Accelerated approval: Bringing patients access to needed medicines

What is the accelerated approval pathway?

The accelerated approval pathway, formally established by U.S. Food and Drug Administration (FDA) regulations in 1992 and later codified in statute in 1997, enables expedited access to medicines that address an unmet medical need for serious and life-threatening diseases and conditions, while preserving FDA's high standards for safety and effectiveness.[1] This pathway has provided timely access to treatments for HIV/AIDS, cancers and rare diseases, leading to better health outcomes for millions of patients.[2]

Importantly, a medicine granted an accelerated approval must meet the same standard of safety and efficacy for approval as medicines awarded traditional approval. However, as opposed to utilizing a direct measure of clinical benefit, the FDA can base an accelerated approval upon measure of a surrogate endpoint—a marker such as a laboratory measurement, radiographic image, physical sign or other measure—or an intermediate clinical endpoint such as a symptom relief that is reasonably likely to predict clinical benefit. For example, in clinical trials for cancer, where most accelerated approvals are granted, researchers may be able to detect a medicine is having an effect on tumor growth before demonstrating an effect on survival or morbidity, which generally requires long, large trials because of the duration of the typical disease course.

When deciding whether a medicine should receive accelerated approval, the FDA carefully considers the scientific data behind the surrogate endpoint and requires substantial evidence for approval, maintaining the same gold standard review and requirements for safety and effectiveness as that used for traditional FDA approval.[3]

The FDA requires sponsors of accelerated approval products to conduct post-approval studies to verify the anticipated clinical benefit, and the Agency can use expedited procedures to withdraw a product or indication approved under the accelerated approval pathway based on a number of reasons, including if the post-approval studies fail to verify the predicted benefit.[4] Congress in 2022 passed the Food and Drug Omnibus Reform Act to give the FDA additional authority regarding initiation and completion of these post-approval confirmatory trials.

Of the 165 therapies that received accelerated approval over the last ten years, only six indications have been withdrawn, and an additional nine sponsors withdrew their applications for accelerated approval indications.[5]

A Look Back: Responding to the HIV/AIDS Epidemic with Accelerated Approvals

The HIV/AIDS epidemic that began in the 1980s drastically reshaped the environment for drug development and approval in the United States.[6] Upon the discovery of the first known AIDS case in the U.S. in 1981 and for years after, an HIV/AIDS diagnosis was often followed by early death. As the crisis worsened, people living with HIV/AIDS and advocates were desperate for treatment options and called on the FDA to provide greater scientifically justified flexibility of their efficacy requirement for new treatments intended to treat fatal diseases.[7]

In recognition of the urgency to broaden access to medicines that had the potential to be lifesaving, the FDA reassessed its approach to assessing efficacy.[8] To get safe and effective medicines to people living with HIV faster, researchers focused on the utility of surrogate endpoints, which correlated with improved outcomes.[9] For example, improved T-cell count was determined to reliably predict fewer secondary infections in HIV patients and was accepted as a surrogate endpoint that could be used to predict the clinical benefit of HIV medicines.[10]

The FDA approved zidovudine (AZT) as the first antiretroviral medicine for the treatment of AIDS in 1987 on the basis of improved CD4 cell count, the first drug approved on the basis of a surrogate endpoint.[11,12] Importantly, following the approval of these antiretroviral therapies based on surrogate endpoints, combinations of many of these treatments and many that followed became known as highly-active antiretroviral therapy (HAART). HAART transformed the treatment of HIV enabling patients today to live close to normal life spans.[13] In fact, since the introduction of HAART, the HIV/AIDS death rate in the United States has fallen by 91%.[14]

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The Impact of Accelerated Approval for Patients

The accelerated approval pathway has provided timely access to therapies that treat serious conditions and that fill an unmet medical need. This ability for the Agency to review critically needed medicines earlier than under the Agency's traditional pathway has improved and even extended patients' lives. Since inception, over 250 new drugs and biologics to treat serious or life-threatening illnesses have been approved through the accelerated approval program.[15]

From 1992 through roughly 2010, accelerated approval was primarily used to approve drugs indicated for the treatment of HIV (39.7% of approvals), cancers (35.6% of approvals) and rare disease treatments and specialty drugs (24.7% of approvals).[16] Between 2010 and 2020, FDA's use of accelerated approval has notably shifted to oncology medicines—rising from 35.6% to 85% of approvals.[17]

The accelerated approval pathway has succeeded in making therapies available to patients many years, a median of 3.2 years, earlier than under traditional approvals, resulting in faster access and driving further gains in life expectancy and improved clinical outcomes.[18]

One assessment found that for just five of the 250 medicines that have received accelerated approval, millions of patients have gained faster access to clinical benefits, gaining additional life years, years of symptom control, or disease complication-free years over standard of care.[19] For example, accelerated approval awarded to two therapies for treatment of patients with non-small cell lung cancer (NSCLC) that had progressed or did not respond to prior therapy resulted in earlier access for over 500,000 patients and nearly 200,000 additional years lived compared with expected survival had the drugs not been available.

The accelerated approval pathway makes it possible to develop medicines that otherwise may not attract R&D investment because the long timeline required for traditional approval would make it impossible to earn a return on investment. It is estimated that up to 66% of medicines awarded accelerated approval would be at high-risk of not coming to market or from being developed at all if the accelerated approval pathway were not available. This could impact up to 3.6 million patients. [20]

Case Study: Multiple Myeloma

In multiple myeloma, the FDA has noted that 10 medicines have been granted accelerated approval using this pathway and "the average life expectancy for a common hematological malignancy is now anywhere between 8-10 years, when prior it was about two years" – attributing that improvement "greatly due to drugs that were approved under accelerated approval." And most of these approvals were approved based on response rate or time to progression, rather than overall survival.[21] In fact, since the early 1990s, 5-year survival rates for multiple myeloma have increased by nearly 90%, due to significant advancements in treatment.[22] And though the ultimate impact on survival may have not been known at the time of approval, the impact of ensuring patients could access these treatments sooner via an accelerated approval pathway undoubtedly benefited many patients who may have otherwise been required to wait additional years for a traditional FDA approval of these medicines.

Coverage and Reimbursement for Products Granted Accelerated Approval

A 2018 Centers for Medicare and Medicaid Services (CMS) letter[23] stated Medicaid programs must cover medicines approved by the FDA through the accelerated approval pathway. However, increasingly, some stakeholders have issued proposals that seek to limit Medicaid coverage, in contravention of the CMS guidance and the Medicaid Drug Rebate Program, or increase mandatory rebates for medicines approved under the accelerated approval pathway[24], asserting that there is insufficient or limited evidence despite these medicines meeting the FDA's safety and efficacy standards.[25]

In June 2021, the Medicaid and CHIP Payment and Access Commission (MACPAC) issued recommendations to Congress to subject FDA-approved medicines granted accelerated approval to higher rebates until the manufacturer is granted traditional FDA approval, and be subject to increased inflationary rebates if the manufacturer fails to complete the confirmatory trial after a specified number of years.[26] However, Medicaid spending data illustrates that the patient benefits of accelerated approval medicines far outweigh their cost, and support preserving access to these drugs for patients diagnosed with serious or life-threatening diseases or conditions.[27]

Analysis of Medicaid spending from 2007 to 2018 shows:

- Accelerated approval drugs accounted for less than 1% of Medicaid spending consistently every year;
- Medicaid spending on accelerated approval drugs remained steady at 0.6% to 0.8% a year after the 2012 passage of the Food and Drug Safety and Innovation Act, which encouraged accelerated approval for rare conditions, in addition to oncology and HIV/AIDS.[28]

In seeking to limit Medicaid coverage, states presume that any future savings are worth restricting access for patients who have limited to no other treatment options—individuals for whom the accelerated approval pathway was developed. Despite claims of budgetary concerns, an analysis on drivers of Medicaid spending demonstrates that accelerated approval medicines have a minimal impact on spending while also addressing a significant unmet medical need.[29]

Looking to the Future

As we near the 30-year anniversary of this important pathway, it is essential that any potential changes to coverage for accelerated approval medicines be designed to strengthen the areas where accelerated approval has been successful and reinforce the importance of this pathway in broadening patient access to medicines that can treat serious and life-threatening diseases and conditions.[30]

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