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Food and Drug Administration process for development and approval of drugs and radiopharmaceuticals: Treatments in urologic oncology

Yang-Min Ning, M.D., Ph.D.*, V. Ellen Maher, M.D.

Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

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Abstract

Regulatory advice and assessment play an important role in the successful development of new drugs and radiopharmaceuticals for the treatment of urologic malignancies. Cooperation between the US Food and Drug Administration (FDA) and the pharmaceutical industry has led to the approval of more than 20 new urologic oncology products in the last 2 decades. Despite these advances, more effective treatments need to be developed and approved for the treatment of urologic malignancies. This review provides general information about the FDA's role in the development of investigational new drugs, with an emphasis on the regulatory process and the requirements for marketing approval. In addition, this review summarizes the products for the treatment of urologic malignancies that were approved by the FDA in the last 30 years and the key issues concerning urologic oncology products that were discussed publicly at Oncologic Drug Advisory Committee meetings in the past 10 years. Published by Elsevier Inc.

Keywords: Treatments in urologic oncology; FDA approval; Oncologic Drug Advisory Committee; Prostate cancer; Renal cancer; Bladder cancer

Introduction

Nearly 400,000 new urologic malignancies are expected to occur in the United States in 2014, resulting in approximately 60,000 deaths [1]. The malignancies primarily consist of cancers of the prostate, bladder, kidney, testis, and ureter. Currently, there are more than 20 Food and Drug Administration (FDA)–approved products for the treatment of urologic malignancies.

This review summarizes key FDA regulatory concepts involved in the development and approval of new cancer treatments, with a focus on the evaluation of drugs and radiopharmaceuticals to treat urologic malignancies at the Center for Drug Evaluation and Research (CDER).

Basis for FDA regulation of drugs in the CDER

Since 1906, the Congress passed 3 major laws that authorize the FDA to regulate new drugs to ensure their safety and effectiveness before marketing in the United States [2]. In addition to these laws, a number of regulatory initiatives have been implemented to expedite the development and approval of products intended to treat life-threatening diseases such as cancer. One of these initiatives is the Accelerated Approval approach [3,4]. It allows a drug or biologic to be marketed based on an improvement in a surrogate end point that is reasonably likely to predict clinical benefit. It has resulted in earlier patient access to important treatments in areas of unmet medical need, including treatments for urologic malignancies [5].

Evaluation of investigational new drugs for clinical studies

Clinical studies of an investigational new drug (IND) must be evaluated and conducted under an IND application submitted to the FDA [6]. This requirement generally does not apply to off-label use or a clinical investigation of an approved drug unless the investigation is intended to support a new indication; is intended to change the labeling or advertising of the approved product; or involves a route of

* Corresponding author. Tel.: +1-301-801-7300.
E-mail address: ningy@cder.fda.gov (Y.-M. Ning).

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administration, dosage level, patient population, or other factors that significantly increase the risks or decrease the acceptability of the risks associated with the use of the drug product [7,8]. However, the investigation must still be conducted in compliance with requirements for institutional review and informed consent. An IND application should include adequate information on a drug's chemistry, manufacturing, and control; nonclinical toxicology and pharmacology; previous human experience, if any; an investigator's brochure; and a clinical study protocol or protocols [9]. This allows the FDA to comprehensively evaluate the IND for its safe use in the intended study patients. It should be noted that the FDA review does not replace the requirement for review by an institutional review board that oversees clinical research at the institution(s) where the study is carried out.

INDs that are intended to treat urologic malignancies are evaluated in the CDER's Office of Hematology and Oncology Products (OHOP). Phase 1 protocols in these INDs are reviewed by a multidisciplinary team, which generally consists of a chemist, a toxicologist, a clinical pharmacologist, and a medical oncologist. All disciplines must complete their review of new INDs within 30 days after the FDA receives the application. For all phases of clinical investigation, the reviews focus on the safety of the proposed clinical study and the rights of the subjects [10]. For phases 2 and 3 trials that have the potential to lead to marketing approval, the review team also includes biostatisticians and other disciplines as needed, and the review focuses not only on the safety and protection of patients but also on the scientific quality of the clinical investigations. Deficiencies that have potential for clinical hold are conveyed to the IND sponsor within the 30-day review period. The review team's goal is to allow a protocol to proceed when it is reasonably safe to do so after resolving any identified deficiencies before the 30-day review date. Instances where deficiencies are not satisfactorily resolved result in a clinical hold, i.e., subjects may not be given the investigational drug [11].

To facilitate a successful IND submission, the sponsor may seek advice on the IND proposal to identify or clarify additional information needed before the IND submission [12]. This approach has helped in the development of a number of oncology drugs, including products to treat urologic malignancies (e.g., abiraterone acetate and enzalutamide).

Throughout the development of an IND, the FDA plays an oversight role. This includes providing advice on the design and conduct of trials intended to support a new drug application (NDA) and monitoring safety. During the process, a number of meetings are generally held between the FDA and the sponsor to review detailed clinical protocols, statistical analysis plans, and other issues related to manufacturing and clinical pharmacology and toxicology studies [13].

Evaluation of NDAs for marketing approval

For a new drug to receive marketing approval in the United States, a NDA must be submitted and must include substantial evidence of effectiveness for the claimed indications from adequately designed and well-conducted clinical trials, all relevant data on the safety of the drug, and a discussion of why the benefits exceed the risks [14]. The FDA evaluates the complete NDA submission, including information regarding chemistry and manufacturing, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, and clinical data and statistical analyses. Once an NDA is filed, the FDA's Prescription Drug User Fee Act's goal is to review and act on drug application designated as a standard review within 10 months and to conduct a priority review within 6 months. The designation of priority review depends on whether the drug offers a major advance in treatment or provides a treatment where none existed.

Evaluation of the reported clinical efficacy and safety data and an analysis of the benefit-risk profile are the key parts of the NDA clinical and statistical reviews. For approval of anticancer drugs, the general principle is that such products should demonstrate clinical benefit [15–19]. This can be measured by an improvement in end points such as overall survival (OS) or the relief of tumor-related symptoms. Products that have shown a clinical benefit in adequate and well-controlled trials generally receive regular approval.

Since the implementation of the Accelerated Approval approach in 1992, numerous anticancer products have received accelerated approval based on an improvement in a surrogate end point that is reasonably likely to predict clinical benefit [3–5]. An example of a commonly used surrogate end point is response rate. Following accelerated approval, additional trials are required to confirm the clinical benefit predicted by the surrogate end point.

For an NDA where there are issues concerning the interpretation of the data and analyses or the benefit-risk assessment, the OHOP seeks external advice from either a Special Government Employee (acting as a consultant) with expertise in the topic or the Oncologic Drugs Advisory Committee (ODAC). The ODAC includes expert oncologists and hematologists, statisticians, consumer representatives, patient representatives, and a nonvoting industry representative [20]. The ODAC discussion occurs at a public meeting where both the applicant and the FDA review team present key findings from the trial(s) used to support the application. These presentations focus on specific issues such as trial design and conduct, reliability of the findings, interpretation of the results, and the benefit-risk assessment. The ODAC members discuss the issues, elaborate their views, and then vote on questions asked by the OHOP. These questions typically involve an assessment of the acceptability of the benefit-risk profile of the product for the intended use. The discussion, voting results, and recommendations from the meeting are summarized and considered carefully in making a regulatory decision on the application's approval. The ODAC does not make a regulatory decision but provides nonbinding recommendations.