What It Means To Be "Breakthrough": Expediting Drug Development—the New FDA Breakthrough Therapy Designation

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The Regulatory Sciences section submitted this article.

In July 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law. Little did we know at the time, but the drug development process was about to be altered forever. This bill expanded many of the existing governing powers of the Food and Drug Administration (FDA), but also added one intriguing new provision—the breakthrough therapy (BT) designation, intended to expedite the development and review of drug candidates, which has certainly found favor in the industry.

The agency has received over 100 applications as of fiscal year (FY) 2013.[1] The Center for Drug Evaluation and Research (CDER) reports that between Oct. 1, 2012, and Nov. 22, 2013, it had 92 requests for BT designation, 31of them were granted and 50 denied. The Center for Biologics Evaluation and Research had 14 requests and of these, twelve were denied.

The data on BT designation show that the bar for granting requests has been set high. To qualify as a breakthrough therapy, a drug must be intended to treat a serious condition and have preliminary clinical evidence indicating that it may demonstrate a substantial improvement on a clinically significant endpoint over other available therapies.

FAST-TRACK ADVANTAGES PLUS GUIDANCE

Candidates deemed breakthrough therapies will get the advantages offered by fast-track designation—i.e., expedited development/review and rolling review—plus intensive guidance on efficient drug development during the investigational new drug process, beginning as early as phase 1.

FDA is stressing that the ability to meet the expedited review goals of the BT pathway will hinge on the sponsor intensifying its upfront chemistry, manufacturing, and control (CMC) coordination and communication internally; with outside contractors involved with drug substance and product manufacturing, testing, and packaging; and with the agency. The new 33-page guidance[2] explains how the BT pathway fits in with and combines elements of three other programs—fast track, accelerated approval, and priority review—that FDA already had in place to facilitate and expedite the development and review of new drugs and biologics that target unmet medical needs.

The agency has also posted on its website, and continues to update, Frequently Asked Questions[1] specifically on the BT designation: what the designation means, how it differs from the fast-track and other expedited review programs, eligibility, and how and when to apply.

USER FRIENDLY FOR EMERGING BIOTECH AND GAINS FOR LARGER COMPANIES

From most accounts, BT is a very user-friendly process with FDA rendering its decision within 60 days of submission. One of the benefits that will accrue from having the designation is that it should expedite patient enrollment for planned phase testing because physicians and their patients will be encouraged that the drug's therapeutic potential has been validated.

Another important benefit is the increased attention FDA will provide in its ongoing dialog about the forthcoming trial. The designation gives a "special focus" for the agency, which flagged it as an important potential therapy that could change practice.

Most of the initial companies that reported receiving BT designation for one or more of their candidate products are large pharmaceutical firms. However, several smaller emerging biotech sponsors have also now begun to achieve such recognition.

The challenges and opportunities for commercial manufacturing readiness in BT programs and the impact of accelerated development for these kinds of products on CMC and good manufacturing practices (GMP) issues need to be considered in developing both large and small molecule drugs.

INTENSIFIED UPFRONT DIALOGUE ON CMC PLANS REQUIRED

In sorting through the implications of the BT provisions in FDASIA, both FDA and industry are recognizing that the compressed clinical timelines in the provision push the CMC development process onto the new drug clearance critical path.[3] This significantly heightens the profile of the related issues and forces attention on the constraints of the current CMC review paradigm and how to deal with them.

In the draft guidance on breakthrough and other expedited approval programs[2] released in June 2013, and in addressing BT implementation from the podium, FDA has indicated the need for sponsors to develop and present a well-thought-out CMC plan relatively early in the discussion process. FDA has stressed that more upfront communication and coordination will have to take place among all those involved to assure the plan is viable and executed.[4]

Industry, on the other hand, has been wrestling with the problem of how to adjust its normal CMC development process to keep pace with the expedited clinical timelines and is asking the agency to clarify how it is going to provide the regulatory flexibility for these adjustments.

Opening the risk/benefit door in the BT context is prompting a reevaluation of the CMC review paradigm in the USA that has potentially significant international implications.

CLINICAL PACE WILL CHALLENGE CMC

FDA cautions that a key challenge in the expedited review context will be to keep the manufacturing development process on pace with the accelerated clinical program. Toward this goal, the guidance advises that the sponsor's product quality and CMC teams should meet with the agency and be prepared to propose a commercial manufacturing development plan that will support the agency's

review needs and ensure availability of quality product at the time of approval. The proposal should consider estimated market demand and a timeline for development of the manufacturing capabilities with goals aligned with the clinical development program.[3]

FDA is looking for the plan to encompass the manufacturing process, facilities and equipment, validation activities including scale-up and comparability, and stability and potency studies. After the initial discussion following designation, the guidance calls for "frequent communication during development" to facilitate meeting the manufacturing and product quality goals.[3]

FDA is also looking for earlier submission of the CMC section of applications to meet the review timelines, and "critically," for inspection planning. A "comprehensive" meeting with FDA's product quality review office well prior to submission is recommended to help with the quality assessment needs.[3]

FDA PROVIDES FURTHER INSIGHT

In a session focused on breakthrough therapy CMC issues in June 2013, CDER Office of Compliance Division of GMP Assessment Director David Doleski provided additional insight on the challenges both industry and FDA face in integrating the manufacturing component into the expedited review timelines targeted for breakthrough therapies.[5]

In his presentation, Doleski stressed the importance of early sponsor/agency meetings to discuss CMC issues. He pointed to the need for sponsors to convey a well-thought-out manufacturing plan so the agency can make sure that the right reviewing expertise is assigned and the inspection component can be planned. The plan and early discussions should address how marketing demand will be met. What FDA doesn't want, Doleski emphasized, is a situation where there is a lot of demand for the breakthrough product and the manufacturing cannot keep up.

It also may be advisable to continuously update the agency on the plans and progress with respect to manufacturing and development activities. Any risks to the schedule or to quality, such as GMP compliance problems at the facilities that will be involved in the manufacturing, "have to be identified throughout the process and mitigated," Doleski stressed.[4] FDA, in turn, will have to take "some creative approaches" to address the timing of inspections, particularly those overseas—including potentially initiating an inspection prior to receiving the CMC application.

Considerations for Industry and FDA

Efforts will be needed to put the clinical and manufacturing program on the same pathway, so that the development of one program does not surpass the other. This is going to be important to optimize and accelerate the review timeframe of these applications. It will be vital to put appropriate resources into those applications, particularly the manufacturing of those products. So it may be prudent to make decisions much earlier to connect resources.

It may be appropriate to decide on a commercial manufacturing facility: Where is this going to be manufactured? What equipment is going to be used? What is the scale of manufacturing? All of these conditions may have to be made much earlier to have the manufacturing portion of the application in step with clinical. From an industry perspective, it will be important to utilize effective project management and put key activities on a critical path.

There must be communication and coordination with FDA. It may be advisable to update the agency continuously on plans and progress with respect to manufacturing and development activities. It is going to be equally important to coordinate and communicate with contract manufacturers, the testing labs—all the different facilities that are involved in manufacturing the product.

Any risks to schedule or to quality will have to be identified throughout the process and mitigated. It is going to be important to have some type of plan for commercialization of the product to meet market demand after approval.

Success with BT products will require:

- Extensive communication between FDA and the sponsor,
- Communication within the sponsor and between the company and contract manufacturers and testing labs,

- Decisions made much earlier in the process than normally is the case,
- Planning for an accelerated schedule regarding product and process development and commercial development, and
- Emphasis on manufacturing activities that will have to start fairly early in the process to make certain that the clinical program does not outpace the CMC program.

NOT SO FAST, OPTIMISTS

As exciting of a time as this might be for biotechnology and pharmaceutical sponsors, there are a lot of factors still to play out here. Genentech Technical Regulatory Policy Director Earl Dye provided additional insights on benefits and challenges, as well as CMC strategy considerations for small molecules and for biologics, respectively.[6]

CMC Challenges and Strategy for Small Molecules

Timelines are going to be compressed; designation may occur during or shortly after the completion of phase 1 studies. So the pivotal studies essentially become an expanded phase 1b or phase 2. Under this scenario, some of the phase 3 activities will need to be accelerated or potentially deferred to a postapproval setting:

- The active pharmaceutical ingredient attributes impacting the formulation and drug product will likely be the main focus along with the pharmacokinetics and patient safety for the drug product process.
- Development activities around quality and process knowledge will have to take priority over yield and cost of goods. In other words, the optimal process may not exist going into launch. It may be that some of the optimization issues will be addressed postapproval.
- There will be a need to lock the formulation at the start of phase 3 to avoid the bioequivalence studies.

In terms of the launch site, it may be that the launch may occur from a clinical site. Registration batches may have to be manufactured at a commercial site with a minimum pilot scale for drug product material. The expectation, however, is that the clinical manufacturing facility used for launch would need to meet the same quality expectations as commercial manufacturing facilities.

From the standpoint of validation, there likely will not be as much manufacturing experience. Ranges that are being validated may be narrower, and product distribution may move forward concurrent with release or approval for release.

In addition, the control strategy will be based on limited manufacturing experience:

- Tentative specifications and process controls may be filed that would need to be updated in a postapproval setting.
- Negotiated provisional critical process parameters that would be updated, again in postapproval, may be required.
- The control strategy may have more analytical methods initially to compensate for less process robustness and then potentially be revised to remove some of the redundant testing.
- Second generation processes and optimization will require management through a life-cycle approach.

Stability may become a serious issue as timelines are compressed, and there is not as much commercial manufacturing time available to collect the real-time stability data. In the place of real-time data, modeling based on forced degradation and accelerated stability studies to predict expiries, or optionally leveraging stability data from early development lots and getting agreement with the agency up front to provide periodic stability updates according to a stability protocol may be a useful approach.

Another important consideration is the pharmaceutical quality system—that is, being certain that the pharmaceutical quality system in place has enough flexibility that it can accommodate these accelerated development activities and remain within the scope of global standards and processes that are part of that quality system.

CMC Strategy for Biologics

Biologic issues are very much like those for small molecules drugs:

- Sacrificing process optimization for increased titer or yields and focusing

FDA's Explanation of Breakthrough Therapy Designation in Its FAQs

"Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. A breakthrough therapy designation conveys all of the fast track program features…as well as more intensive FDA guidance on an efficient drug development program."[1] The designation will entail intensified FDA communication with the sponsor and senior review staff oversight in the shepherding of the drug through the application development and review process.

on process reliability is a consideration with optimization to follow;

- Front-loading analytical understanding to offset more limited process robustness;
- The use of not-yet-validated methods for qualification lot release and stability assessments to be completed prior to the preapproval inspection;
- Leveraging this life-cycle validation principle of continued verification to launch;
- Flexibility to come back and modify the control strategies;
- And then stability: From the standpoint of stability, the amount of real-time stability that is going to be available, and the kind of approaches that could be used for leveraging early development data and providing updates to the real-time stability.

CONTENT OF SUBMISSIONS AND WHAT IS DEFERRABLE

The concerns about the constraints in the existing CMC review process and FDA's willingness to loosen them were highlighted in industry's response to the agency request for input on its expedited review draft guidance.

FDA states that the sponsor of a product that receives an expedited drug development designation will probably need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The agency lists activities a sponsor should take to ensure availability of high-quality product at the time of approval. It also states that sponsors allow for earlier submission of the CMC section for timely review and inspection planning.[5]

A recurrent refrain in the industry comments to the docket, released by the agency in September 2013, was the need for FDA to further clarify those aspects of manufacturing development that could be negotiated with the sponsor for completion either during review of the marketing application or as part of a postapproval commitment.

In line with the life cycle process validation approach, the filing, for example, could provide for conducting more tests initially and justifying elimination of some postapproval. It could also contain broader in-process control and product specification acceptance criteria that could be tightened as process consistency is demonstrated.

This would be much akin to a "Postapproval Life Cycle Management Plan" with the application that would "provide detailed timelines, deliverables, and types of regulatory filings for completing" the agreed-to CMC activities.[5] Such an approach could allow for initial product launch:

- from clinical sites before transferring to the commercial site, and
- with a provisional control system and process to be upgraded/optimized as manufacturing experience is gained, and with reduced stability and validation packages that would be filled in postmarketing.

MOVING FORWARD

The BT designation is a monumental step in potentially bringing clinically superior drugs to market years ahead of the schedule, but let us not forget that such a designation is only half of the battle. Once approved, efficacy and marketing approval is the other half. Too many drugs show plenty of promise, only to flop miserably in pivotal clinical studies. In sum, keep your emotions and expectations in check.

Note: A more detailed analysis is provided in the Monthly Update, *Int Pharm Qual*, Vol. 4, No. 7, Sept. 2013. AAPS members can receive a complimentary copy by contacting customersvc@ipqpubs.com.

DISCUSSION POINT

We want to know your opinion!

Please discuss the following question with your colleagues via the *AAPS Blog*. To find the blog entry associated with this article, visit, http://aapsblog.aaps.org/tag/aaps-newsmagazine.

If a drug is designated a breakthrough therapy, will the timeline for bringing a revolutionary drug to market be reduced?

Learn more about the AAPS Regulatory Sciences section; visit the section's webpage at www.aaps.org/RS.

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