

Policy Brief

Background

There are multiple routes for approval of new drugs or indications for existing medications through the United States Food and Drug Administration (FDA), many of which are targeted for therapies in niche or rare disease treatment areas. Not all pathways require the same timelines or rigor of review, and in recent years, this has disproportionately affected the field of neurology.

Currently, there are more than 500 neurology-specific therapeutics in the drug-approval pipeline across various disease states.¹ A very high percentage of these drugs meet eligibility for consideration through an “alternative” FDA approval pathway and/or meet eligibility criteria for orphan drug designation (i.e., drugs intended to treat rare diseases defined as affecting <200,000 individuals nationwide). At present, nearly 15 percent of neurologic therapeutics have an orphan drug designation. As we continue to learn more about the genetics of neurologic disorders, additional targeted biologics and gene therapies are on the horizon, a considerable number of which may pass through an alternative FDA approval pathway. For this reason, understanding the nuances of FDA approval are of increasing importance.

FDA Standard Approval Process²

There are several pathways by which drugs are approved by the FDA. This typically begins with an investigational new drug (IND) application which is commonly based on pre-clinical data. There are three types of IND applications: investigator IND, emergency use IND, and treatment IND. All require information regarding animal pharmacology and toxicology, manufacturing information on composition and stability, and proposed clinical indications.

Following obtainment of clinical trial data which demonstrates efficacy on standard endpoints in a disease state, a sponsor will submit a new drug application (NDA). A sponsor can be an individual, corporation, manufacturer, etc. leading the development and regulatory compliance of the new drug. Not all drugs that have filed for an IND will move forward with an NDA since clinical benefit must be demonstrated. There are three types of NDAs:

1. 505(b)(1): Traditional pathway
2. 505(b)(2): Drugs with similar active ingredients to a previously approved drug
 - Drug can rely on prior drug’s data supporting an accelerated pathway because less “new” information is required
3. 505(j) Abbreviated New Drug Application: Bioequivalent drugs (generics)

FDA “Alternative” Approval Processes^{1,3}

There are four “alternative” approval processes currently used by the FDA. Each pathway has unique eligibility criteria and sponsor benefits. These pathways, except for a breakthrough therapy, are applied at the NDA stage of approval.



Priority Review

Priority Review was authorized in 1992 by the Prescription Drug User Fee Act (PDUFA) which created the two-tiered FDA drug review system (standard v. priority). This pathway shortens application review from 10 months (standard) to 6 months (priority). The FDA determines if a drug receives a standard or priority review, although sponsors may request a priority review. Priority review is granted if a new drug would result in a significant improvement in safety and effectiveness compared to existing therapies.

EXAMPLE: *In 2020, aducanumab was granted priority review to treat Alzheimer's disease.*

Fast Track

Drugs for the treatment of serious conditions that address an unmet medical need receive an expedited review. The purpose of this pathway is to get important new drugs to patent earlier, for conditions such as Alzheimer's disease, epilepsy, depression, and multiple sclerosis. Any drug being developed to treat or prevent a condition with no current therapy is prioritized.

If there are available therapies, the new drug must:

1. Show superior efficacy
2. Avoid serious side effects of the available therapy
3. Decrease clinically significant toxicity of an available therapy
4. Address an emerging or anticipated public health need

Fast Track designation should come at the time of submission and be requested by the manufacturer, although it can be requested at any time in the approval process. Once in the Fast Track pathway, there are more frequent meetings with the FDA to discuss the development plan and appropriate data needed to support drug approval. Drugs in the Fast Track pathway are also eligible for accelerated approval and priority review if relevant criteria are met.

EXAMPLE: *In 2019, neflamapimod was granted Fast Track review as a treatment for dementia with Lewy bodies.*

Accelerated Approval Pathway

Authorized in 1992 and updated in 2012, this pathway is applied to new therapies that treat serious or life-threatening conditions for which there is an unmet medical need and have a "clinically meaningful" outcome. Drugs that are eligible for this pathway must be reasonably likely to improve a surrogate endpoint if a standard endpoint would require long-term evaluation.

EXAMPLE: *Drug X treats glioblastoma multiforme. A surrogate endpoint would be a decrease in tumor size whereas a standard endpoint would be survival at five years.*

If given conditional approval, the sponsor must conduct post-marketing clinical trials to ensure endpoints are met. If the standard endpoints are not met, the FDA can withdraw approval. This pathway allows the approval time to be reduced by approximately 40 percent, from a mean of eight years to 4.8 years.

EXAMPLE: *In 2019, Vyondys 53 (golodirsen) injection was approved to treat Duchenne muscular dystrophy with a specific gene mutation.*

Breakthrough Therapy

This designation is designed to expedite the development and review of drugs that are intended to treat serious conditions and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on clinically significant endpoints.

EXAMPLE: *In 2018, the oral agent fingolimod was approved for the treatment of children and adolescents >10 years with relapsing multiple sclerosis.*

Other Drug Access Issues

Orphan Drug Act (ODA)⁴

ODA is a pathway by which therapeutics for illnesses that affect <200,000 people can apply for “orphan drug status” that entitles the sponsor to development incentives (e.g., tax credits, waived prescription drug user fee), enhanced patent protection and marketing rights, and clinical research subsidies.⁵ Granting of this status does not alter the standard regulatory requirements and process for obtaining marketing approval. Safety and effectiveness of compounds must be established through adequate and well-controlled studies.

The ODA has largely been viewed as positive for patients since prior to its enactment in 1983, only 38 drugs were approved in the United States for orphan diseases.

Sponsor abuses of the ODA, however, have occurred, with former Rep. Henry Waxman (D-CA), the original sponsor of the 1983 act reporting, “*The industry has taken advantage of the incentives to charge excessive profits and to reap windfalls far in excess of their investments in the drug.*”⁶

Issues with the ODA include repurposing of older, inexpensive non-orphan drugs to new rare disease designations;^{7,8} high revenue in certain disease states at the expense of patients;⁹ and creation of diseases within diseases by sponsors to meet eligibility criteria for orphan drug designation.¹⁰

Expanded Access

Otherwise known as compassionate use, expanded access is an FDA pathway intended to allow terminally ill patients access investigational drugs outside of a clinical trial. A physician must request access to the treatment on behalf of the patient and strict rules determine if a patient qualifies for this pathway. Since 2015, the FDA has approved nearly 99 percent of all compassionate use requests.¹¹

Right to Try¹²

Right to Try is a law passed in 2018 that also allows terminally ill patients to access experimental therapies that are not FDA-approved and may be in early development. The FDA, does not review Right to Try requests, only informed consent by the prescribing physician is required.

There may not be safety data for these therapies, making fully informed consent very difficult and problematic for prescribing physicians due to an inability to appropriately anticipate or manage side effects and/or toxicity. To date, the law has not resulted in many patients receiving therapies because safety monitoring and administrative issues must be borne by the physician.¹³

Policy Discussion

The FDA's Center for Drug Evaluation and Research (CDER) has used at least one expedited approval pathway for 60 percent of all novel drugs approved in 2019.¹⁴ As more neurology-specific therapies approved by the FDA fall into one or more accelerated approval pathways, providers and insurers may face challenges when the use of surrogate endpoints or narrow clinical trial populations result in a smaller data set than required to support the label indication.

Although mechanisms exist to limit regulatory burden for drug sponsors through alternative FDA approval pathways, pricing has not followed suit. High drug cost is correlated with decreased medication compliance and medication rationing which has become common among patients receiving high-cost neurologic therapeutics.¹⁵ Policymakers have considered measures such as caps on revenue to limit abuse for "blockbuster" therapeutics.

In addition, although early drug development data is often funded by government pathways, late-stage development is managed by sponsors. The federal government subsidizes research,¹⁶ but patients are ultimately still left with high drug costs.

One mechanism for control of drug costs has been the advent of use of both generic and bioequivalent medications. Many therapies designed in these pipelines are approved through expedited pathways given similarity in composition to an existing drug. The benefits of using both generics and bioequivalents is that they are considered lower-cost alternatives to available formulations.

Generic and bioequivalent medications may have similar safety profiles compared to approved drugs, but certain diseases such as epilepsy and multiple sclerosis rely on accurate and predictable pharmacodynamics, creating potential issues for some patients.

Neurology is one of the top specialties with breakthrough drugs in the pipeline,¹⁷ but patients continue to cite access to therapies as being particularly challenging. Neurologists also face increased regulatory burden and high costs as barriers to treating patients with appropriate therapies.

Conclusion

There are multiple FDA approval pathways for pharmacologic therapies and drugs for neurologic conditions disproportionately use alternative approval mechanisms. Understanding these pathways and their relationship to high drug costs, access to care and treatments, and the use of generics and bioequivalents is a high priority for neurologists who continue to modify treatments within the changing therapeutic landscape. Unique situations such as the COVID-19 public health

emergency also highlight the necessity of patient safety and timely access to breakthrough treatments as science evolves. It is of the utmost importance to maintain a highly credible drug development system, free of political interference, to provide the safest and most accessible drugs to our patients.

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REFERENCES

- ¹ Medicines in Development for Neurological Disorders 2018 Report. PhRMA, <https://www.thepharmaletter.com/article/new-report-shows-over-500-neurological-meds-in-development-by-us-firms>.
- ² Development & Approval Process | Drugs. US Food & Drug Administration, <https://www.fda.gov/drugs/development-approval-process-drugs>.
- ³ Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. US Food & Drug Administration, <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review>.
- ⁴ Orphan Drug Act of 1983. Pub L. No. 97-414, 96 Stat. 2049.
- ⁵ Designating an Orphan Product: Drugs and Biological Products. US Food & Drug Administration, <https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products>.
- ⁶ Conversations with Mike Milken, Henry Waxman. Milken Institute, 26 May 2020, <https://milkeninstitute.org/sites/default/files/2020-05/Conversations%20with%20MM%20-%20051%20Henry%20Waxman%20-%2005-26-20%20%282%29.pdf>.
- ⁷ Lanthier M. Insights into rare disease drug approval: trends and recent developments. US Food & Drug Administration, 17 October 2017, <https://www.fda.gov/media/108099/download>.
- ⁸ Thorat C, Xu K, Freeman S, Bonnel R, Joseph F, Phillips M, Imoisili M. What the Orphan Drug Act Has Done Lately for Children with Rare Diseases: A 10-Year Analysis. *Pediatrics* 2012;129(3):516-521.
- ⁹ Murphy S, Puwanant A, Griggs R. Unintended Effects of Orphan Product Designation for Rare Neurological Diseases. *Annals of Neurology* 2012; 72(4):481-490.
- ¹⁰ Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development. Field MJ, Boat TF, editors. Washington (DC): National Academies Press (US); 2010. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK56189/>
- ¹¹ Expanded Access (compassionate use) submission data. US Food & Drug Administration, <https://www.fda.gov/news-events/expanded-access/expanded-access-compassionate-use-submission-data>
- ¹² Right to Try. US Food & Drug Administration, <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try>
- ¹³ March, R. Is Right-to-Try Legislation a Bust? Time for a Second Opinion. *FDAREview.org*, 17 October 2019, <https://www.fdaareview.org/2019/10/17/is-right-to-try-legislation-a-bust-time-for-a-second-opinion/>
- ¹⁴ Novel Drug Approvals for 2019. US Food & Drug Administration, <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019>
- ¹⁵ Reynolds EL, Burke JF, Banerjee M, Kerber KA, Skolarus LE, Magliocco B, Esper GJ, Callaghan BC. Association of out-of-pocket costs on adherence to common neurologic medications. *Neurology* 2020;94(13):1415-1426.
- ¹⁶ Cleary EG, Beierlein J, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010–2016. *Proceedings of the National Academy of Sciences* 2329–2334. 6 March 2018.
- ¹⁷ Trends to watch in 2020. Optum, <https://www.optum.com/business/resources/library/trends-to-watch-2020.html>