Breakthrough Therapy Designation. The FDA has new authority to expedite the approval process for drugs intended to treat serious or life-threatening conditions.

WHAT’S THE ISSUE?

The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, introduced several reforms that are intended to streamline the FDA’s premarketing approval process for drugs and devices. Among these reforms was the creation of a new expedited development pathway for drugs that are intended to treat serious or life-threatening conditions. Under this pathway, a drug candidate may be designated by the FDA as a “breakthrough therapy” if early clinical evidence indicates that the drug may demonstrate a substantial improvement over existing therapies. Once a drug has been granted this status, the FDA commits to working particularly closely with the drug’s sponsor to create an efficient development plan and facilitate its approval.

The FDA released draft guidance on this new pathway in June 2013, and the pharmaceutical industry has responded enthusiastically to the opportunity for a drug to be designated a breakthrough therapy. As of April 2014 the agency had received 178 requests for breakthrough therapy designation. Of those requests, forty-four have been granted, and six drugs have been subsequently approved for use. It will likely be several years before the full impact of this designation is clear, and the degree of impact will ultimately depend on the successful implementation of other reforms currently under way, such as those aimed at expediting the development and review of co-diagnostics. However, it carries significant implications for approaches to clinical development, advancement of regulatory science, patient access to new drugs, and public health.

WHAT’S THE BACKGROUND?

Breakthrough therapy designation is not the only tool available to expedite the development and review of promising drugs and biologics. There are three others, all of which have been in place for more than fifteen years: fast-track designation, accelerated approval, and priority review. All of these designations are intended to expedite approval for drugs used to treat serious conditions. However, each has different qualifying criteria and administrative processes (see Exhibit 1 for an overview) and may be used in conjunction with each other to further accelerate the drug development and review process when appropriate. For example, a drug sponsor may request fast-track designation when it submits an investigational new drug application to the FDA prior to beginning clinical trials, and then request a priority review designation when it later submits a new drug application for marketing approval. In 2013 alone, three drugs were approved under the breakthrough therapy designation; two of the three were
also granted fast-track status. All three were granted priority review and approved through accelerated approval.

Though these mechanisms have the potential to reduce a drug’s time to market, the development process still typically requires standard clinical testing, which usually involves three phases of large-scale, controlled trials. However, recent advances in drug development, particularly for targeted therapies (for example, therapies aimed at patients who have certain biological features, such as the presence of a particular gene mutation), have produced drugs that show dramatic benefit at very early stages in the clinical testing process. The emergence of these therapies led many to question the traditional approach to drug development and approval. The FDA acknowledged these issues in a 2011 report, “Driving Biomedical Innovation: Initiatives to Improve Products for Patients,” in which the agency also described the potential creation of a rapid drug development pathway for targeted therapies as a key priority.

The 2011 Friends of Cancer Research and the Brookings Institution’s Conference on Clinical Cancer Research provided further impetus for the development of a new pathway. One of the panels at the conference—which included representations from senior FDA staff, the pharmaceutical industry, and other key stakeholders—focused on building consensus around specific proposals that might allow for faster development and approval of drugs that show extraordinary effects in early testing. The resulting white paper that emerged from this panel discussion would later directly inform section 902 of FDASIA, which provides the statutory framework for breakthrough therapy designation.

**WHAT’S IN THE LAW?**

Under section 902 of FDASIA, a breakthrough therapy must meet two general criteria: 1) It must be intended to treat a serious or life-threatening disease or condition; and 2) there must be early clinical evidence indicating “that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.” The manufacturer must present this clinical evidence when it applies for breakthrough designation, and the FDA must respond to the application within sixty days of receipt. The FDA may also rescind the designation if further evidence reveals that the drug no longer meets the qualifying criteria.

### Exhibits

#### Exhibit 1

<table>
<thead>
<tr>
<th>Overview of the Food and Drug Administration’s (FDA’s) Expedited Drug Approval Programs</th>
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<tbody>
<tr>
<td><strong>Date established</strong></td>
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<td><strong>Qualifying criteria</strong></td>
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<td><strong>Time frame for application and FDA response</strong></td>
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<td><strong>Key program features</strong></td>
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*Information in this table was adapted from the FDA’s “Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics” (June 2013).*
According to the draft guidance released last year, determining whether a treatment meets these criteria will depend on the magnitude of the drug’s effect, the importance of the clinical outcome it affects, and how that effect compares to other available therapies. It is easier, for example, to demonstrate “substantial improvement” in cases where the drug treats a disease with no other available therapy. Even in such cases, however, the drug ultimately must have a positive impact on significant endpoints such as serious symptoms, disease progression, or mortality, in order to gain market approval. The FDA also notes that an expedited clinical development program must still provide enough data to demonstrate that a drug meets the long-standing statutory requirements for safety and effectiveness. Like fast-track designation and priority review, breakthrough therapy is a designation program, not an outright approval. The designation is intended to expedite the remaining clinical development program, through close coordination with the FDA, to design the most efficient studies to demonstrate safety and efficacy of the drug.

Once a drug is designated as a breakthrough therapy, the FDA may take a number of steps to ensure expedited development, most of which are intended to increase the frequency and intensity of communication with the manufacturer regarding trial design. The FDA may also include more senior management staff in the review process and may designate a cross-disciplinary project lead to act as a liaison across the various departments involved in the review process. Breakthrough therapy designation also includes the same features granted under fast-track designation, such as rolling review. In this process, the manufacturer may submit sections of its marketing approval application as they are completed, instead of waiting to submit the entire application package at once.

Though similar in certain respects to the other expedited review pathways, breakthrough therapy designation is distinct in terms of the level of evidence required to support it. Fast-track designation, for example, may be granted based on promising preclinical data, whereas breakthrough therapy designation requires clinical evidence that the drug may demonstrate substantial improvement over existing therapies. Accelerated approval is specifically granted based on the use of surrogate endpoints (a substitute for clinical endpoints such as disease progression or mortality), and it generally requires that the manufacturer conduct postmarketing trials to confirm a drug’s clinical benefit. (Accelerated approval is also distinct in that it is an approval pathway, rather than a designation program designed to facilitate the clinical development process.) Breakthrough therapy designation may be granted based on a broader range of clinical endpoints than accelerated approval and does not require confirmatory trials unless the breakthrough therapy is also granted accelerated approval. Breakthrough designation also entails a greater commitment of resources by the FDA, involving early and intensive communication with the manufacturer throughout the drug development process. One senior FDA official described it as an “all hands on deck” approach.

**WHAT’S THE DEBATE?**

The goal of the FDA’s breakthrough therapy designation is to accelerate patient access to life-saving drugs. Though a faster clinical development process can, in theory, translate directly into faster access, time to approval is not the only factor at play. Accelerating the clinical development timeline increases the pressure on other components of the drug development process, all of which may need to be similarly accelerated. Furthermore, breakthrough therapies are likely to be specialty drugs that come at a high cost, and there is no guarantee that health insurers will cover a substantial portion of those costs. More broadly, early access and a shortened development and review timeline carry risks as well as benefits, and some have raised concerns about the public health consequences of the breakthrough therapy designation.

**MANUFACTURING SCALE-UP AND COMPANION DIAGNOSTICS:** Drug sponsors need time to produce and distribute a drug on a commercial scale and in compliance with regulations pertaining to current good manufacturing practices. This process can be particularly challenging for biologic products that require complex manufacturing processes, and some may struggle to scale up at a rate that matches the clinical development process. Many targeted therapies also require companion diagnostics, which are used to identify the patients who may benefit from that particular therapy. These companion diagnostics must be approved by the FDA through a separate process. However, the reforms implemented under FDASIA apply only to therapies. There is no parallel breakthrough designation program for diagnostics (though, as with drugs, they may be granted priority review), which
178

**Total requests**

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creates the possibility of a therapy being approved months before the companion diagnostic can be made available. The FDA has not released formal guidance on how it will adapt its diagnostics review process to reflect the accelerated breakthrough therapy timeline, and it is possible that legislative action will be required.

**FDA Resources:** Another key issue relates to the increased demands that breakthrough therapy designation places on the FDA, which has been underfunded for years. The “all hands on deck” approach is particularly resource-intensive, and the agency received no additional funding to cover breakthrough-related activities. The number of drug candidates granted breakthrough status has significantly exceeded expectations (the agency originally predicted that only about two to four candidates would qualify in a given year), and some have raised concerns that this may have spillover effects on the review process for other drugs, which may be clinically important but may not demonstrate this high-magnitude effect in early testing. However, there is no evidence to suggest that this is occurring, and the FDA has historically performed well in terms of meeting its review time obligations. Regardless, some industry observers have speculated that the initial surge of applications likely reflects a high number of later-stage products rushing to take advantage of the new designation and that demand will taper off over time.

**Cost and Coverage:** Drug manufacturers set prices based on a range of factors, including the perceived value of a drug relative to other therapies, the size and characteristics of that drug’s market, the unique characteristics of the drug, and its development costs. It is possible that a manufacturer’s pricing strategy will be driven in part by its ability to market a drug based on its status as a breakthrough therapy. All six of the therapies approved to date carry large price tags, ranging from $41,000 to $300,000 for an annual course of therapy. However, these prices are in line with some of the newer biologic drugs on the market, and it is not clear that their status as breakthrough therapies is significantly linked to their market price.

Their high prices have nevertheless raised concerns about the burden that such drugs place on the health care system and the extent to which patients will be able to access them. It is unclear how payers will approach high-cost drug products, in general, and breakthrough therapy drugs, in particular. While breakthrough products will likely be covered for on-label use, payers may restrict their use in the case of off-label prescribing. Even with coverage, some patients may struggle to make copays without additional assistance. More work will be needed to bring payers to the table with manufacturers to determine appropriate levels of coverage and reimbursement that reward successful drug development while still keeping the soaring costs of the health care system in check.

In the case of drugs that are eligible for expedited review and approval, the FDA must consider the public health benefits of earlier access against the risk that a drug may have serious safety issues that do not appear in early-stage clinical trials. Breakthrough therapy designation does not change the legal evidentiary standards for approving a drug, but critics of the program have argued that shortening the clinical development timeline may nonetheless affect those standards and contribute to the approval of drugs that have unknown safety risks. When a drug is approved based on relatively small trials—as was the case with all six approved breakthrough therapies mentioned earlier—postmarketing surveillance becomes even more important in identifying risks that only emerge once the drug is on the market. At present, the drug safety surveillance system depends largely on adverse-event reporting from manufacturers and the public, and it has well-known limitations in terms of its ability to ensure early detection of safety concerns.

**Public Health and Safety Concerns:** The accelerated pace of development also raises public health and safety concerns. Some public health advocates argue that important safety risks may not emerge even in the context of a standard development and approval process and that shortening the development timeline increases the probability that these risks may not be detected until after approval. However, such concerns are not specific to breakthrough therapy designation. They have been raised in response to all of the FDA’s expedited approval programs and reflect longstanding debates over how the FDA should evaluate risks and benefits more generally. There is no fixed equation for these calculations. Rather, they depend on multiple, often complex factors that may be difficult to assess. Weighing the benefits and risks of a drug that treats eczema, for example, is different from evaluating a cancer drug, especially if that cancer has few or no good treatment alternatives.
WHAT’S NEXT?

The full impact of the breakthrough therapy designation will not be clear for some time, but efforts are under way to address some of the issues described in this brief. The FDA is considering ways to facilitate the development of co-diagnostics intended for use with breakthrough therapies, including granting automatic priority review for co-diagnostics associated with breakthrough therapies. The agency is also working with the pharmaceutical industry on ways to boost manufacturing capacity and streamline the facility inspection process, which may mitigate delays in ramping drug production up to commercial scale.

As part of its commitments under the 2012 reauthorization of the Prescription Drug User Fee Act of 1992, the FDA will also continue its efforts to strengthen postmarketing safety surveillance. The most notable of these efforts is the Mini-Sentinel pilot project, a multiyear project aimed at developing a national active safety surveillance monitoring system. The Mini-Sentinel uses routinely collected electronic data from some of the nation’s largest private health insurers to rapidly evaluate the safety of medical products in very large populations when safety concerns arise. This system supplements other tools the agency has in place to monitor the safety of regulated products.

Breakthrough therapy designation was established as an additional regulatory tool that would allow the FDA and sponsors to be more responsive to the current state of science, establish a more collaborative approach to drug development and approval, and provide a mechanism for demonstrating the safety and efficacy of promising new drugs while minimizing patient exposure to less efficacious treatments. While the long-term impact of this designation remains to be seen, it will likely continue to evolve in conjunction with new scientific discoveries.

RESOURCES


Food and Drug Administration Safety and Innovation Act, Public Law No. 144, July 9, 2012.
