

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Mary Beth Hamel, M.D., M.P.H., *Editor***New FDA Breakthrough-Drug Category —
Implications for Patients**

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U.S. pharmaceutical regulations are based on the principle that patients should not be exposed to new prescription drugs until their efficacy and safety have been shown. Since 1962, the Food and Drug Administration (FDA) and Congress have balanced the efficient review of investigational drugs with the need to withhold judgment until sufficient evidence is available to clarify the benefit–risk relationship. Misjudging these competing interests in either direction causes important problems. On the one hand, the evidentiary hurdles of the FDA are often criticized by pharmaceutical companies and patient advocacy groups for slowing access to promising therapies. On the other hand, truncated premarket review can lead to the approval of drugs that are ineffective, unsafe, or both.

These dangers were once again made clear in October 2013 when approval was briefly suspended for ponatinib, a medication to treat leukemia that had been approved just the year before on an accelerated basis. Emerging data showed that 24% of the patients who had been followed for a median of 1.3 years and 48% of those who had been followed for a median of 2.7 years had serious thromboembolic events, including myocardial infarction and stroke.¹ The drug was allowed back on the market in December 2013 with more limited indications and a restricted distribution system.

The latest development in the FDA approach to ensuring the safety and effectiveness of marketed prescription drugs occurred in July 2012, when Congress created a new category of “breakthrough therapy” in the FDA Safety and Innovation Act (FDASIA). A breakthrough therapy was defined as a new product to treat a serious disease for which preliminary clinical evidence suggested substantial superiority over existing options on one or more clinically significant end points.² Lawmakers intended the designation to speed to market a limited number of prod-

ucts that showed “exceptional results for patients.”³ Lauded by policymakers,⁴ consumer advocates,^{5,6} and the FDA itself,⁷ the breakthrough-drug pathway has been embraced by industry⁸ and has produced early results far exceeding predictions. From October 2012 through September 2013, the FDA received 92 applications for the breakthrough-therapy designation, of which 27 were approved and 41 denied (24 applications were still pending).⁹ Although some of these agents may end up being truly transformative for patient care, the breakthrough-therapy designation also raises the possibility of a surge in new drugs that have been approved on the basis of limited clinical data.

There is ongoing controversy over the FDA standards for the approval of investigational drugs. In this article, we briefly summarize prior or government efforts to expedite the availability of new therapeutics, and we discuss the clinical, ethical, and regulatory implications of the breakthrough-therapy designation.

 HISTORY OF EARLY-ACCESS
AND EXPEDITED-APPROVAL PROGRAMS

The Food, Drug, and Cosmetic Act (FDCA) of 1938 prohibited the routine therapeutic use of investigational drugs, although in practice physicians easily obtained such drugs outside of clinical trials.¹⁰ A sea change came when the 1962 Kefauver–Harris Amendments to the FDCA required affirmative FDA approval on the basis of trials in humans before new drugs could be marketed. Regulations in 1963 divided these trials into three phases — small, phase 1 safety trials; intermediate-size, phase 2 efficacy studies; and large, controlled, phase 3 studies — forming the basis for a new drug application (NDA).

There was concern that extended study before approval could prevent timely patient access to potentially lifesaving medicines. The FDA first

responded by adopting pathways to allow treatment use before approval. In the 1960s, early-access programs (also called compassionate-use programs) allowed limited patient access to investigational drugs, although these programs had no written rules and were flexibly applied. The demand for experimental cancer drugs was particularly strong, leading the FDA to publish in 1979 its first official early-access policy for such drugs.

Pressure from physicians and patients intensified with the AIDS crisis of the 1980s, a pivotal episode in the evolution of the FDA drug-approval policies. Demonstrations by AIDS activists at FDA headquarters brought widespread attention to the lag times between submission and agency approval of new medications,¹¹ although the perception that the FDA did not rapidly assess drugs intended for patients with human immunodeficiency virus (HIV) infection may have been exaggerated.¹² In 1987, regulations for treatment investigational new drug applications (treatment INDs) formalized the procedures for obtaining early access to investigational drugs outside of clinical trials.¹³ Three years later, the FDA proposed making unapproved drugs for HIV/AIDS available even sooner by means of a parallel-track mechanism¹⁴ for patients with HIV/AIDS who were unable to enroll in clinical trials.

In the 1980s, early-access options were joined by FDA initiatives to hasten drug approval. In 1988, the FDA created a fast-track component (Subpart E) of its rules to “expedite the development, evaluation, and marketing of new therapies”¹⁵ for serious and life-threatening conditions by, for example, eliminating phase 3 trials. The provisions were modeled on the testing and approval of the HIV drug zidovudine, which occurred over a period of only 2 years and included a single, well-designed phase 2 trial. In 1992, the FDA initiated an accelerated-approval pathway (Subpart H) to allow approval on the basis of surrogate end points that were seen as reasonably likely to predict patient benefit.¹⁶ Subpart H shortened the clinical-investigation process by permitting trials to end before the occurrence of hard clinical end points (e.g., hospitalization, myocardial infarction, and death).

The same year that the FDA finalized Subpart H, Congress enacted the Prescription Drug User Fee Act (PDUFA), which authorized the FDA to collect “user fees” from pharmaceutical manufacturers. Although increased Congressional ap-

propriations to the FDA had already reduced NDA review times by the late 1980s,¹⁷ PDUFA allowed the FDA to hire more scientists and further expedite the review of drug applications.¹⁸ PDUFA also set formal deadlines of 6 months for priority applications and 12 months for standard applications (shortened to 10 months in 2002). Within 1 year after the enactment of PDUFA, the FDA had acted on 93% of NDAs within the new deadlines.¹⁹ The user fees were restricted to the approval of products; it was not until 2007 that the FDA had the authority to allocate them to postapproval drug-safety activities.²⁰ Under FDASIA, the FDA review deadlines now begin to run 60 days after NDA submission.²¹

BENEFITS AND RISKS OF EXPANDED ACCESS AND EARLY APPROVAL

The FDA has estimated that more than 100,000 patients have received investigational drugs for serious or life-threatening conditions through the use of treatment INDs.²² For investigational drugs that ultimately prove to be superior to existing options, these early-access programs benefit patients by allowing new therapies to reach them sooner. In addition, expedited development and approval programs have shortened the clinical development period, allowing earlier access for the broader patient population. Subpart E, for example, reduced the average clinical development time from 8.9 to 6.2 years, whereas drugs benefiting from accelerated approval averaged just 4.2 years.²³ NDA review times have also decreased dramatically, from more than 30 months in the 1980s to 14.5 months by 1997²⁴ and to 9.9 months for applications received in 2011.²⁵

The immediate result of PDUFA was a spike in approvals during the mid-1990s as backlogged applications were processed,²⁶ but the number of approvals each year soon returned to historical averages.²⁷ Although the FDA was once considered by some to approve drugs too slowly,²⁸ drug approvals since 2000 have been quicker in the United States than in Canada or Europe. From 2001 through 2010, the FDA approved 64% of novel therapeutic agents earlier than the European Medicines Agency.²⁹

However, early access and shortened development and review times have also been associated with negative public health outcomes. Drugs approved shortly before the PDUFA-imposed deadlines have been found to be more likely to

have postmarketing safety problems — including safety withdrawals and added black-box warnings — than were drugs approved at any other time.^{30,31} Other investigators have reported that drugs receiving faster reviews have more spontaneous reports of drug-related adverse events, although these data are controversial.³²⁻³⁵ Among drugs first approved abroad, those with more foreign-market experience before U.S. approval are less often associated with serious adverse drug reactions.^{35,36}

Such findings are predictable because of the more limited data on which expedited drug approvals are based. Although neither the fast-track nor the accelerated-approval pathways changed the legal standard for approval — which is still effectiveness with acceptable risk — they reduced the quantity of evidence needed to meet this standard and altered the nature of that evidence. For example, cancer drugs approved during the previous decade on the basis of limited clinical trials — nonrandomized, unblinded, single-group, phase 1 and phase 2 trials that used intermediate end points rather than patient survival — had a 72% greater odds of serious adverse events occurring in their pivotal trials than did cancer drugs that were approved with more-rigorous studies.³⁷ A recent study showed that drugs benefiting from expedited approval programs were tested for efficacy in a median of only 104 patients, as compared with 580 patients for nonexpedited review.³⁸ Data collected with the use of early-stage clinical-trial methods are unstable and may be subsequently disproved in larger, more-rigorous trials.

Concerns about potentially inaccurate assessments of the benefit-risk ratios led the FDA, beginning in approximately 1970, to condition some approvals on the conduct of postapproval (phase 4) confirmatory studies. The proportion of new drugs that were subject to these postapproval obligations increased from approximately 30% in the early 1980s to approximately 80% in the early 2000s.³⁹ Unfortunately, the performance of these follow-up studies has often been markedly delayed⁴⁰ or not initiated at all.⁴¹ Gemtuzumab ozogamicin was approved in 2000 for the treatment of pediatric leukemia on the basis of limited data, but it was withdrawn from the market in 2010 after confirmatory trials initiated in 2004 showed increased mortality and no efficacy.⁴²

Concern over the timely conduct of post-

approval studies led Congress to strengthen the enforcement authority of the FDA in the FDA Amendments Act of 2007. However, as recently as 2011, postmarketing-study commitments for more than 40% of drugs had not yet been started, whereas the number with delays had doubled since 2007 to approximately 13%.^{38,43} Completion times also appear to range widely: a report from the Office of Oncology Drug Products regarding a sample of oncology drugs approved by way of the accelerated-approval pathway showed that it took 0.8 to 12.6 years before postmarketing trials were completed (median, 3.9 years).⁴⁴ Bedaquiline, a medication for the treatment of multidrug-resistant (MDR) tuberculosis, was approved in 2012 on the basis of the surrogate end point of sputum-culture conversion, even though the pivotal studies also showed an incidence of death (generally from tuberculosis) that was five times as high among patients given the drug than among those randomly assigned to receive standard treatment for MDR tuberculosis. The impact on individual patients must be further studied since there is a need for additional treatment options for this highly contagious disease. The confirmatory randomized trial that was mandated for bedaquiline was not required by the FDA to be completed until 2022.⁴⁵

BREAKTHROUGH THERAPY — RATIONALE AND POTENTIAL OUTCOMES

In approving FDASIA, Congress anticipated that the use of modern evaluation tools earlier in the drug-development cycle could result in “fewer, smaller, or shorter clinical trials.” During Congressional hearings in 2012, advocacy and industry organizations supported the creation of the new breakthrough-therapy designation to abbreviate or combine traditional clinical phases to enhance earlier patient access.^{46,47} Support for the law also came from officials within the FDA Center for Drug Evaluation and Research who, in November 2013, praised the “much larger treatment effect” achieved by some recent “molecularly targeted therapies” that aim to benefit subgroups of patients with “cancer, genetic diseases, and . . . other serious illnesses.”⁷⁷ The article defended the new expedited-development program, suggesting that “when a large effect in a serious disease is observed early in drug development, it seems excessive to conduct a prolonged clinical development program that encompasses

traditional trial phases.⁷⁷ According to this view, the new designation could make possible streamlined clinical development that would lead to more rapid approval.

The breakthrough-therapy designation is the latest addition to the expanded-access and expedited-approval programs of the FDA (Table 1). In recent years, the exceptions have been more common than the rule; among the 39 new drugs approved in 2012, a total of 22 (56%) were approved by means of at least one of the accelerated-approval, fast-track, and priority review programs, and 9 of these (23% of the total) qualified for more than one program.

Regulatory efficiency was identified as a major outcome of the breakthrough-therapy designation,⁸ but the benefits offered in FDASIA are already largely available through existing legislation, regulations, or standard FDA practice. For example, FDASIA commits the FDA to working closely with sponsors of breakthrough therapies.⁷ However, Subpart E (1988) offered “early consultation between FDA and drug sponsors,” emphasized the importance of meeting with the FDA to ensure efficient phase 2 trial design, and specified that senior FDA officials would actively facilitate the conduct and evaluation of clinical trials.⁵⁶ FDASIA notes that breakthrough therapies may also benefit from the assignment of a “cross-disciplinary project lead” to facilitate efficient review, but it is unclear how this will improve on existing coordination of staff efforts.

The breakthrough-therapy designation continued the trend of applying increasingly flexible evidentiary standards to determine the qualification for expedited development and approval programs. Certain drugs have long been approved on the basis of well-established surrogate end points.⁵¹ The accelerated-approval pathway (1992) began to allow approval on the basis of “less than well-established surrogate endpoint[s].”⁵¹ By contrast, one way to qualify for the new breakthrough-therapy designation (2012) is by showing “an effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease.”⁵⁵ This more flexible standard would apply to a broader range of potential new therapies. The law requires that breakthrough drugs must eventually be approved or rejected under the normal FDA approval standards, but as was seen with

the bedaquiline approval for MDR tuberculosis, such confirmation may not be required for years.⁴⁵

Once the breakthrough-therapy status has been granted on the basis of preliminary evidence, it may be difficult to temper demand (whether early access or postapproval) even if the drug is revealed to be less effective or more harmful than initially believed. Decision theory suggests that when a decision is less reversible, more care should be taken in reaching the initial determination.⁵⁷ This tension emerged most recently around bevacizumab, which was approved for the treatment of metastatic breast cancer on the basis of surrogate end points under the accelerated-approval pathway. When subsequent studies showed no increase in patient survival, withdrawing the indication took nearly a year and generated substantial opposition.⁵⁸ Some insurers still cover off-label use of the drug for this non-evidence-based purpose.

Deferring rigorous study until after a drug is approved can also undermine and delay evaluation of its benefit–risk profile.³⁸ Once a drug is approved, enrolling patients in clinical trials to determine efficacy is more challenging than before approval, because patients have the choice of receiving the drug in the normal course of therapy or enrolling in a trial in which they may be randomly assigned to usual care. This concern is magnified when deferred study is paired with earlier designations that may be interpreted as official endorsements.

CONCLUSIONS

The 27 breakthrough-therapy designations granted by the FDA in the first 9 months of 2013 are unlikely to represent a sudden and dramatic increase in the pace of pharmaceutical innovation, given that an average of 25 new molecular entities were approved annually during the previous decade. Another interpretation of the rapid popularity of the designation is that it has created the appearance of progress while enhancing the visibility of promising early-stage drugs that may be no more likely than before FDASIA to confer large benefits to patients. The breakthrough-therapy designation is also likely to further increase public pressure on the FDA to approve such products. Few would argue about the need for pathways to bring safe and effective new drugs to market quickly, especially for life-

Table 1. Early-Access and Expedited-Approval Programs of the Food and Drug Administration (FDA):*

Program	Year Created	Origin	Limited to Serious or Life-Threatening Conditions	Provisions Addressing Efficacy or Evidence of Efficacy
Early access Group C	1979†	FDA and National Cancer Institute	Yes, cancer	NA‡
Orphan Drug Act, with open protocols§	1983†	Congress	No	Applies to all drugs treating diseases occurring in fewer than 200,000 persons in the United States, regardless of efficacy
Treatment IND	1987†	FDA, later codified by Congress	Yes	In the case of serious disease: requires sufficient evidence of safety and effectiveness, and may be made available for use during phase 3 or during phase 2 in “appropriate circumstances”; in the case of immediately life-threatening disease: requires that the “available scientific evidence, taken as a whole . . . provide a reasonable basis for concluding that the drug” may be effective and may be made available “ordinarily not earlier than Phase 2” ¹³
Parallel track	1992	FDA	Yes, HIV/AIDS	Requires “promising evidence of efficacy based on an assessment of all laboratory and clinical data” as well as “evidence of a lack of satisfactory alternative therapy for defined patient populations” ¹⁴
Expedited approval				
Priority review A, B, and C ⁴⁸	1974 ⁴⁹	FDA	No ⁵⁰	A indicates important therapeutic gain, B modest therapeutic gain, and C little or no therapeutic gain
Priority review AA	1987	FDA	Yes, HIV/AIDS	“All [NDAs] for AIDS and HIV-related conditions will be classified as AA . . . regardless of their therapeutic potential” ⁵⁰
Fast-track review, under Subpart E ¹⁵	1988	FDA, later codified by Congress	Yes	Allows drug to be approved after phase 2; process allows approval on the basis of “well-established surrogate endpoints” ⁵¹
Priority review¶	1992 ^{52,53}	FDA	No ⁵¹	Priority review means that the drug appears to represent therapeutic advance; standard review means that the drug appears to have therapeutic qualities similar to those of already marketed drugs
Accelerated approval, under Subpart H	1992	FDA, later codified by Congress	Yes	Approval on the basis of surrogate end points is reasonably likely to predict clinical benefit; post-marketing studies are required “to verify and describe . . . clinical benefit” ¹⁶
Priority-review voucher	2007	Congress	No	Approval of a tropical disease–treating drug entitles sponsor to transferable voucher to obtain priority review of any new drug
GAIN section of FDASIA	2012	Congress	Yes ⁵⁴	Qualified infectious-disease products are automatically eligible for fast-track designation and priority review
Breakthrough therapy	2012	Congress	Yes	Preliminary clinical evidence indicates that the drug may show substantial improvement over existing therapies; designation on the basis of “an effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint” ⁵⁵

* FDASIA denotes Food and Drug Administration Safety and Innovation Act, GAIN Generating Antibiotic Incentives Now, HIV human immunodeficiency virus, IND investigational new drug, NA not applicable, and NDA new drug application.

† Ad hoc FDA procedures made preapproval access available on an informal basis before this date.

‡ Group C drugs were authorized under the treatment IND program, and informally before that.

§ “Open protocols” and “compassionate use INDs” were some of the terms used to describe types of informal “treatment uses” before the codification of the treatment IND in 1987.

¶ This process replaced the A, B, and C system for new drugs.

threatening diseases for which current treatment options are inadequate. Efforts to promote early access, expedited development, and early approval have existed for decades. Unfortunately, these efforts generally have not been followed by equally energetic efforts to develop rigorous confirmatory data that could refine the indications for the drug or even change its approval status.

There has also been little discussion of the implications of approving breakthrough drugs on the basis of limited data for patients considering therapeutic options and for their physicians. Expedited approval has been championed by patient advocacy groups who think that FDA requirements that delay access to new products infringe on personal autonomy. Of course, this view is not universal among patients.⁵⁹ How will patients make informed choices about breakthrough drugs approved with new clinical-trial techniques rather than with traditional randomized trials?

This question is particularly salient for patients with life-threatening illness. Previous research has uncovered important deficiencies in decision making by patients in such precarious situations. One survey showed that, as compared with healthier patients, severely ill patients had less retention of the information that was discussed in the informed-consent process and less-clear understanding of the risks of therapy.⁶⁰ Some have suggested that insurers will act as an effective counterweight in the post-approval marketplace by refusing to cover breakthrough products with clinical activity that is either unconfirmed or does not justify the high cost.⁶¹ In Europe, centralized payers serve as a barrier to the widespread use of available but marginally useful clinical therapies.^{62,63} However, in the United States, the greater fragmentation of the insurance market and the greater sense of entitlement to all available treatments make it unlikely that this counterbalance will be as effective.

Even before the first breakthrough drug has been approved, lawmakers have started discussing the next pathway aimed at further reducing evidentiary requirements to speed drugs to market.⁶⁴ On December 12, 2013, a bill was introduced in Congress that would allow the approval of new antibiotic and antifungal medicines on the basis of alternative end points and data sets of limited size so long as the labeling prominently stated that the drugs were indicated for

use in a limited and specific population of patients.⁶⁵ The bill did not restrict the ability to prescribe such drugs off-label. In the next few years, evidence will accumulate to indicate how well the new breakthrough-therapy designation improves the options of patients with serious and intractable diseases and to what extent it facilitates the market entry of treatments that promise more than they can deliver.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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