Health Affairs

PRESCRIPTION DRUG PRICING

HEALTH POLICY BRIEF SERIES
JULY 2017 | 1

EXPEDITED APPROVAL PATHWAYS

For drugs of particular clinical importance, the Food and Drug Administration offers several expedited development and approval pathways.

The use of expedited drug development and approval pathways, such as Accelerated Approval and Breakthrough Therapy Designation, raises important issues related to pricing policy. For example, the foreshortened development and approval process translates into potentially significant economic advantages to drug developers; these, in turn, could support arguments that the resulting prices should be lower. Conversely, the pathways are intended to support rapid development of drugs that offer significant advantages over available therapies for serious medical conditions—circumstances that would suggest that the resulting therapies may deliver high value that justifies high prices.

Background

The Federal Food, Drug, and Cosmetic Act requires new drugs to show "substantial evidence" of efficacy before approval by the Food and Drug Administration (FDA). Historically, the FDA has interpreted that standard to encourage at least two rigorous clinical trials (preferably randomized, double-blind, placebo-controlled studies) that independently show a statistically and clinically meaningful benefit.

Even as that historical standard developed, the FDA has always made exceptions in cases of serious, unmet need. In the 1980s the AIDS epidemic heightened the need for a formal process to expedite drug approval in the face of poorly treated, life-threatening diseases. To that end, the FDA and Congress created several pathways including Accelerated Approval and Breakthrough Therapy Designation, intended to help shorten the drug development and approval timeline and make new therapies available more rapidly. Such pathways can provide significant economic benefits to drug developers by reducing the cost of premarket studies and allowing earlier market entry. Compared to the traditional model, the pathways also involve different types and levels of clinical evidence of efficacy, thereby increasing uncertainty about claimed benefits and safety of the therapies.

Accelerated Approval: Brief History

Accelerated Approval (AA) was created by FDA regulation in 1992, in response to the emergence of the AIDS epidemic. It was codified by the FDA Safety and

WITH SUPPORT FROM:

The Commonwealth Fund

Drug Pricing Lab
Memorial Sloan Kettering

Innovation Act (FDASIA) in 2012. Using AA, the FDA may grant approval for a new drug that offers a significant benefit compared to available therapies for serious medical conditions where there is unmet medical need, based on preliminary evidence of efficacy. The sponsor must then conduct definitive efficacy trials (called "confirmatory studies") after approval.

"Should shorter development time mean lower prices?"

That model worked well for antiretroviral medicine, allowing approval of therapies based on short-term studies using easy-to-measure "surrogate markers" of efficacy, such as lowered CD4 blood cell counts. Recently, AA has been applied most commonly in oncology, with drugs approved based on short-term studies measuring early indicators of efficacy, such as tumor shrinkage, with later confirmatory studies showing improved survival or durable stabilization in disease.

According to the FDA, from 2012 to 2016 twenty-six new molecular entities were initially approved using the AA pathway—about 13 percent of total FDA drug approvals during that period.

The Accelerated Approval Process

There are several important elements in the AA process.

USE OF SURROGATE ENDPOINTS

Accelerated Approval is often equated with approval based on surrogate markers. However, the two are not the same. Outside of the AA process, the FDA routinely grants approval of drugs based on surrogate endpoints, when the agency believes that the connection between the surrogate endpoint and the desired clinical outcome is well established. For example, the FDA approves hypertension therapies that lower blood pressure (the surrogate endpoint) without requiring evidence that the therapies reduce cardiovascular disease (the desired clinical outcome).

Under the AA pathway, the FDA can base approval on a surrogate marker when the agency does not consider the connection to clinical benefit to be as fully established as it is in the hypertension example. Instead, according to FDA guidance for the industry, the marker must be "reasonably likely" to predict improved clinical outcomes. That standard has never been formally defined. Thus, there is considerable variation and discretion on when a given biomarker "counts" as an acceptable surrogate for AA.

The AA process also allows the FDA to base approval on an "intermediate clinical endpoint," envisioned as a short-term treatment effect on a clinical outcome that is then confirmed in longer-term studies after approval. The decision about whether a given effect qualifies as an "intermediate" clinical benefit is made largely case by case.

GRANTING OF FULL APPROVAL

In crafting the regulations, the FDA specifically avoided defining AA as "conditional approval" or otherwise suggesting that the drug is not fully approved. The semantics are important, both for the FDA's ability to enforce post-approval study requirements and for securing insurance coverage, since many health plans only cover drugs for FDA-approved uses.

"STREAMLINED" WITHDRAWAL

The AA pathway includes a process for "streamlined" withdrawal of a drug's approval in the event that subsequent trials fail to confirm clinical benefit. In practice, however, the streamlined withdrawal process has not worked much differently than the process the FDA follows in any other case where it concludes that a product should be withdrawn from the market for safety or efficacy reasons. To date, there has only been one example of the FDA's formally invoking the AA withdrawal process, leading to the removal of the indication for use of Roche/Genentech's Avastin (bevacizumab) for metastatic breast cancer in 2011.

Breakthrough Therapy: Brief History

The Breakthrough Therapy pathway is a newer regulatory invention than the Accelerated Approval pathway, having been enacted in FDASIA in 2012. The idea was developed via several interdisciplinary

workshops hosted by the patient advocacy organization Friends of Cancer Research and the Brookings Institution.

The goal was to identify therapies offering significant advances in difficult-to-treat cancers early in development, thereby shortening the clinical trial stage. Patient advocates argued that when new, targeted therapies appear to offer unprecedented efficacy, traditional clinical development programs might needlessly expose clinical trial subjects to ineffective or outdated therapies. FDASIA explicitly directed the FDA to consider this potential impact on clinical trial participants when granting Breakthrough status.

The Breakthrough Therapy Process

There are a number of important elements in the Breakthrough Therapy Designation process.

PRELIMINARY CLINICAL EVIDENCE

The Breakthrough pathway involves a formal request by a sponsor for designation, which can be submitted any time during clinical development, up to the time of the filing of the marketing application. To grant Breakthrough status, FDA guidance explains, the agency must find that there is "preliminary evidence" that the drug offers a "substantial improvement" on at least one clinically significant endpoint over existing therapy. That standard is necessarily subjective and is the main reason that, according to the FDA, most Breakthrough Therapy Designation requests are rejected or withdrawn.

UNCLEAR IMPACT ON REGULATORY PROCESS

FDASIA lists steps that the FDA "may" take in reviewing Breakthrough applications, including meetings with sponsors and "timely advice" to ensure an efficient development process. Those obligations are not unique to drugs granted Breakthrough status, however. In addition, unlike many other FDA activities, there are no defined metrics for the FDA to meet for Breakthrough products, such as timelines for scheduling meetings and providing written advice. Thus far, however, the FDA has embraced the spirit of the legislation, with sponsors reporting enhanced interactions with the agency for products gaining Breakthrough Therapy Designation.

INCREASING USE OF THE PATHWAY

Breakthrough status is far more common than anticipated. The FDA has received over 100 designation requests per year. There are more than 175 drugs and biologics with Breakthrough Therapy Designation, including new indications for already-approved products. While the largest proportion is in oncology, there are designated Breakthrough therapies in all FDA review divisions.

Since 2012 twenty-nine new molecular entities, or about 13 percent of all FDA drug approvals, have received Breakthrough Therapy Designation. However, most of those approvals were for applications that were in advanced development before the pathway was created; those products may have benefited from Breakthrough-style engagement by FDA, but not literally from Breakthrough status itself.

Key Questions For Drug Pricing And Coverage Policy

There are several outstanding questions about how or whether expedited approval pathways should affect drug prices and coverage policy.

SHORTER DEVELOPMENT TIME

Should shorter development time mean lower prices? Drug developers have historically cited the high cost of research and development and the long lead time to bring a product to market as factors justifying the price of innovative therapies. Thus, the use of expedited pathways could support an argument that the resulting therapies should be priced lower than they otherwise would have been if they did not benefit from these pathways. A related argument is that the FDA's efforts to expedite development and approval impose a reciprocal obligation on the new drug sponsor to price affordably—analogous to the claim that products of taxpayer-funded research should be subject to increased pricing oversight.

The counterargument is that the Accelerated Approval and Breakthrough pathways are reserved for therapies that offer significant potential benefits for unmet medical needs—and are therefore at the high end of the value spectrum for new therapies. That

might argue that payers should accept higher prices for expedited therapies.

IMPACT OF UNCERTAINTY

Should pricing and coverage policy reflect the uncertainty of pending confirmatory trials? Expedited pathways involve different types and levels of premarket evidence at the time of approval than do standard pathways. As a result, there may be less safety information than is the case for most newly approved therapies, which increases the risk of unexpected findings after approval. Those concerns were highlighted in a 2015 Government Accountability Office (GAO) report.

For Accelerated Approval therapies in particular, there may also be considerable uncertainty in the efficacy data at the time of approval. While the FDA has always carefully defined those drugs as fully approved, some payers may take a different approach in their coverage policies. In a rare example of this dynamic, some insurers recently took the position that Sarepta's Exondys 51 (eteplirsen), granted Accelerated Approval to treat Duchenne muscular dystrophy, should still be considered "experimental" for coverage purposes.

ENFORCEMENT OF CONFIRMATORY STUDIES

Can the FDA enforce confirmatory studies? The agency has been challenged to ensure that "mandatory" postmarket confirmatory studies are completed in a timely fashion. The gaps in that process were highlighted in a 2009 GAO report. One option is to give the FDA enforcement tools (such as civil monetary penalties) that are less blunt than the withdrawal of approval of the underlying application. The FDA already has the authority to fine manufacturers for failure to meet timelines for mandatory safety studies. Another option would be to create a formal "conditional" approval process, whereby the underlying license to market the new drug will expire unless confirmatory studies are submitted on time.

Key Terms

- Substantial evidence of efficacy**:** "Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or pro- posed labeling thereof." *(FDA Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics, May 2014)*

- Surrogate endpoint**:** "For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit." *(New Drugs, 21 U.S. Code Sec. 355, 2010)*

- Confirmatory studies: Sponsors of drugs granted Accelerated Approval are required to conduct post-approval studies "to verify and describe [a drug's] clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome." *(Applications for FDA Approval to Market a New Drug, 21 CFR 314, 2016).*

HealthAffairs

Health Policy Briefs are produced under a partnership of *Health Affairs* with the generous support of the Commonwealth Fund and Memorial Sloan Kettering Cancer Center. Text highlighted in blue is hyperlinked to outside sources in the online version of this brief.

Written by **Michael McCaughan**, Prevision Policy LLC. Editorial review by **Aaron Kesselheim**, Harvard Medical School and Brigham and Women's Hospital; **Allan Coukell**, The Pew Charitable Trusts; **Laura Tollen**, consulting editor, *Health Affairs*.

Cite as: "Health Policy Brief: Expedited Approval Pathways," *Health Affairs*, July 21, 2017. DOI: 10.1377/hpb2017.2

7500 Old Georgetown Road, Suite 600 | Bethesda, Maryland 20814-6133 USA |