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what you need to know about expedited approvals

The availability of novel drugs often results in new treatment options for patients. Having access to these drugs can extend the life of patients or significantly improve their quality of life; however, many diseases and conditions still lack adequate therapies. For this reason, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have paved the way for rapid innovation by creating several mechanisms for expediting the approval of drugs that have never been used in clinical practice.

The FDA mechanisms include: Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval. The EMA mechanism for expedited approval is an application process called PRIME (PRIority MEdicines).

Because each mechanism expedites the approval process, there's often confusion about the impact of each mechanism and the distinctions among them. As such, it's helpful to examine each mechanism separately before discussing their similarities and differences.

FDA Mechanisms for Expedited Approval

Fast Track Designation

Fast Track designation is designed to facilitate the development and expedited review of drugs intended to treat serious conditions and fill an unmet medical need. The goal is to get novel drugs to patients faster.

A serious condition is one where the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition will become more severe if left untreated. The drug fills an unmet medical need when it provides a therapy where none exists or when it provides a therapy which is potentially significantly better than any available product.

A drug that receives Fast Track designation is eligible for the following:

- More frequent meetings with the FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written communication from the FDA about such things as the design of the proposed clinical trials and use of biomarkers
- Accelerated Approval and Priority Review, if relevant criteria are met
- Rolling Review, which means that a Sponsor can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section is completed before the entire application can be reviewed

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The Sponsor can request Fast Track designation at any time during the drug development process. Within 60 days, the FDA will decide whether the drug fills an unmet medical need for a serious condition.

Breakthrough Therapy Designation

The Breakthrough Therapy designation expedites the development and review of drugs that are intended to treat a serious condition and that have preliminary clinical evidence indicating that the product may demonstrate substantial improvement over an available therapy on a clinically significant endpoint. A clinically significant endpoint generally refers to an endpoint that measures the effect on irreversible morbidity or mortality, or on symptoms that represent serious consequences of the disease.

A drug that receives Breakthrough Therapy designation is eligible for the following:

- All Fast Track designation features
- Intensive guidance on an efficient drug development program, beginning as early as Phase 1

The Sponsor must request Breakthrough Therapy designation. If the request isn't made, the FDA may suggest that the Sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for Breakthrough Therapy designation and (2) the remaining drug development program can benefit from the designation.

Accelerated Approval Pathway

Accelerated Approval is perhaps the most distinct of the mechanisms for drugs intended to treat a serious disease because it is an approval pathway rather than a designation. An approval pathway is a mechanism to market authorization whereas a designation, which is granted to a drug based on meeting certain criteria and which provides certain benefits, such as speeding the approval process for Priority Review designations or providing tax credits and exclusivity for orphan drug designations

The Accelerated Approval pathway is mindful of a drug's "clinical benefit," which is the positive therapeutic effect that is clinically meaningful in the context of a disease. Because it may take an extended period to measure a drug's intended benefit, the FDA allows drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint. Using surrogate endpoints significantly reduces the time it takes for the Agency to approve a drug.

A surrogate endpoint used for Accelerated Approval is a marker such as a laboratory measurement, radiographic image, or physical sign that is thought to predict a clinical benefit. For instance, instead of having to wait to learn if a drug actually extends survival for cancer patients, under the Accelerated Approval pathway, the FDA may approve a drug based on evidence that the drug shrinks tumors because tumor shrinkage is considered reasonably likely to predict a real clinical benefit. Drugs using the Accelerated Approval pathway must also generally provide a meaningful advantage over available therapies.

After approval, the Sponsor will still need to conduct Phase 4 confirmatory trial studies to corroborate that tumor shrinkage predicts that patients will live longer. Until the benefit has been confirmed in a post-market setting, the labeling has special language to indicate that the use of the drug has not yet been shown to have a clinical benefit.

Approval of a drug may be withdrawn, or the labeled indication of the drug changed, if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug.

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Priority Review Designation

Priority Review must be requested by the Sponsor with the initial NDA submission.

The Priority Review designation sets a goal for the FDA to act on an application within six months, compared to the ten-month timeframe the Agency has to review applications undergoing a standard review. To qualify for Priority Review, the Sponsor must show that, if approved, the drug would provide a significant improvement in safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition.
This mechanism directs attention and resources to the evaluation of applications for drugs that would prompt significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.
After Priority Review has been requested, the Agency must inform the Sponsor of approval or disapproval within 60 days of the receipt of the original application or efficacy supplement. It's important to note that a Priority Review designation does not alter the scientific or medical standard for approval, nor does it alter the quality of evidence necessary for approval.

Comparing Similar Mechanisms

Understanding the nuances of similar mechanisms is crucial. This knowledge will help Sponsors choose the most appropriate and expeditious track for their drug development program.

Fast Track and Breakthrough Therapy

Fast Track and Breakthrough Therapy are the most similar mechanisms, as they are both designed to expedite the development of drugs for serious conditions. The most significant difference between these two mechanisms is the type of data needed to substantiate the request.
Fast Track can be granted based on preliminary data, such as activity in a nonclinical model, pharmacological data, or a mechanistic rationale. Breakthrough Therapy must use preliminary clinical data, and therefore activity in a nonclinical model or a mechanistic rationale alone would not be enough.
Sponsors should also note the subtle differences in the designation criteria: drugs seeking Fast Track must only have the potential to address an unmet medical need, while drugs seeking Breakthrough Therapy must have preliminary data which demonstrate substantial improvement on clinically significant endpoints over available therapies.
Drugs that are granted Breakthrough Therapy designation have all the benefits of Fast Track drugs, but are also given intensive guidance on an efficient drug development program and have the involvement of FDA senior managers. It's not uncommon for a drug with a Fast Track designation to also be granted Breakthrough Therapy during the drug development process.

Leveraging All Four FDA Mechanisms

Drugs intended to treat an unmet medical need for a serious condition will often use more than one expedited mechanism. A Sponsor wishing to use all four mechanisms could first seek Fast Track designation with nonclinical data, followed by a request for Breakthrough Therapy designation using clinical data. They could then discuss the possibility of using Accelerated Approval and obtain FDA agreement on endpoints before moving forward with clinical trials. Finally, the Sponsor could request Priority Review upon the submission of the original NDA.

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2020 Usage of FDA Expedited Mechanisms

The Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval mechanisms significantly enhance a manufacturer's ability to get their product to patients quickly. As such, a significant percentage of novel drugs are processed through these mechanisms each year.

The Center for Drug Evaluation and Research (CDER) reports that there were 53 novel drugs approved in 2020, including Veklury (remdesivir), the first FDA-approved treatment for COVID-19. Despite the challenges of the pandemic, approval of novel drugs in 2020 significantly surpassed the average yearly total of 40 approvals since 2011. Here is how the usage of the expedited development and review pathways broken down by category:

> Expedited mechanisms significantly enhance a manufacturer's ability to get their product to patients quickly.

Fast Track

The FDA designated 17 novel drugs (32%) as Fast Track. Drugs designated with Fast Track status were: Artesunate, Ayvakit, Detectnet, Dojolvi, Enspryng, Evrysdi, Margenza, Monjuvi, Olinvyk, Orladeyo, Qinlock, Rukobia, Tepezza, Trodelvy, Tukysa, Veklury, and Viltepso.

Breakthrough Therapy

The FDA designated 22 novel drugs (42%) as Breakthrough Therapies. Drugs designated with Breakthrough Therapy status were: Artesunate, Ayvakit, Blenrep, Danyelza, Ebanga, Enspryng, Gavreto, Imcivree, Inmazeb, Koselugo, Monjuvi, Oxlumo, Pemazyre, Qinlock, Retevmo, Rukobia, Tabrecta, Tepezza, Trodelvy, Tukysa, Uplizna, and Zokinvy.

Accelerated Approval

The FDA approved 12 novel drugs (23%) under the Accelerated Approval pathway. The drugs were: Blenrep, Danyelza, Gavreto, Lampit, Monjuvi, Pemazyre, Retevmo, Tabrecta, Tazverik, Trodelvy, Viltepso, and Zepzelca.

Priority Review

The FDA gave 30 novel drugs (57%) Priority Review status. These drugs were: Artesunate, Ayvakit, Blenrep, Danyelza, Detectnet, Ebanga, Evrysdi, Gavreto, Imcivree, Inmazeb, Inqovi, Koselugo, Lampit, Monjuvi, Orgovyx, Oxlumo, Pemazyre, Qinlock, Retevmo, Rukobia, Tabrecta, Tauvid, Tazverik, Tepezza, Trodelvy, Tukysa, Veklury, Viltepso, Zepzelca, and Zokinvy.

EMA Accelerated Approvals Pathway

PRIME Designation

For expedited approvals, the EMA has a process for accelerated assessments. The PRIME (PRIority MEdicines) designation can be granted for products that target unmet medical needs or are of major interest to public health and therapeutic innovation, which is based on the submission of an application.

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Our experts can help determine your product's eligibility for accelerated approval and develop the appropriate documentation to support an accelerated or PRIME application. We serve as a liaison with the rapporteur from the EMA's Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT) and can help prepare scientific advice requests at key development milestones.

Expedited Approval Expertise

More important than the quantity of new drug approvals is their medical value and ability to advance patient care. This is the underlying factor that has motivated both the FDA and EMA to provide expedited approval mechanisms for novel drugs.

If you think that your drug development program would benefit from using an expedited approval mechanism, ProPharma can help. Our team provides a strategic element to your program. We know what it takes to navigate the complex paths of an expedited approval process. Let us help you with the selection of the most appropriate mechanism(s) and framing the story surrounding the seriousness of a condition and the unmet need for the drug. With ProPharma as your partner, you can effectively leverage the expedited approval process and get your drug to market faster.

improve the health and safety of patients.

From early concept development through each clinical phase, product launch, and commercialization, we partner with pharmaceutical, biotechnology, and medical device clients to tackle complex challenges. We help to ensure regulatory expectations are met, business goals are achieved, and patient health and safety is improved.

Our team of experts brings a comprehensive portfolio of regulatory and compliance solutions to help solve complex challenges in a dynamic regulatory environment. With our mission to improve the health and safety of patients, we are focused on delivering the highest quality of services throughout the full product lifecycle.

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