Break on Through to the Other Side: An Update on Breakthrough Therapy Designation Requests

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A recent public meeting on Breakthrough Therapy (BT) Designation, held 2½ years after implementation of the BT program, provided interesting insight and trend information, and we thought some of the data presented at the meeting would be instructive for companies considering whether to pursue the BT option.[1]

Manufacturing Changes

The Food and Drug Administration (FDA) noted that manufacturing changes or considerations can affect BT status. For example, changes in the manufacturing process during development, particularly with a complex biologic, can make it difficult to assess whether early efficacy results can be replicated when the product is made in even a slightly different way. The agency said, "we [FDA] can't judge a product when it's been made three different ways for three different patients, because we don't know whether it can be made the same way for the fourth patient." In fact, FDA has denied some BT requests, because sponsors did not have enough data with one consistent manufacturing process. FDA also expressed concern that sponsors might not be able to ensure that their manufacturing and quality operations can keep pace with the accelerated clinical development and review timeline. The agency recommended that rolling submissions can help ensure early FDA identification of manufacturing or facility issues that may threaten BT designation.

Results and Review

Review divisions evaluate designation requests using a standardized template that includes an overview on the disease, available therapy, clinical data supporting the request and safety. A Medical Policy Council is involved in every designation request. The agency said it doesn't consider other products that are in the pipeline when making BT decisions. Through May 1, 2015 and since inception of the BT program, less than a third of the requests have been granted. Orphan diseases do not seem to have a higher success rate of obtaining BT designation.

Review of Trends

- There is no one-size-fits all characterization of a BT drug nor a definitive threshold for what constitutes "substantial improvement."
  - The reliability and persuasiveness of clinical evidence is critical to making the designation decision; trial analysis issues, followed by lack of substantial improvement, were the top denial rationales.
  - Some preliminary patterns were observed in the BT program and decision characteristics, such as: (1) high quality data from one trial tends to be better than lower quality data from many trials; (2) BT is a popular program, particularly in the oncology, hematology and antiviral classes; (3) most successful designation requests were from large U.S. sponsors with regulatory experience; (4) requests for indications that had prognostic biomarkers had a higher proportion of grants; (5) most decisions were based on phase 1 and phase 2 trial data; (6) there was no

1 A copy of our previous Bulletin on BT Designation can be accessed at http://www.agg.com/Is-Breakthrough-Therapy-Designation-a-Sponsors-Golden-Ticket-10-29-2013/.

discernable pattern to trial enrollment and appropriate enrollment depended on the specific indication; and (7) most request withdrawals occurred for administrative reasons or because the division indicated to the sponsor the request for BT designation would be denied.

AGG Observations

- 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. However:
  - 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 the likelihood of approval;
  - it might be a Willy Wonka golden ticket or a road to nowhere.

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