

A Review of Implications of FDA Expedited Approval Pathways, Including the Breakthrough Therapy Designation

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Since 1962, the United States (U.S.) Food and Drug Administration (FDA) has required that manufacturers demonstrate drugs are effective and safe prior to patient exposure.¹ This review and approval process is intended to ensure sufficient evidence demonstrates the benefits of therapy outweigh the risks. However, one major criticism has been the delay of getting new medications to market, particularly for medical conditions with few treatment options. To expedite the drug development process and facilitate approval of drugs indicated for serious or life-threatening conditions, the FDA has created expedited approval programs to allow faster approval of drugs and address unmet medical needs in the treatment of serious conditions. The purpose of this newsletter is to review the different accelerated approval pathways and designations with a focus on the latest breakthrough therapy designation (BTD), discuss the strengths and limitations associated with these pathways, and evaluate the evidence concerns behind some of the specific non-oncology drug approvals.

Accelerated Approval Pathways

The FDA created four accelerated approval pathways and designations (Table 1). Although each pathway has different qualifying and approval features, the drugs approved via these routes must address an unmet clinical need in the treatment of a serious condition.² The FDA defines a serious disease or condition as one that is associated with morbidity that has substantial impact on day-to-day functioning, leaving much of it up for interpretation and clinical judgement.³ A recent study identified drugs approved through these expedited pathways and documented a significant increase in the number of drugs qualifying for one of these approvals, with an increase of 2.4% each year from 1987 to 2014.² Additionally, the authors found an increasing number of drug approvals that are less likely to be innovative or clinically transformative.²

Table 1: FDA Expedited Approval Pathways³

Pathway and Designation	Qualifying Features	Approval Features
Fast-track designation	Nonclinical or clinical data demonstrate the potential to address an unmet clinical need	Increased communication to facilitate development and incorporates a rolling review
Accelerated approval pathway	Meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit	Allows approval based on a surrogate or intermediate endpoint
Priority review designation	If approved would provide a significant improvement in safety or effectiveness	Shorter clock for review of application (6 months vs. 10 months with standard)
Breakthrough therapy designation	Preliminary clinical evidence indicates it may demonstrate substantial improvement over available therapies on a clinically significant endpoint	Provides all features associated with the fast track designation, intensive guidance on efficient drug development and organizational commitment from senior agency officials

The passage of the FDA Safety and Innovation Act of 2012 provided the most recent expedited approval pathway, the “breakthrough therapy designation” (BTD).⁴ Drugs are eligible for the BTD if they treat a serious or life-threatening disease or condition and a surrogate endpoint (e.g., laboratory measurement, radiographic image, or physical sign) suggests an improvement over existing therapy.^{3,5} Since approval is based on a surrogate endpoint, the clinical evidence required for approval is considered preliminary and drugs commonly include language in their official labeling stating that the clinical benefit has not been established. FDA requires the manufacturer to conduct post-approval trials to confirm the drug’s efficacy.⁶ The BTD has become quite widespread since its inception, likely because of the close attention and guidance given by

FDA officials, as early as during phase 1 studies. Since introduction of the BTD in July 2012 through the end of 2017, the FDA has approved 91 drugs or new indications through the BTD, and 32 in the year 2017 alone.⁷ Approximately two-thirds of these approvals have been for small molecules and non-biologic drugs, and more than 50% are oncology drugs.

Concerns and Limitations

Surrogate Outcomes: The FDA frequently approves new drugs on the basis of trials that use surrogate markers of disease instead of clinical outcomes for primary endpoints. Surrogate endpoints include markers such as laboratory measurements or radiographic images. However, these surrogate endpoints may not translate into a meaningful benefit for the patient. Additionally, the required post-approval trials to confirm clinical efficacy can be significantly delayed. It has been shown that only half of the required post-approval studies are completed within 3 years after drug approval, the quality of the studies varies widely, and even confirmatory trials frequently depend on surrogate endpoints.⁸ Furthermore, the ability to secure approval based on unvalidated surrogate endpoints reduces the incentive for pharmaceutical companies to conduct high quality trials that evaluate clinical benefits and risks of a drug therapy.

Table 2 includes examples of drugs approved through the BTD based on a surrogate outcome that has not been proven to impact clinical disease activity and/or does not have a well-defined minimal clinically significant change associated with it.

Table 2: Drugs Approved with a BTD Based on a Surrogate Outcome

Drug or Drug Class	Approved	Primary Outcome	Approximate 30-day cost
CF modulators*	Cystic Fibrosis	Forced expiratory volume in one second (FEV ₁)	\$25,103 - \$28,675
Pimavanserin	Parkinson’s disease	Adapted scale for assessment of positive symptoms (SAPS-PD scale)	\$3,334
Direct Acting Antivirals**	Chronic hepatitis C	Sustained Virologic Response	\$15,840 - \$113,400 (per treatment course)
VMAT 2 Inhibitors†	Tardive dyskinesia	Abnormal involuntary movement scale	\$3,946 - \$7,470

*Cystic Fibrosis Modulators: ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor
 **Direct Acting Antivirals: sofosbuvir, sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir; dasabuvir, ombitasvir/paritaprevir/ritonavir, grazoprevir/elbasvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir
 †Vesicular Monoamine Transporter 2 inhibitors: valbenazine, deutetrabenazine

For approval of both pimavanserin and the vesicular monoamine transporter 2 (VMAT2) inhibitors, observed changes in subjective scales were used as the primary outcome. In the primary approval trial for pimavanserin, efficacy was determined based on a new Parkinson’s disease (PD) adapted scale, SAPS-PD, to assess the frequency and severity of hallucinations and delusions associated with PD. This was the first use of this scale in a clinical trial and remains an unvalidated tool to evaluate Parkinson’s disease psychosis. Pimavanserin demonstrated a mean 3.06 point reduction in SAPS-PD compared to placebo at 6 weeks.⁹ Although further information is needed to establish a minimal clinically important difference in the SAPS-PD, review by the FDA suggested that a 5 to 7 point change may be necessary to demonstrate a clinical improvement.¹⁰

Likewise, the VMAT2 inhibitors were approved based on changes in the Abnormal Involuntary Movement Scale (AIMS) to assess the severity of tardive dyskinesia symptoms. No minimal clinically important difference has

been established and evidence has not demonstrated that improvement in the AIMS translates into improved function or quality of life for patients.¹¹ For the cystic fibrosis oral modulators, the primary outcome of forced expiratory volume in one second (FEV₁) does not prove that the drug prolongs survival or prevents complications. Lastly, in chronic hepatitis C, achieving a sustained viral response does not verify the drug prevents progression of liver disease or prevents the need for a transplant.

Safety: A concern with the expedited approval pathways is that minimizing the data collection time prior to FDA approval and exposing drugs to fewer patients in clinical trials could lead to drugs approved with underlying major safety issues identified post approval. A recent study found that drugs approved through expedited pathways had a rate of 0.94 safety-related label changes for each drug per year, compared with 0.68 for drugs approved through the traditional pathway.⁶ This concern was further validated with post-approval reports of possible reactivation of hepatitis B and liver injury in patients receiving direct acting antivirals.

Additionally, during FDA review of pimavanserin, the medical reviewer recommended against approval due to an unacceptable rate of serious adverse effects including death.¹² These concerns were confirmed in November 2017 when the Institute of Safe Medical Practices issued a warning based on significant reports of serious adverse effects with pimavanserin including hallucinations (n=487), confusion (258), deaths (n=244), and lack of efficacy (n=333).¹³ Almost 75% of these reports came from health professionals. With a controversial approval based on one clinical trial demonstrating a minimal benefit on a surrogate outcome and significant safety concerns, patients and prescribers need to know that long term safety and efficacy remain unproven.

Drugs Approved for Rare Diseases

Table 3 includes drugs approved with the BTD which are the first FDA approved therapies for rare inherited genetic diseases. These drugs clearly provide some benefit over existing therapy and satisfy that specific BTD criteria. Nonetheless, many of the pivotal trials for these drugs suffered from significant methodologic concerns such as small sample sizes, use of a retrospective, historical control as a comparator, and a lack of established surrogate markers to assess clinical efficacy, all of which raise questions about clinical significance and long-term benefits. Several of the indications of these drugs are extremely rare which does make researching them properly incredibly challenging. However, significant questions remain about whether these agents provide meaningful benefits for unfortunate patients with these diseases.¹⁴ Cost is also a significant concern with drugs approved for rare diseases. According to one analyst, the cost of treating a rare disease averaged \$140,000 a year in 2016, and all of the treatments included in **Table 3** are over \$400,000 per year. Although these treatments offer options for the first time for these rare illnesses, because of the high cost and limited data available demonstrating clinical efficacy, they are unlikely to be cost-effective based on widely accepted thresholds for cost-effectiveness.

Table 3: New Drugs Approved for Rare Diseases

FDA approved drug	Indication	Patients	Comparator	Approximate 30-day cost
Sebelipase alfa	Lysosomal acid lipase deficiency	N=75	Historical control	\$49,008*
Asfotase alfa	Hypophosphatasia	N=70	Historical control	\$41,184*
Uridine Triacetate	Hereditary orotic aciduria	N=4	Historical control	\$54,000*
Cerliponase alfa	Neuronal ceroid lipofuscinosis type 2	N=42	Historical Control	\$64,800

*Dosing is weight based causing variability in pricing based on age and weight

Conclusion

The intent of the BTD and other FDA expedited approval pathways is to provide quicker access to medications for patients who have rare conditions or

conditions with suboptimal therapies available. While some medications approved through these programs will prove to demonstrate a significant advancement in the treatment of a disease, healthcare professionals and patients should be aware of the uncertainties and heterogeneity in the quality of the evidence leading to these approvals. Additionally, the 21st Century Cures Act was signed into law in December 2016 and is designed to help accelerate medical product development and bring drugs to the market even faster. This bill may allow drug approvals based on limited evidence to assess the safety and efficacy of drugs without the need for rigorous clinical trials. It will become even more critical for both patients and providers to evaluate the potential long-term benefits and risks of new drugs approved via an expedited pathway.

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