Accelerated Drug Approval

History, Misconceptions & Potential for Neurology Patients

A Clinical Awareness Initiative White Paper

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Clinical Neurological Society of America

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Introduction

Bringing a new medication to market invariably takes many years, as manufacturers follow the standard U.S. Food and Drug Administration approval process and the extensive clinical trial requirements it entails. Patients with serious or rare diseases that have limited treatment options often cannot wait that long.

The FDA's Accelerated Approval Program can cut years off the review and approval timeline, giving those patients new hope.

While accelerated approval was implemented decades ago, misconceptions persist about how it works. These misconceptions have the potential to undermine the program's success and limit patient access to effective therapies.

The History & Benefits of Accelerated Approval

The FDA's Accelerated Approval Program emerged in 1992 in response to the deadly HIV crisis. It allows the FDA to speed approval of innovative medications that hold promise to fill an urgent unmet clinical need "for a serious or life-threatening disease or condition,"[1] often when no effective therapy exists at all.

Use of Surrogate Endpoints

Instead of requiring years of exhaustive clinical trials, accelerated approval allows manufacturers to evaluate a medication's efficacy based on the use of surrogate endpoints that are "reasonably likely to predict clinical benefit".[1] These endpoints can be a marker such as a radiographic image, laboratory measurement or even a physical sign – like the ability to shrink a tumor – that indicates a clinical benefit but is not a direct measure of "irreversible morbidity or mortality."[1,2]

Confirmatory Clinical Trials

If the medication is approved under the program, the FDA then requires manufacturers to undertake further confirmatory clinical trials, to verify the benefits indicated by the surrogate endpoint studies, to permit these medications to remain available to patients.[3] Using surrogate endpoints saves crucial time in the early stages of the review process for serious medical conditions that are deemed by FDA to present the greatest immediate clinical need.[4]

Over the last 30 years, more than 278 medications have been made available to patients through the Accelerated Approval Program, representing approximately 14% of all new FDA approvals.[5] Almost two-thirds of those medications have already completed confirmatory trials, of which 81% confirmed the benefit, with a recent median time of 2.3 years. Overall, 12% of accelerated approvals have been withdrawn from the market, either by the sponsor or by FDA proceedings, with a recent median time of 3.5 years.[6] The Accelerated Approval Program represents a thoughtful and deliberate balance between the long timeframes typically required to complete definitive clinical trials and the immediate needs of patients contending with serious or life-threatening illnesses.

Program Growth

The program has continued to become more useful in the development of innovative medications. The FDA Center for Drug Evaluation and Research approved 50 new medications in 2021, more than one-fourth via the Accelerated Approval pathway. That was a higher percentage than previously, with the number of expedited approvals steadily increasing year over year since 2018.

The scope of the Accelerated Approval Program has also expanded. Since its initial focus on HIV in the early 1990s, the program now supports medications that treat many other conditions as well. From 1992 to 2010, about one-fourth of accelerated approvals were related to rare diseases Patients with rare diseases and no current treatment options stand to benefit significantly from faster medication approvals. Of the roughly 7,000 rare diseases that have been identified, more than 90% have no FDA-approved treatment.[7]

The Accelerated Approval Program also plays a major role in the development and approval of medications for cancer. About 85% of accelerated approvals from 2010 to 2020 were focused on oncology.

Different Pathways for Expedited Review & Approval

Accelerated approval is one of four different FDA programs designed to speed up approvals. The others are Fast Track, Priority Review and Breakthrough Therapy. Each offers a slightly different way to get novel medications to patients.

Fast Track facilitates the development of new medications to treat serious medical conditions for which there is currently no approved treatment. Medications that receive fast track designation will have eligibility for Accelerated Approval and Priority Review, if relevant criteria are met.

Breakthrough Therapy also facilitates the development of innovative medications that show the potential to provide substantially better outcomes than what patients experience with existing medications. To get this designation, medications need to have a clinically significant endpoint, which usually measures an effect on irreversible morbidity or mortality of the disease.

Priority Review status is conferred upon new medications that the FDA has committed to determining application approval or denial within six months.

Accelerated Approval grants approval based on a surrogate endpoint for medications that fill an unmet medical need relative to a serious illness.[8]

Treatment Options for Neurology Patients

Regardless of the particular program, expedited FDA review and approval can benefit patients dealing with life-altering or life-threatening medical conditions. This can be particularly true for patients living with neurogenerative diseases, many of which have no cure. Two neurological medications that have recently received accelerated approval are elivaldogene autotemcel and aducanumab.

Treatment for CALD

Elivaldogene is the first FDA-approved medication shown to slow the progression of neurologic dysfunction in boys ages four-17 with early, active cerebral adrenoleukodystrophy. Also known as CALD, this rare, progressive, neurodegenerative disease primarily affects young boys, causing irreversible, devastating neurologic decline. Symptoms include the loss of communication, cortical blindness, the need for tube feeding, incontinence, wheelchair dependence or complete loss of voluntary movement. Nearly half of patients who do not receive treatment die within five years.

Prior to the advent of elivaldogene autotemcel, treatment was limited to blood stem cell transplant therapy, which can be complicated by serious or sometimes fatal adverse events. Clinical trials are ongoing to confirm elivaldogene's effectiveness.[9]

Treatment for Alzheimer's Disease

Accelerated approval was also granted for aducanumab.[10] The medication treats Alzheimer's disease, which affects about 6.5 million Americans over the age of 65.[11]

The medication was developed to target and remove specific forms of beta-amyloid that accumulate into plaques. It was the first FDA-sanctioned medication to address the underlying biology of the disease. Build-up of beta-amyloid may contribute to cell death and tissue loss in areas of the brain particularly important for memory, thinking and learning. Removing this plaque may also help other brain processes to operate more efficiently.[12]

Aducanumab was approved after three initial studies found that Alzheimer's patients who took the medication at specific doses for a period of time saw reduction of amyloid beta plaque. As required by the FDA, the manufacturer is now conducting a randomized, controlled clinical trial to substantiate the medication's benefit.

As with all accelerated approval medications, the FDA may withdraw its approval if the confirmatory trial does not verify clinical benefit.[13]

Conceptions & Misconceptions about Accelerated Approval

Overall acceptance of medications developed via accelerated approval is good, yet some questions persist among the general public and even among health care providers, including neurology clinicians.

This was illustrated by a recent study from the Clinical Neurological Society of America. It surveyed neurologists, as well as neurology nurse practitioners and physician assistants, to gauge their awareness, attitudes and experiences with accelerated approval.

Survey results showed broad acceptance and support for accelerated approval, but it also identified several **misconceptions** about the program.

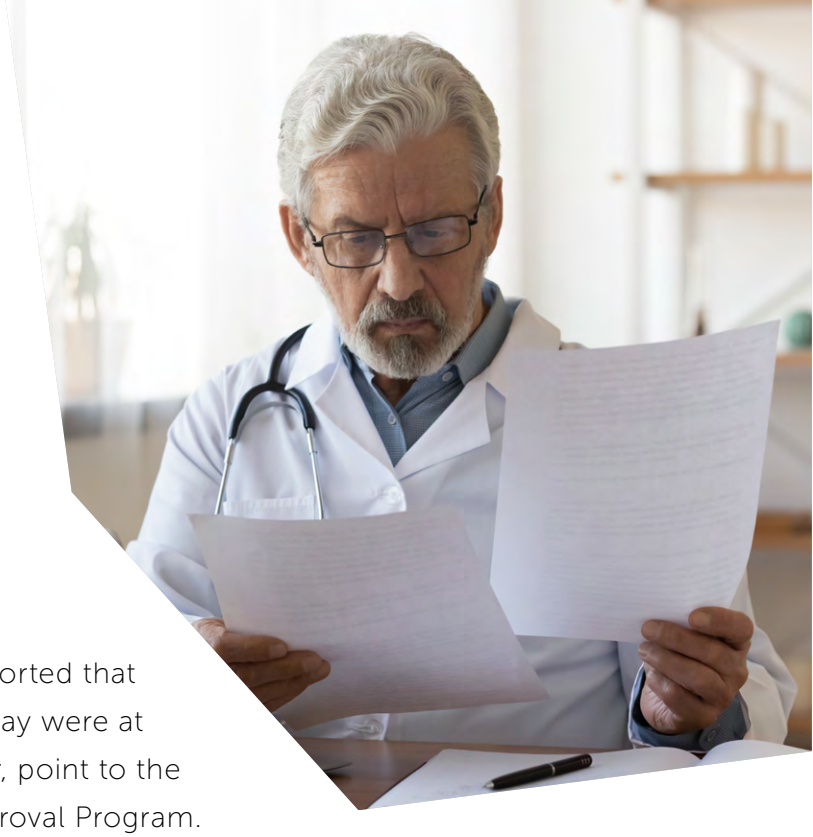
23%
of clinicians surveyed

Perceive medications approved through an accelerated pathway as less safe than other FDA-approved therapies.

24%
of clinicians surveyed

Consider the process to be less thorough than traditional approval pathways and harbor concerns that the FDA prioritizes speed at the risk of patient safety.

Dispelling the Myths about Accelerated Approval



Two issues, in particular, warrant a closer look.

1 Safety Concerns

In the Clinical Neurological Society of America's survey, 23% of surveyed neurology clinicians reported that medications approved via the accelerated pathway were at least somewhat unsafe. Several factors, however, point to the safety and thoroughness of the Accelerated Approval Program.

Safety & Efficacy Requirements

When considering accelerated approval requests, the FDA aims for the standard of evidence to be as close as possible to that used for traditional approvals. The agency concludes that the medication is safe for use, but also acknowledges an element of uncertainty about whether the surrogate endpoint that's used will correlate to an ultimate clinical efficacy and benefit.

For patients facing serious neurological diseases, accepting that uncertainty is often a necessary trade-off for access to treatments that could potentially help them alleviate their symptoms and manage their conditions.[14]

Post-Market Monitoring

Clinical trials provide important information on a medication's safety and efficacy, but it is impossible to have complete information about the safety of a medication at the time of approval. That applies equally to medications that receive traditional or accelerated FDA approval.

After approval, the FDA continues to monitor the performance of prescription and over-the-counter medications for months, even years. If problems arise, the FDA can decide to add caution statements to the dosage or usage information. In serious cases, the agency can revoke its approval and remove the medication in question from pharmacy shelves.[15]

Post-Approval Trials

After a medication is brought to market via accelerated approval, the manufacturer is required by the FDA to conduct studies confirming the clinical benefit predicted by the use of a surrogate endpoint. These are known as phase 4 confirmatory trials and, if successful, are followed by traditional FDA approval.

If the confirmatory trial does not show clinical benefit, the FDA has regulatory procedures in place that could lead to removing the medication from the market.[16]

2 Balancing Safety & Speed

When asked if the FDA does a good job of balancing approval timeliness with safety and efficacy for the accelerated pathway, 20% of surveyed neurology clinicians disagreed and 5% strongly disagreed. Only 10% strongly agreed.

In reality, however, the measures described above intend to make accelerated approval eventually as rigorous as traditional approval.

Reliance on Expert Advisors

Doubts may have been fueled by recent media attention to the accelerated approval of Alzheimer's medication aducanumab. The highly publicized process stirred controversy about the FDA's willingness to override the advice of its advisory committee and allow the medication to reach patients.[17] There is room for improvement in the process. In general, however, the FDA typically does rely on its advisors.

Precautions & Improvements

And the FDA recently has taken a harder line on medications in the accelerated approval pathway. The agency requires that manufacturers show meaningful progress in timely follow-up studies and pull medications from the market if those studies don't verify patient benefits.[18] Precautions like these help balance proven efficacy with timely access.

Like any regulatory process, accelerated approval could be strengthened in certain ways. While the current process is safe, improved policies can help alleviate some of the medical community's concerns. In 2022, Congress passed reforms that strengthened the pathway, including providing the FDA with stronger authority to ensure the timeliness of confirmatory trials and withdrawal procedures for indications earned via accelerated approval, along with additional reporting requirements.[19]

Access Issues

Despite reservations among some clinicians about safety, 84% of neurology providers report that they are comfortable prescribing accelerated approval medications. Access issues, however, remain a concern.

Coverage Barriers

Insurance coverage barriers, such as prior authorization and step therapy, were cited as the most common challenges to patient access. Surveyed neurology providers overwhelmingly agreed that these medications should be covered by commercial health plans as well as by Medicare and Medicaid.

That is not always the reality for medications approved via accelerated approval, however. For aducanumab, for example, the Centers for Medicare and Medicaid Services determined that patients must be actively enrolled in a clinical trial to gain access to the medication. The same restriction applies to newly approved lecanemab.

Medicaid Challenges

Medicaid programs can also present access challenges. In 2021, MACPAC recommended federal restrictions on accelerated approval medications,[20] and states including Massachusetts and Tennessee have sought federal approval to curtail coverage.[21] Recent research found that restricting Medicaid support for accelerated pathways could result in as many as two-thirds of medications in the program failing to reach between 66,000 and 319,000 patients.[22] Medications for cancer and neurologic diseases would likely bear the brunt of those losses.

High Out-of-Pocket Costs

The high retail costs of these new medications present a related barrier. Out-of-pocket costs and availability at pharmacies are also considered a challenge, along with misinformation and lack of educational materials to help patients understand the process and feel confident taking these medications.

Working Together on Accelerated Approval

The FDA Accelerated Approval Program has tremendous potential for getting safe and innovative medications to at-risk patients in record time. Lack of awareness and understanding among the general public, as well as persistent misconceptions among neurology clinicians, stands to weaken access to these medications for patients who may otherwise benefit.

Now is the time for clinicians, policymakers and other stakeholders to work together to raise awareness about the program, dispel myths and collaborate on ways to strengthen understanding and access.

References

1. Mehta, G. U., de Claro, R. A., & Pazdur, R. Accelerated Approval Is Not Conditional Approval: Insights From International Expedited Approval Programs. JAMA oncology, 8(3), 335–336. 2022. Available from: https://doi.org/10.1001/jamaoncol.2021.6854
2. Accelerated Approval Program. December 1, 2022. U.S. Food & Drug Administration. Available from: https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program
3. Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns. September 29, 2022. U.S. Department of Health and Human Services. Available from: https://oig.hhs.gov/oei/reports/OEI-01-21-00401.asp#:~:text=Of%20all%20278%20drug%20applications,104%20have%20incomplete%20confirmatory%20trials
4. Accelerated Approval. January 4, 2018. U.S. Food & Drug Administration. Available from: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval
5. Monge, A. N., Sigelman, D. W., Temple, R. J., & Chahal, H. S. Use of US Food and Drug Administration Expedited Drug Development and Review Programs by Orphan and Nonorphan Novel Drugs Approved From 2008 to 2021. JAMA network open, 5(11), e2239336. 2022. Available from: https://doi.org/10.1001/jamanetworkopen.2022.39336
6. Beakes-Read, G., Neisser, M., Frey, P., & Guarducci, M. Analysis of FDA's Accelerated Approval Program Performance December 1992-December 2021. Therapeutic innovation & regulatory science, 56(5), 698–703. 2022. Available from: https://doi.org/10.1007/s43441-022-00430-z
7. FDA's Accelerated Approval Pathway: A Rare Disease Perspective. National Organization for Rare Disorders. Available from: https://rarediseases.org/wp-content/uploads/2021/06/NRD-2182-Policy-Report_Accelerated-Approval_FNL.pdf
8. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. February 23, 2018. U.S. Food & Drug Administration. Available from: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
9. bluebird bio Receives FDA Accelerated Approval for SKYSONA® Gene Therapy for Early, Active Cerebral Adrenoleukodystrophy (CALD). September 16, 2022. bluebird bio. Available from: https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-receives-fda-accelerated-approval-skysonar-gene
10. Special Report: 2021 Neurology Drug & Device Approvals. June 7, 2021. Practical Neurology. Available from: https://practicalneurology.com/articles/2022-jan/special-report-2021-neurology-drug-device-approvals
11. Alzheimer's Disease: Facts & Figures. October 5, 2022. BrightFocus Foundation. Available from: https://www.brightfocus.org/alzheimers/article/alzheimers-disease-facts-figures
12. Aducanumab Approved for Treatment of Alzheimer's Disease. 2023. Alzheimer's Association. Available from: https://www.alz.org/alzheimers-dementia/treatments/aducanumab
13. FDA Grants Accelerated Approval for Alzheimer's Drug. June 7, 2021. U.S. Food & Drug Administration. Available from: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug
14. Analysis of FDA's Accelerated Approval Program Performance December 1992–December 2021. July 28, 2022. Springer Link. Available from: https://link.springer.com/article/10.1007/s43441-022-00430-z
15. Step 5: FDA Post-Market Drug Safety Monitoring. January 4, 2018. U.S. Food & Drug Administration. Available from: https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring
16. Accelerated Approval Program. January 30, 2023. U.S. Food & Drug Administration. Available from: https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program
17. Controversial Alzheimer's drug approval could affect other diseases. June 29, 2021. Nature. Available from: https://www.nature.com/articles/d41586-021-01763-9
18. FDA Takes Tougher Line on Fast-Tracked Drugs. December 5, 2022.l The Wall Street Journal. Available from: https://www.wsj.com/articles/fda-takes-tougher-line-on-fast-tracked-drugs-11670170262?st=xp49nt02hfn5jsv&reflink=desktopwebshare_permalink
19. Prescription Drug Policy, 2022 And 2023: The Year In Review And The Year Ahead. January 9, 2023. Health Affairs. Available from: https://www.healthaffairs.org/content/forefront/prescription-drug-policy-2022-and-2023-year-review-and-year-ahead
20. April 2021 MACPAC Public Meeting. April 8, 2021. MACPAC. Available from: https://www.macpac.gov/public_meeting/april-2021-macpac-public-meeting/
21. Curtailing Medicare coverage of accelerated approval therapies threatens patients' access. May 3, 2021. The Hill. Available from: https://thehill.com/opinion/healthcare/551514-curtailing-medicaid-coverage-of-accelerated-approval-therapies-threatens/
22. Calculating the Value and Impact of Accelerated Approvals: Final Findings. November 15, 2022. Vital Transformation. Available from: https://vitaltransformation.com/2022/11/calculating-the-value-and-impact-of-accelerated-approvals-final-findings/

CNSA's Clinical Awareness Initiative

The Clinical Neurological Society of America has nearly 50 years of experience bringing together leading experts and clinical neurologists for educational programming. The society's clinical awareness initiatives focus on increasing awareness about important topics within the practice of health care and the policy and regulatory environment that shapes that care.

CNSA recognizes the project's advisors for the accelerated approval clinical awareness initiative.

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Clinical Neurological Society of America

The Clinical Neurological Society of America was created in 1974 as an organization for neurologists practicing in clinical and academic settings. Since then, the society has grown into a nationwide organization of clinicians with a mission to improve clinical practice and patient care through education.

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