Expediting Drug Development — The FDA's New “Breakthrough Therapy” Designation

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Background

- Developing new molecular entities (NMEs) requires significant time, expense, and financial risk.
- The median time for clinical development from investigational new drug application to marketing approval for oncology NMEs has been reported to be 7 to 8 years, and for some nononcologic indications, this development time may exceed 10 years.
- Total pharmaceutical research and development costs, from initial drug synthesis to successful registration, have been recently reported as $2.6 billion per drug.
- Many people with serious or life-threatening illnesses for which there are no satisfactory treatments
- Eager to gain access to new therapies
- Many patients and their advocates continue to believe that clinical development is sometimes prolonged beyond what is necessary

Background continues…

- Over the past 25 years, the US Food and Drug Administration (FDA) has adopted four new regulatory approaches in an attempt to increase the speed of drug approval for serious medical conditions, including cancer.
- Three of these attempts (Priority Review, 1992; Accelerated Approval, 1992; and Fast Track, 1997) have been unsuccessful in altering the rate of marketing approval for new drug applications.
- During the congressional considerations leading up to passage of the FDA Safety and Innovation Act of 2012 (FDASIA), a variety of provisions related to this theme were put on the table.
- When the bill was enacted, two modifications of the Federal Food, Drug, and Cosmetic Act addressed the issue of drug development for serious illnesses:

a new "breakthrough therapy" designation for investigational drugs and expansion of the statute regarding accelerated approval. The breakthrough-therapy designation has since been introduced into the FDA portfolio of expedited programs for serious conditions.

Criteria

- This designation can be applied only within the context of a “serious or life-threatening disease or condition.”
- It must be predicated on “preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints.”

The FDA has interpreted the second criterion to mean that data from studies in animals or conducted in vitro showing that a drug has promise are not sufficient to justify this designation; data from clinical trials in humans are needed.

How?

+ Increased level of collaboration between senior management at the FDA and the sponsor regarding data analysis, clinical trial design, and approval strategy.
+ Input from the FDA's Medical Policy Council and early consultation with quality regulators regarding manufacturing specifications for commercial drug production.

How?

Once a drug is designated as a breakthrough therapy,

+ the FDA commits to working particularly closely with the drug sponsor to devise the most efficient pathway for generating additional evidence needed about safety and efficacy.
+ The amount of additional data needed will vary, depending on the disease, the magnitude and robustness of the initial data, and the availability of alternative therapies.
+ In addition, rapid clinical development for breakthrough-therapy drugs will put more pressure on other components of drug development, such as drug manufacturing: development of a final formulation and scale-up of processes will have to occur more rapidly than they traditionally do. It is possible that manufacturing will become the rate-limiting step in some breakthrough-therapy drug-development programs.

Result

- It is not expected that all products designated as breakthrough therapies will in fact turn out to have the potential suggested by the early clinical data.
- Subsequent trials may reveal a smaller treatment effect, or unacceptable adverse effects may occur.
- It is also important to recognize that a breakthrough-therapy designation is not a drug approval. Like all drugs in development, drugs designated as breakthrough therapies will be reviewed by the FDA to determine whether they are safe and effective for the intended use before they can be approved for marketing.
- This review will be expedited for drugs designated as breakthrough therapies, if the clinical findings warrant doing so.
- After enactment of the FDASIA, within 1 year, more than 80 requests for a breakthrough-therapy designation have been submitted to the FDA, and 26 have been granted.

Table 1. Drugs with Breakthrough-Therapy Designations Announced as of September 30, 2013.*

Investigational Drug Designated as Breakthrough Therapy	Indication	Sponsor	Date Announced
Ivacaftor	Cystic fibrosis	Vertex	January 6, 2013
Ivacaftor–lumacaftor combination	Cystic fibrosis	Vertex	January 6, 2013
LDK378	Metastatic non–small-cell lung cancer	Novartis	March 15, 2013
Ibrutinib	Mantle-cell lymphoma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, small lymphocytic lymphoma	Pharmacyclics	April 8, 2013†
Palbociclib	Breast cancer	Pfizer	April 10, 2013
Lambrolizumab	Advanced melanoma	Merck	April 24, 2013
Daclatasvir–asunaprevir–BMS-791325 triple combination	Chronic hepatitis C	Bristol-Myers Squibb	April 25, 2013
SD-101	Epidermolysis bullosa	Scioderm	April 29, 2013
Daratumumab	Multiple myeloma	Janssen	May 1, 2013
ABT-450/r–ABT-267–ABT-333 triple combination	Genotype 1 hepatitis C	AbbVie	May 6, 2013
Obinutuzumab	Chronic lymphocytic leukemia	Genentech	May 15, 2013
Sebelipase alfa	Lysosomal acid lipase deficiency	Synageva	May 20, 2013
Asfotase alfa	Hypophosphatasia	Alexion	May 28, 2013
Serelaxin	Acute heart failure	Novartis	June 21, 2013
Drisapersen	Duchenne's muscular dystrophy	GSK	June 27, 2013
Sofosbuvir–ledipasvir combination	Hepatitis C	Gilead	July 25, 2013
Bimagrumab	Sporadic inclusion-body myositis	Novartis	August 20, 2013
Amifampridine phosphate	Lambert–Eaton myasthenic syndrome	Catalyst	August 27, 2013
Entinostat	Advanced breast cancer	Syndax	September 11, 2013
Ofatumumab	Chronic lymphocytic leukemia	Genmab and GSK	September 13, 2013
Volasertib	Acute myeloid leukemia	Boehringer Ingelheim	September 17, 2013
Alectinib	Advanced non–small-cell lung cancer	Roche	September 23, 2013

* Some sponsors do not publicly announce the receipt of a breakthrough-therapy designation.
† Multiple breakthrough-therapy designations were announced.

Difference

- Fast track, which was implemented under the FDA Modernization Act of 1997,
  - is for drugs that are intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need.
  - This tool allows applicants opportunities for frequent interactions with the FDA review team and permits the applicant to submit portions of an application to the FDA for review before submitting the complete application.
- Priority-review status is given when a new drug application is filed for a drug that, if approved,
  - would provide a significant improvement in safety or effectiveness for a serious condition. Priority review shortens the target period for FDA review by 4 months.
- Accelerated approval allows for approval of drugs, again in the context of serious illness,
  - that demonstrate an effect on a surrogate end point or intermediate clinical end point that is reasonably likely to predict clinical benefit and that also provide a meaningful advantage over available therapies.
  - The FDASIA included language that provided flexibility in application of the accelerated-approval pathway and clarified the use of an intermediate clinical end point as a basis for accelerated approval.

Table 2. Comparison of the FDA's Various Expedited Programs for Serious Conditions.*

Variable	Fast-Track Designation	Breakthrough-Therapy Designation	Accelerated-Approval Pathway	Priority-Review Designation
Qualifying criteria	A drug that is intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need†	A drug that is intended to treat a serious condition and that preliminary clinical evidence indicates may demonstrate substantial improvement over available therapies on a clinically significant end point or end points	A drug that treats a serious condition, generally provides a meaningful advantage over available therapies, and demonstrates an effect on a surrogate end point that is reasonably likely to predict clinical benefit or on a clinical end point that is reasonably likely to predict an effect on "irreversible morbidity or mortality" or other clinical benefit	An application (original or efficacy supplement) for a drug that treats a serious condition and that if approved would provide a significant improvement in safety or effectiveness‡
Features	Opportunities for frequent interactions with FDA; possible eligibility for priority review; rolling review	All fast-track designation features; intensive guidance on an efficient drug-development program, beginning as early as phase 1; organizational commitment involving FDA senior managers	Approval based on an effect on a surrogate or intermediate clinical end point that is reasonably likely to predict a drug's clinical benefit	Shorter period for review of marketing application (6 months, as compared with the 10-month standard review)

* Information in the table is from the FDA draft guidance regarding expedited programs for serious conditions.[1]
† Certain antibacterial and antifungal drugs are eligible for fast-track designation by law even if they do not otherwise meet the qualifying criteria.
‡ Certain applications and supplements are eligible for priority-review designation by law even if they do not otherwise meet the qualifying crite

Conclusion

- The breakthrough-therapy designation program is of great interest to patients and patient advocates.
- Because designations are given to drugs in development, it will be some time before the program's effect on access to important therapies can be assessed.
- This program may represent the initiation of a new paradigm for investigational drugs undergoing development in a setting of extensive mechanistic understanding of disease pathogenesis.
- As the pace of scientific discovery continues to increase, drug-development pathways will need to evolve in parallel.


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