Is Breakthrough Therapy Designation a Sponsor's Golden Ticket?

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Is the Food and Drug Administration's (FDA) Breakthrough Therapy Designation a golden ticket to instant success or a mirage leading us down a road to nowhere (with a nod to the Talking Heads)?

Many of us remember fondly the classic movie, Willy Wonka & the Chocolate Factory, where children buy chocolate bars to win a golden ticket and tour the chocolatier's factory. Once inside the factory, the children and their guardians tour the amazing manufacturing site, meet the Oompa Loompas, and taste many new candies. However, not all is rosy as, one by one, the kids misstep and are miniaturized by Wonka Vision, turned into a blueberry, fall into a chocolate river and get sucked through an extraction pipe system, or rejected as a "bad egg." Ever our hero, Charlie, makes a mistake and almost loses it all. Bottom line: what looks like Paradise is fraught with challenges, obstacles, and easy missteps.

The Food and Drug Administration Safety and Innovation Act (FDASIA), enacted on July 9, 2012, amended section 506 of the Federal Food, Drug, and Cosmetic Act and established a new way to expedite the review of drugs and biologics manufactured for serious or life-threatening conditions.[1] Breakthrough Therapy (BT) designation requires preliminary clinical evidence indicating that the drug or biologic may demonstrate substantial improvement over existing therapies on at least one clinically significant endpoint.

While FDA has other expedited review programs, such as fast track designation, priority review, and accelerated approval, the intent behind BT designation is to encourage outside-the-box product development where the FDA, in certain cases, might speed up a product review by, for example, allowing sponsors to rely upon non-clinical information, rather than clinical evidence. It is important to recognize that BT products are not guaranteed approval, although there are some in the business world that might think so.

FDA issued guidance in June 2013 describing its expectations for BT designation, although every case will be different.

Qualifying Criteria

In order for a drug or biologic to be designated as a BT, it must fulfill certain criteria:

Intended to Treat a Serious or Life-Threatening Disease or Condition

The product must be "intended . . . to treat a serious or life-threatening disease or condition." The agency defines "serious disease or condition" as:

> Disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will

1 While the section of the law specifies that Breakthrough Therapy designation is applicable to drugs, FDA also permits biologics to use the pathway.

progress from a less severe condition to a more serious one.

Examples of BT-designated therapies, to date, include several diseases related to muscle degeneration and to numerous types of cancer. According to the agency, the product must be "intended to have an effect on a serious aspect of a condition," e.g., a product intended to improve diagnosis of a serious condition, which would lead to improved outcomes.

Preliminary Clinical Evidence

The sponsor must submit a designation request for each product indication, accompanied by "preliminary clinical evidence [that] indicates that the drug may demonstrate *substantial improvement over existing therapies* on 1 or more clinically significant endpoints." FDA encourages a sponsor to obtain preliminary data early in the drug's development demonstrating that the therapy is superior to an existing therapy, or to a placebo if no existing therapy is available, or to develop data comparing the new treatment plus the current U.S. Standard of Care (SOC) to the SOC alone. In practice, FDA has frequently relied on Phase II studies and, at least partly, on Phase III studies in at least two BT-related cases to designate a drug as a "breakthrough therapy." The agency also recommends that a sponsor include a "sufficient number of patients in such studies," but does not further clarify on what constitutes "sufficient."

i. *Substantial Improvement Over Existing Therapies*

The evidence must provide for the possibility that the therapy provides "substantial improvement over existing therapies." Whether improvement over existing therapy is substantial or as the agency also calls it, has a "clear advantage," depends on the duration of the effect and the importance of the clinical outcome. According to FDA, substantial "improvement will be clear" when there is no existing therapy, or the existing therapy demonstrates "a modest response and the new therapy shows an effect on an important outcome." "Substantial improvement" can also be shown if the sponsor demonstrates that the new drug has an "important safety advantage" as shown by the occurrence of serious adverse events when compared to existing therapies and yet has a similar efficacy profile.

Some studies that FDA has relied upon to grant BT designation have demonstrated:

- that the drug extended progression-free and overall survival, and that it had "a very acceptable tolerability profile;"
- an 80% response rate in patients who had experienced disease progression after a treatment with another drug;
- patients who received the drug had a 37% reduction in mortality at six months after an acute heart failure compared to those who received conventional treatment, that the drug helped patients breathe better both during and after acute heart failure, that the drug reduced the rate of heart failure worsening, that its side effects are comparable to conventional therapy, and that the drug is well tolerated; and
- a drug's regimen provided high sustained viral response rates with 12 weeks of therapy in patients who had not beenpreviously treated and in those who had failed prior therapy.

The agency considers "existing" or "available therapy" to mean those therapies that are approved or licensed in the U.S. for the same indication for which the new product is being developed and which are relevant to the current SOC for the indication at the time FDA is deciding whether to grant designation. To determine the current SOC, the agency considers recommendations from scientific institutions, such as the National Comprehensive Cancer Network. In at least four recent cases, FDA has designated therapies to treat a disease or the disease's symptoms for which there was no alternative therapy and, in at least two cases, has granted designation for therapies in which there were limited alternative therapies.

ii. *Clinically Significant Endpoint*

The required evidence of substantial improvement must relate to one or more clinically significant endpoints. FDA defines

this type of endpoint as one that "measures an effect on irreversible morbidity or mortality or on symptoms that represent serious consequences of the disease." Examples of findings that would satisfy this requirement include a "significantly improved safety profile" over existing therapy with evidence of similar efficacy, plus findings necessary for Accelerated Approval (i.e., an effect on a surrogate endpoint or intermediate clinical endpoint reasonably likely to predict a clinical benefit).

Features

FDA must grant or deny a BT designation request within 60 calendar days of receipt of the request. If FDA grants the request, the following benefits are available:

- All Fast Track Designation features such as more frequent meetings and correspondence with FDA about the drug's development plan, required data, design of clinical trials and use of biomarkers, plus eligibility for Accelerated Approval and Priority Review and a Rolling Review of sections of its Biological License Application (BLA) or New Drug Application (NDA) when they are completed, rather than when the entire application is submitted.

- Meetings between the sponsor and the FDA review team throughout the therapy's development, as early as Phase I;

- FDA advising sponsors in a "timely" manner to ensure that the therapy's development program is "as efficient as practicable;"

- "Intensive" involvement of agency senior managers and experienced review staff in a proactive, collaborative, cross-disciplinary review; and

- FDA assigning a cross-disciplinary project lead to act as a liaison between the review team and the sponsor.

During these interactions, the agency or the sponsor may suggest alternative clinical trial designs, such as adaptive designs or use of historical controls, which may lead to smaller trials or more efficient trials requiring less time to complete.

Withdrawl of BT Designation

Sponsors should be aware that FDA may withdraw the designation if, for example, BT designation is no longer supported by data, e.g., if designation is granted using early clinical testing that show a higher response rate than existing therapies, but subsequent data show a substantially smaller response. Further, if the agency grants designation to two products developed for the same indication and one of them is approved, the second product will not retain its designation unless additional evidence to support its superiority is provided. This withdrawal could be detrimental to companies in late stages of the designation process, and thus, companies should carefully monitor competitor activity.

AGG Observations

FDA has, for the most part, been able to grant or accept designation within 60 days of receiving the request, even with the number of BT designation requests on the rise. From July through September 2012, the Center for Drug Evaluation and Research (CDER) granted one designation request and denied the other request that it received, while the Center for Biologics Evaluation and Research received none. Since October 1, 2012, CDER has granted 26 designations and denied 34 of the 83 requests it has received, with the rest pending, and CBER has denied 8 of its 10 requests, with two pending as of the date of this publication.

BT designations come with an FDA promise to commit significant resources to work with the sponsor and potentially allow a company to rely on shorter, smaller trials. In addition, the mere designation allows a company to publicize

that its product is considered "breakthrough" in the eyes of FDA, which is a powerful tool to attract possible business development partners or investors. There may be an expectation that the product will be approved sooner, rather than later.

There is no question that BT designation has significant BT potential benefits – to sponsors, to patients, and even to FDA. However, let's remember Willy Wonka and that not all candy-filled streets lead to Paradise.

- The BT designation only indicates that a product's review is expedited, not necessarily that it will be approved faster, if at all. Designation may have no correlation with approval. It merely connotes potential positive advance; and products that are designated as BT may have a higher likelihood of approval.

- With other expedited review designations and approval pathways already exist, some of which have similar criteria and features as explained above, FDA may be in danger of overextending itself. Though FDA has been able to meet its 60-day response deadline, given that the agency will need to provide timely advice and "intensive" involvement by high level officials to sponsors of BT-designated studies, it remains unclear whether the agency's limited resources will permit a true expedited review for the 85 BT designations it has granted to date.

- If the BT-designated products receive the special attention that the designation purports to provide, products indicated for other diseases that are still essential to patients may be burdened by a slower review process, a concern expressed by the Leukemia & Lymphoma Society in a letter to FDA.

- FDA must be judicious in how it grants BT designation. It cannot simply designate every promising life-saving therapy as BT. Not every product is "breakthrough," and not all sponsors can receive a golden ticket. By making BT designation decisions, the agency is making a commitment to the sponsor and is signaling its belief that a particular therapy may be deserving of special treatment. FDA has to be careful, and will be careful, whom it designates potential winners. This may explain, although it is mere speculation, why more requests have been denied than have been approved by CDER, and why CBER's approval rate is so low.

- The BT program is new. It offers promise, but FDA might move very cautiously as the agency reviews more requests and sorts the wheat from the chaff. This program may be the ultimate case-by-case review, by which the industry has to carefully dissect FDA's thinking as drug development programs are planned.

The BT designation program is one of good intent and excellent promise. FDA's execution remains to be seen. Only time will tell if the agency will be able to meet its goal of providing quicker review for the drugs worthy of such review, in its eyes, and in turn, ideally more approvals.

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