology are blinded, leading to potentially biased assessment, and missing data frequently complicate the interpretation of HRQOL. The multiple components of HRQOL tools require statistical adjustment for endpoint multiplicity. In addition, the clinical significance of data score changes may be unclear. HRQOL data may not provide additional information compared with a careful recording of toxicity and symptom data. If HRQOL tools are used, they need to be treated rigorously, with specified hypotheses and a rigorous statistical analysis plan.

Recent Oncology Drug Approvals
Over the past 12 years, the FDA has approved 52 oncology drugs as full approval and 10 oncology drugs as accelerated approval. Of these 62 approvals, 43 were based on endpoints other than survival. Of the 52 full approvals, 25 were based on tumor response, supported by an improvement in symptoms for 10 of these full approvals. Symptom improvement provided support for 13 of the 52 full approvals. Nine of the 10 accelerated approvals were based on tumor response. Drugs given accelerated approval include irinotecan, capecitabine, imatinib mesylate, liposomal doxorubicin, docetaxel, liposomal cytarabine, temozolomide, liposomal doxorubicin, and gemtuzumab ozogamicin.

During drug development, the Agency communicates repeatedly with the pharmaceutical company about the proposed development strategy. End-of-Phase 2 meetings and Special Protocol Assessments allow the Agency and pharmaceutical company to agree on trial design and endpoints, facilitating initiation of the major trials and providing as much assurance as possible that if the trials meet their goals, the drug will be approved. Agency decisions concerning the NDA approval process such as accelerated or full approval, fast-track designation, or review priority help bring safe and effective drugs to patients as expeditiously as possible.

References


