Expedited Programs for Serious Conditions: An Update on Breakthrough Therapy Designation

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ABSTRACT

Purpose: Our aim was to describe the regulatory pathways made available by the US Food and Drug Administration (FDA) to expedite the drug development and approval process, with a focus on the benefits and limitations of the Breakthrough Therapy Designation (BTD) pathway.

Methods: Published materials consisting of journal articles, press releases, government documents, and news articles from pharmaceutical publishers were identified through online databases (ie, Medline and Scopus), the FDA website, and Internet search engines (eg, Google).

Findings: To encourage pharmaceutical innovation and increase the number of products being approved each year, the FDA has introduced 4 expedited regulatory pathways to accelerate the drug development and approval process. The most recent program, enacted in July 2012, was BTD that is given to drugs that treat a serious or life-threatening disease or condition; and preliminary clinical evidence suggests the potential for these drugs to provide a substantial improvement over the current standard of care. The primary basis for the creation of BTD is to provide patients with serious conditions with earlier access to FDA-approved medications. In 2014, 22% of the new molecular entities approved within the Center for Drug Evaluation and Research had BTD status, as opposed to only 11% in 2013, which indicates both the popularity and success of this expedited pathway. Additionally, the creation of BTD has produced a more collaborative working relationship between the pharmaceutical industry and the FDA because both parties have a vested interest in the drug's success. Some of the more notable concerns surrounding these approved breakthrough therapies have been the abbreviated tolerability and efficacy evidence available from accelerated clinical development programs, ensuring the manufacturing aspects keep pace with these accelerated clinical programs, and finally, managing the strain on resources for both the pharmaceutical companies and the FDA.

Implications: BTD has already had many positive and negative impacts on various stakeholders, including sponsors, investors, regulatory agencies, third-party payors, and patients. The ultimate goal of the BTD program is to identify promising drug candidates early in the clinical development timeline, expedite the development and review processes via intensive guidance from the FDA, and provide patients access to approved therapies as quickly as possible. With the first few batches of BTD product approvals, the FDA and other stakeholders have been working collaboratively to address the various expected and unexpected challenges that have arisen during the BTD process in order to refine and improve this already successful program. (*Clin Ther*. 2015;37:2104–2120)

Key words: Breakthrough Therapy Designation, BTD, CDER, drug development, FDA, NME.

TRADITIONAL REVIEW OF NEW PRODUCTS

Since the passage of the Kefauver-Harris Act in 1962, the traditional timeline for drug development has been to conduct a complete clinical development plan involving 3 phases of clinical trials all under an Investigational New Drug (IND) application; a Phase I study in approximately 50 healthy volunteers to establish safety profile, tolerability, and dosing; a Phase II study in a few hundred patients with the disease to establish preliminary efficacy and tolerability; and a Phase III

Accepted for publication July 13, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.07.011
0149-2918/$ - see front matter

study or studies in thousands of patients with the disease to demonstrate definitive efficacy and tolerability.[1,2] To receive marketing approval, the US Food and Drug Administration (FDA) encourages sponsors (eg, the companies submitting the IND applications) to conduct at least 2 Phase III trials, which will serve as the pivotal studies needed to provide conclusive evidence of efficacy and tolerability for their drug product; however, in limited circumstances, one adequate and well-controlled trial might be sufficient.[1] This traditional drug development process allows sponsors to request at least 2 milestone meetings with the FDA to discuss any issues that might arise during the clinical development program. The FDA must grant the sponsor's request for these 2 milestone meetings, which are designated as the end-of-Phase II and pre–New Drug Application (NDA) meetings. If the product is being investigated for a life-threatening or serious condition, the sponsor can also request a pre-IND or an end-of-Phase I meeting.[3,4]

The marketing application (MA), which can be either an NDA or a Biologics License Application (BLA), is a summary of all the information accumulated by the sponsor conducting nonclinical, clinical, and manufacturing studies to support a marketing authorization. The NDA or BLA is submitted to the FDA for evaluation by the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research, respectively.[2] As part of the 2012 Prescription Drug User Fee Act (PDUFA) enacted by Congress, the FDA's PDUFA goal for a standard review of an MA is 10 months after a 60-day filing period to verify the suitability of an application for review, which ultimately gives the FDA 12 months to complete their evaluation for a New Molecular Entity (NME).[2,5]

Several studies have reported that the clinical portion of the drug development timeline has historically taken more than 7 years, which has created frustration for patients with serious and life-threatening conditions who are looking for tolerable and effective FDA-approved drug therapies now. Pharmaceutical companies are, at the same time, frustrated when drugs that clearly show substantial effectiveness over the standard of care are still required to conduct additional studies that might not be absolutely necessary; meanwhile, valuable resources are being needlessly wasted and allocated inefficiently.[6] These protracted timelines and concerns expressed by both the patients and the pharmaceutical companies have prompted the FDA to reanalyze the drug development process and create new programs to help expedite the traditional development timeline.[1,7] The purpose of this review is to describe the regulatory pathways made available by the FDA to expedite the drug development and approval process, with a primary focus on the benefits and limitations of the Breakthrough Therapy Designation (BTD) pathway. Because BTD is still very young, published materials consisting of journal articles, press releases, government documents, and news articles from top pharmaceutical publishers were identified through online databases (ie, Medline and Scopus), the FDA website, and Internet search engines (eg, Google) in order to capture a complete picture of this program.

EXPEDITED DRUG APPROVAL PROGRAMS FOR SERIOUS CONDITIONS

There are currently 4 programs in place to expedite the traditional drug development process for new and promising medications; Accelerated Approval (AA), Fast-Track Designation (FTD), Priority Review (PR), and BTD (**Table I**). These programs were intended to expedite the development and approval of either NME or previously approved products applying for additional indications that address an unmet medical need in the treatment of serious or life-threatening conditions.[8]

The AA pathway allows a drug to receive FDA approval based on the utilization of a surrogate end point when the drug has a meaningful advantage over currently available therapies. The FDA defines a surrogate end point as an end point "that is reasonably likely to predict clinical benefit" or an end point "that can be measured earlier than irreversible morbidity or mortality."[8] For example, in oncology, the surrogate end point of objective response rate is considered likely to predict the clinical benefit of prolonged survival.[9] Full approval via this pathway comes with the requirement that the sponsor must conduct one or more postmarketing confirmatory trials to verify and describe the anticipated clinical benefit predicted by the use of a surrogate end point.[8] The FDA also has the authority to withdraw an approved NME or a specific indication of an already approved drug if the subsequent trial(s) fail to confirm the clinical benefit, if the sponsor fails to conduct the confirmatory trial(s), if the benefit–risk assessment is no longer favorable, and if the applicant distributes false or misleading promotional material.[8,9]