KPMG

Center Insight Brief

Center for Healthcare Regulatory Insight

February 2023

FDA Accelerated Approval Program Reforms included in the 2023 Omnibus

On December 29, 2022, President Biden signed the *Consolidated Appropriations Act, 2023*[1] ("the Omnibus") into law. In addition to providing federal funding for FY 2023, the Omnibus bill included several noteworthy healthcare-related provisions, such as reforms to the FDA Accelerated Approval Program. Section 3210 of the Omnibus "modernizes" the Accelerated Approval Program, which was established in 1992 and codified in 2012 to expedite approval of drugs that address a serious condition "associated with morbidity that has substantial impact on day-to-day functioning," offer "meaningful advantage over available therapy," and demonstrate an "effect on an endpoint that is reasonably likely to predict clinical benefit."[2]

The proportion of drugs granted accelerated approval has increased in recent years. In 2021, 14 of 50 novel drugs were approved by the FDA (28%) through this pathway,[3] up from 22.6% (12 of 53) in 2020, 18.7% (9 of 48) in 2019, and 6.7% (4 of 59) in 2018. As of early 2021, roughly half of drugs receiving accelerated approvals had gone on to receive full approval as safe and effective by the FDA with a median time to approval of 3.2 years. An additional 6.3% of approvals had been withdrawn by the drug sponsor and 44.3% have been on the market a median of 1.9 years.[4] Increased use of the program, and lags in accelerated approvals being converted to full approval, have led to growing questions about whether the program is being used as intended and its impact on patients.

Demand for reform further intensified after Biogen's Aduhelm, an amyloid beta-directed monoclonal antibody indicated to treat Alzheimer's disease, was granted Accelerated Approval on June 7, 2021 despite a recommendation against approval by FDA's Peripheral and Central Nervous Systems (PCNS) Drugs Advisory Committee due to uncertain clinical benefit.[5] This Aduhelm approval, and growing concerns about drugs receiving accelerated approval without sufficient clinical benefit evidence or remaining on the market for extended periods of time without demonstrating benefit in post-approval studies, prompted Congress to act in the year-end appropriations package. While pressure was growing for legislative and/or regulatory changes to the program, FDA approved just 6 novel drugs through the Accelerated Approval Program in 2022 (16% of total novel approvals in 2022),[6] fewer than in each of the preceding three years.

[1] Consolidated Appropriations Act, 2023. Public Law No: 117-328. Available at https://www.congress.gov/117/bills/hr2617/BILLS-117hr2617enr.pdf.
[2] Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. US Food and Drug Administration. May 2014. Available at https://www.fda.gov/media/86377/download
[3] Advancing Health Through Innovation: New Drug Therapy Approvals 2021. US Food and Drug Administration. January 2022. Available at https://www.fda.gov/media/155227/download
[4] Strengthening the Accelerated Approval Pathway: An Analysis of Potential Policy Reforms and Their Impact on Uncertainty, Access, Innovation, and Costs. Institute for Clinical and Economic Review. April 26, 2021. https://icer.org/wp-content/uploads/2021/04/Strengthening-the-Accelerated-Approval-Pathway-_-ICER-White-Paper-_-April-2021.pdf
[5] Adcomm gives big thumbs down to aducanumab. Regulatory Affairs Professionals Society. November 6, 2020. Available at https://www.raps.org/news-and-articles/news-articles/2011/11/adcomm-gives-big-thumbs-down-to-aducanumab
[6] Advancing Health Through Innovation: New Drug Therapy Approvals 2022. US Food and Drug Administration. January 2023. Available at https://www.fda.gov/media/164429/download.

Meanwhile, drugs already submitted for accelerated approval prior to passage of the Omnibus may not be subject to the full requirements of the law (i.e., post-approval study protocol and timing requirements) as the FDA begins implementation of the new standards. Most notably, FDA granted accelerated approval to Eisai-Biogen's Alzheimer's treatment Leqembi on January 7, 2023,[7] while declining to grant accelerated approval to Eli Lilly's Alzheimer's drug donanemab on January 19, 2023.[8]

In this issue brief we summarize the Accelerated Approval Program reforms included in the Omnibus bill and highlight some questions and considerations as FDA implements these new requirements.

Summary of Accelerated Approval Program Reforms

Section 3210 of the Omnibus bill, Modernizing Accelerated Approval, amends Section 506(c) of the Federal Food, Drug, and Cosmetic Act (FFDCA) to do the following:

Revoking approval

- Clarify FDA's authority to revoke a drug's approval based on new safety or efficacy data with new specific procedures and processes that must be followed, including providing
    - "Due notice" to the drug sponsor,
    - "An explanation for the proposed withdrawal,"
    - "An opportunity for a meeting with the [FDA] Commissioner or the Commissioner's designee,"
    - "An opportunity for written appeal" to the FDA Commissioner or "a designee of the Commissioner who has not participated in the proposed withdrawal of approval,"
    - "An opportunity for public comment on the proposal to withdraw approval,"
    - "A summary of the public comments received, and the Secretary's response to such comments, on the [FDA] website," and,
    - "Convening and consulting an advisory committee on issues related to the proposed withdrawal, if requested by the sponsor and if no such advisory committee has previously advised the Secretary on such issues with respect to the withdrawal of the product prior to the sponsor's request."

Drug Sponsor Requirements

- Allow FDA to require "as appropriate, a study or studies to be underway prior to approval, or within a specified time period after the date of approval, of the applicable product."
- Require drug sponsor to provide study progress reports "including progress toward enrollment targets, milestones, and other information as required by the Secretary, not later than 180 days after the approval of such drug and not less frequently than every 180 days thereafter, until the study is completed or terminated."

FDA Requirements

- Require FDA to specify conditions for a post-approval study or studies, which "may include enrollment targets, the study protocol, and milestones, including the target date of study completion."
- In cases where FDA determines a post-approval trial is not necessary, require FDA to publish on its website "the rationale for why such study is not appropriate or necessary."
- Require the FDA Commissioner to issue draft guidance not later than 18 months after enactment and final guidance not later than one year after the close of public comment. Guidance must describe the following:
    - "How sponsor questions related to the identification of novel surrogate or intermediate clinical endpoints may be addressed in early-stage development meetings" with FDA,
    - "Use of novel clinical trial designs that may be used to conduct appropriate post-approval studies,"
    - "The expedited procedures" described in the FFDCA, and
    - "Considerations [on] the use of surrogate or intermediate clinical endpoints that may support the accelerated approval… including considerations in evaluating evidence related to… such endpoints."

[7] FDA Approves LEQEMBI™ (lecanemab-irmb) Under the Accelerated Approval Pathway for the Treatment of Alzheimer's Disease. Eisai and Biogen. January 7, 2023. Available at https://www.eisai.com/news/2023/pdf/enews202301pdf.pdf.

[8] U.S. Food and Drug Administration Issues Complete Response Letter for Accelerated Approval of Donanemab. Eli Lilly. January 19, 2023. Available at https://investor.lilly.com/news-releases/news-release-details/us-food-and-drug-administration-issues-complete-response-0.

- Establish an intra-agency Accelerated Approval Council within one year of enactment, with the following members: Director of the Center for Drug Evaluation Research, Director of the Center for Biologics Evaluation and Research, Director of the Oncology Center of Excellence, Director of the Office of New Drugs, Director of the Office of Orphan Products Development, Director of the Office of Tissues and Advanced Therapies, Director of the Office of Medical Policy, and at least 3 directors of review divisions or offices overseeing products approved under accelerated approval, including at least one director within the Office of Neuroscience. The Council must convene not fewer than 3 times per calendar year to "discuss issues related to accelerated approval, including any relevant cross-disciplinary approaches related to product review with respect to accelerated approval" and "engage with product review teams to support the consistent and appropriate use of accelerated approval."

Enforcement

- Increase enforcement of program noncompliance by making failure to conduct the required studies a violation of the FFDCA. Specifically, the bill amends section 331 with a new section requiring sponsors to conduct such post-accelerated approval studies "with due diligence" and to "submit timely reports."

Outstanding Questions and Next Steps

Given recent comments from the FDA Commissioner Robert Califf, we can likely expect that the agency intends to aggressively take advantage of the new authorities granted to it in operating the Accelerated Approval Program. At the JPM Healthcare Conference, Califf noted that "Congress gave us some teeth to really enforce" the requirement that drug sponsors be "committed to getting the answer as to whether [an accelerated approval drug] actually really works."[9] However, many outstanding issues and questions will likely not be fully addressed until FDA provides the statutorily required guidance. Among other issues, guidance could clarify the following:

- Whether FDA will use its authority to require that post-approval studies be underway prior to accelerated approval and, if so, whether the requirement will apply to all drugs or selected drug classes, for example.
- Further details on which surrogate endpoints and evidence can be used to receive accelerated approval. The use of surrogate endpoints could vary across different drug types, depending on the nature of available evidence and the level of need for additional therapeutics in a clinical area.
- How the agency plans to work with drug sponsors to develop post-approval trials.
- The process FDA will use to develop study protocols and other requirements.
- The process for withdrawal of a product, including what is considered "due notice," how the appeal process will work, the public comment process, and the role of the advisory committee in reassessing the withdrawal.
- How FDA will use its additional enforcement authority, including whether it will criminally prosecute companies that do not meet study requirements "with due diligence" or miss progress report deadlines. Although the agency may use less severe enforcement tools, such as warning letters, for less egregious violations, the threat of prosecution could impact the way that drug sponsors approach post-approval studies.

The reforms of the Accelerated Approval Program included in the Omnibus are likely to address some of the most serious concerns of lawmakers, patient advocates, and other stakeholders; however, how aggressively the FDA will use this new authority remains to be seen. Forthcoming guidance will provide much needed insight on outstanding issues, such as how FDA will implement its new authorities, what steps drug sponsors need to take now for drugs currently under or expected to be pursued for accelerated approval, the timing and level of evidence required in post-approval trials, and the role of the public and other stakeholders in informing decisions about what products should be granted accelerated approval and based on what evidence.

[9] Bell et al. JPM23: Califf on accelerated approvals, biotech startups' looming cliff and an explanation from Editas. BioPharma Dive. January 10, 2023. Available at https://www.biopharmadive.com/news/jpm-2023-califf-fda-startups-funding-cliff-editas/640107/.

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