A survey of breakthrough therapy designations

Saurabh (Rob) Aggarwal

As of last month, 41 products have been granted breakthrough therapy designations by the US Food and Drug Administration—drugs against cancer, hepatitis C and monogenetic diseases predominate.

In 2012, the US Food and Drug Administration (FDA) created a new expedited pathway called 'breakthrough therapy designation' (BTD) to facilitate rapid approval of therapies that have shown substantial activity in early trials[1,2]. As of March 7, the FDA had received 155 BTD applications, of which 41 have been granted BTDs and 3 drugs with 4 BTDs have received marketing authorizations (**Table 1**). The new pathway promises faster approval and earlier access to therapies for unmet needs. Despite the popularity of this new process, several areas of uncertainty still exist, especially the data requirements for the designation, the definition of "substantial improvement" and "existing therapies," the scenarios for handling product failures, and the potential impact of the BTD on pricing and reimbursement.

To shed light on some of these topics, I review here the BTDs up to the beginning of March, assessing the available data on safety and efficacy, mechanisms of action, type of molecule and indications. In addition, I analyze the available clinical and marketing data for the three approved products that have received BTDs.

Clinical data were obtained from manufacturers' press releases, conference abstracts or peer-reviewed journals. (Unless specified, for all clinical end points $P < 0.05$.) To provide relevant context, the BTD process is also briefly reviewed. The latest full list of publicly disclosed BTDs is available at http://www.novelhealthstrategies.com/breakthrough.htm.

Saurabh (Rob) Aggarwal is at Novel Health Strategies LLC, Bethesda, Maryland, USA, and the Institute for Global Policy Research, Washington, DC, USA.
e-mail: sa2@novelhealthstrategies.com and arob@globalpolicyinstitute.org

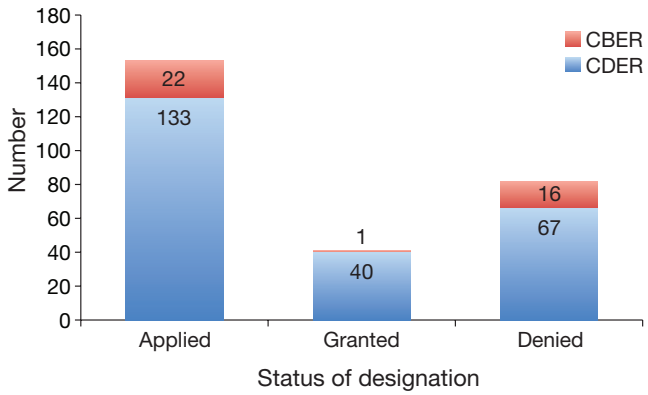

Figure 1 Number of BTDs applied for, and number of BTDs granted and denied by CBER and CDER from July 9, 2012 to March 7, 2014. See Supp. Fig. 1.

(Yet) another expedited approval pathway

The BTD is the fourth expedited pathway to be added to FDA's portfolio, joining fast-track designation, accelerated approval pathway and priority review designation[1]. The BTD was established as part of the FDA Safety and Innovation Act of 2012 (FDASIA), which mentions two general criteria according to which the FDA may designate an investigational drug as a breakthrough therapy: the designation can be applied only within the context of a serious or life-threatening disease or condition, and it must be predicated on preliminary clinical evidence demonstrating substantial improvement over existing therapies on one or more clinically significant end points[1].

Like the three other expedited pathways, BTD is only available for drugs addressing serious conditions (**Table 2**). Fast-track designation (usually used for an investigational new drug (IND) application) is for drugs addressing unmet medical needs (or drugs designated as a qualified infectious disease product (QIDP) under the Generating Antibiotic Incentives Now or GAIN Act, part of FDASIA) and provides rolling review, expedited development and review (FDA must respond within 60 days of request). Accelerated approval (generally applied when a sponsor is moving toward confirmatory trials) is for drugs that show meaningful benefit over existing therapies and provides an FDA approval based not on a clinical end point but on an effect or surrogate or intermediate end point that is reasonably likely to predict a drug's clinical benefit. A last path, priority review (associated with a biologic license application, new drug application or supplemental application)—which is for drugs providing significant improvement of safety or effectiveness or requiring a labeling change under a pediatric indication or with a QIDP designation or accompanied by a priority review voucher—provides shorter review of a sponsor's marketing application (6 months rather than the standard 10-month review).

Overall, a BTD offers all the advantages of a fast-track designation, but importantly also provides sponsors with intensive guidance from agency officials during an IND, beginning as early as phase 1 trials. Notably, the designation comes with organizational commitment from senior agency officials. It is likely