KPMG

Center Insight Brief

Center for Healthcare Regulatory Insight

April 2022

FDA's Accelerated Approval Program: Accelerated Pathway for Reform?

The Accelerated Approval Program was established by the Food and Drug Administration (FDA) in 1992 to allow for earlier approval of drugs that treat serious conditions and that fill an unmet medical need based upon a surrogate endpoint that is likely to predict a clinical benefit.[1] The pathway was codified in 2012 with the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA). Drugs approved through the Accelerated Approval Program must 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] As of December 31, 2021, the FDA had granted 278 accelerated approvals.[3] The proportion of drugs granted accelerated approval has increased in recent years. In 2021, 14 of 50 drugs approved by the FDA (28%) used the pathway, up from 22.6% (12 of 53) in 2020, 18.7% (9 of 48) in 2019, and 6.7% (4 of 59) in 2018.[4]

Sponsors of drugs approved through the Accelerated Approval Program must produce data establishing that the surrogate endpoint or intermediate clinical endpoint is "reasonably likely" to predict a drug's intended clinical benefit and agree to conduct post-marketing confirmatory stud(ies) to verify such benefit. Failure to demonstrate clinical benefit may result in withdrawal of approval or adjustment of the labeled indication. As of early 2021, roughly half of drugs receiving accelerated approvals have 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 An additional 6.3% of approvals have been withdrawn by the drug sponsor and 44.3% have been on the market a median of 1.9 years.[5]

Increasing Demand for Reform

On June 7, 2021, FDA granted accelerated approval to Biogen's Aduhelm, an amyloid beta-directed monoclonal antibody indicated to treat Alzheimer's disease, despite a recommendation against approval by FDA's Peripheral and Central Nervous Systems (PCNS) Drugs Advisory Committee due to uncertain clinical

[1] Accelerated Approval. US Food and Drug Administration. Available at https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

[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] CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint. US Food and Drug Administration. December 31, 2021. Available at https://www.fda.gov/media/151146/download

[4] 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

[5] 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

benefit.[6] 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, have led to increased calls for reforms to the Program. In fact, during his confirmation process, FDA Commissioner Robert Califf pledged to Senate Finance Chair, Ron Wyden (D-OR), that reforming the accelerated approval pathway would be "a high priority" and that the agency would "encourage the diligent initiation of well-designed confirmatory studies."[7] Indeed, FDA recommended in its FY2023 budget justification that Congress grant FDA additional authority to impose stricter requirements for drug sponsor use of the Accelerated Approval Program, including requiring follow-on studies that are "adequately designed … and can be completed in a timely manner."[8]

On March 7, 2022, House Energy and Commerce Committee Chair, Frank Pallone (R-NJ), introduced the *Accelerated Approval Integrity Act of 2022* (H.R. 6963).[9] The following day, the Committee's Ranking Member, Congresswoman Cathy McMorris Rodgers (R-WA), introduced an alternative bill, *Accelerating Access for Patients Act of 2022* (H.R. 6996).[10] While the two bills both seek to tighten Accelerated Approval Program pathway requirements, they take different approaches to similar goals, summarized below:

Key Provisions of the *Accelerated Approval Integrity Act of 2022* (H.R. 6963)

- Codifies requirements for manufacturers to conduct post-approval studies on drugs that receive accelerated approval;
- Requires manufacturers to enter into an agreement with FDA on how the studies will be conducted before the agency can grant accelerated approval, which may include details like enrollment targets, milestones, and study design;
- Allows FDA to require studies to be underway at the time of approval;
- Requires more frequent updates on post-approval studies, including updates on enrollment targets, milestones, and study design;
- Outlines expedited procedures for withdrawing approval, which would include due notice and opportunity for a written appeal to FDA, an opportunity for public comment, and may include FDA convening and consulting an advisory committee;
- Specifies additional instances in which an accelerated approval may be withdrawn, including manufacturer failure to achieve agreed-upon enrollment targets, milestones, or timely study completion;
- Automatically expires accelerated approval status one year after post-approval studies are scheduled to be completed, and in no case later than five years after approval, unless the post-marketing study has been completed and verified the clinical benefit, or the Secretary of Health and Human Services determines that adequate progress has been made;
- Requires additional information on accelerated approval drugs' labels; and
- Makes failure to submit reports or act with due diligence on post-approval studies prohibited acts subject to penalties.

Key Provisions of the *Accelerating Access for Patients Act of 2022* (H.R. 6996)

- Expands eligibility for accelerated approvals to include consideration of product safety and effectiveness based on known benefit-risk profile, taking into account "the severity, rarity, or prevalence of the disease or condition and the availability or lack of alternative treatments;"

---

[6] 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

[7] Dr. Robert Califf letter to Senator Ron Wyden. February 8, 2022. Available at https://www.finance.senate.gov/imo/media/doc/020822%20Califf%20letter%20to%20Wyden%20on%20Accelerated%20Approval.pdf

[8] Food and Drug Administration. Fiscal Year 2023 Justification of Estimates for Appropriations Committees. Available at https://www.fda.gov/media/157192/download

[9] Accelerated Approval Integrity Act of 2022, H.R. 6963, 117th Congress (2022). Available at https://www.congress.gov/117/bills/hr6963/BILLS-117hr6963ih.pdf

[10] Accelerating Access for Patients Act of 2022, H.R. 6996, 117th Congress (2022). Available at https://www.congress.gov/117/bills/hr6996/BILLS-117hr6996ih.pdf

- Requires creation of a Comprehensive Clinical Development Plan with HHS-established procedures for drug sponsors to meet with FDA officials to determine applicability of Accelerated Approval requirements and agree upon surrogate or intermediate clinical endpoints, post-approval study design, milestones, and strategy for inclusion of diverse populations;
- Requires HHS to approve study protocol or ask for changes to a company's post-market study plan within 60 days of submission;
- Permits use of clinical evidence, patient registries, or other sources of real-world evidence to verify clinical benefits in post-approval studies;
- Specifies instances in which an accelerated approval may be withdrawn;
- Requires HHS to issue a report annually to the House Energy and Commerce Committee and Senate HELP Committee describing the number of applications submitted for approval that included real world evidence in post-approval studies, and the number of applications for which real world evidence was deemed appropriate to support or fulfill post-approval studies;
- Requires FDA to issue draft guidance within 18 months of enactment and final guidance within 18 months of public comments closing; and
- Allows FDA to grant accelerated approval to products prior to issuing initial draft or final guidance.

Further details of provisions of the respective bills are included to this Brief as an Appendix.

Next Steps and Implications

As of this writing, there is no companion legislation to either bill in the Senate and the legislative days in this Congress are dwindling. Furthermore, Senate HELP Committee Ranking Member, Richard Burr (R-NC), recently expressed support for broadening the use of the Accelerated Approval Program, particularly to increase access to treatments for rare diseases and neurological disorders, suggesting possible interest in expanding, rather than narrowing, the scope of the program.[11]

As evidenced by these bills, there is acknowledgement that some drugs under the Accelerated Approval Program pathway may be too hastily approved and/or not held to a high enough standard for post-approval studies to validate clinical benefit. However, there is also support from some Members and patient groups for expanding the Accelerated Approval Program, despite programmatic shortcomings. It is therefore possible that program reforms, as well as some program expansion, could be considered and addressed in some fashion as part of the reauthorization legislation for Prescription Drug User Fee Act VII, which expires on September 30, 2022, to ensure there is no disruption in funding for FDA's drug review process.

[11] Beth Wang. GOP Senators Urge Broader Use of FDA's Accelerated Approval Path. Inside Health Policy. April 6, 2022. Available at https://insidehealthpolicy.com/daily-news/gop-senators-urge-broader-use-fda%E2%80%99s-accelerated-approval-path/

To learn more about the KPMG Center for Healthcare Regulatory Insight, please visit us online at kpmg.com/us/hcls-hcinsight.

You can also subscribe to our weekly news roundup, Around the World of US Healthcare in 360 Words or Less.

Contact us

S. Lawrence Kocot
Principal and National Leader
Center for Healthcare
Regulatory Insight
202-533-3674
lkocot@kpmg.com

Tracey McCutcheon
Specialist Director
Center for Healthcare
Regulatory Insight
202-533-5380
traceymccutcheon@kpmg.com

Ross White
Director
Center for Healthcare
Regulatory Insight
202-533-3691
rosswhite@kpmg.com

Appendix	
Accelerated Approval Integrity Act of 2022 (H.R. 6963)	Accelerating Access for Patients Act of 2022 (H.R. 6996)
	Accelerated Approval Eligibility • Expands eligibility for accelerated approval to include consideration of product safety and effectiveness based on known benefit-risk profile, taking into account "the severity, rarity, or prevalence of the disease or condition and the availability or lack of alternative treatments"

Post-approval studies:
• Requires drug sponsor to "conduct appropriate, adequate, and well-controlled post-approval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit"
• Requires sponsor to enter into an agreement with FDA on how the studies will be conducted before the agency can grant accelerated approval, which "may include requirements regarding enrollment targets, study protocol, and milestones, including the target date of study completion"
• Allows FDA to require studies to be underway at the time of approval
• Requires more frequent updates on post-approval studies, including updates on enrollment targets, milestones, and study design
	Clinical Development Plan and Post-Approval Studies
	• Requires HHS Secretary to establish procedures for drug sponsor seeking accelerated approval to meet with FDA officials to develop a plan to "provide clarity for the sponsor regarding applicability of the requirements" for accelerated approval. The plan shall include
	  ○ Determination as to whether the product is intended to treat an unmet medical need
	  ○ Agreement on surrogate or intermediate clinical endpoints to be assessed
	  ○ Agreement on design of studies to support approval
	  ○ Plan for post-approval study to satisfy requirements, including reaching agreement on study design
	  ○ Plan for reaching agreement on types of developmental milestones to be met
	  ○ Strategy for inclusion of diverse populations
	• Approval is subject to one or both of the following:
	  ○ Sponsor conducts appropriate post-approval studies (including clinical evidence, patient registries, or other sources of real world evidence) to verify and describe predicted effects on irreversible morbidity or mortality or other clinical benefits
	  ○ Sponsor submits copies of all promotional materials related to the product during pre-approval review period and, following approval and for any period thereafter determined appropriate by HHS Secretary, at least 30 days prior to dissemination of materials

Appendix	
Accelerated Approval Integrity Act of 2022 (H.R. 6963)	Accelerating Access for Patients Act of 2022 (H.R. 6996)
	• HHS Secretary shall issue guidance a) describing criteria, processes, and other general considerations for determining safety and effectiveness, and b) on the use of novel clinical trial designs that may be used to conduct post-approval studies • HHS Secretary must approve study protocol or ask for changes to a company's post-market study plan within 60 days of submission
	Evidence • States evidence to support an endpoint is likely to predict clinical benefit may include epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers

Withdrawal of Approval
• Outlines reasons an accelerated approval can be withdrawn using expedited procedures
  ○ failure to conduct any required post-approval study of the product with due diligence
  ○ failure to achieve agreed-upon enrollment targets, milestones, or timely study completion
  ○ failure to submit required reports
  ○ post-approval studies fail to verify or show reduction in morbidity/mortality or other clinical benefit
  ○ other evidence showing the product is not safe or effective under conditions of use
  ○ dissemination of false or misleading promotional material
• Outlines expedited procedures for withdrawing approval, which would include due notice and opportunity for a written appeal to FDA, an opportunity for public comment, and may include FDA convening and consulting an advisory committee
	Withdrawal of Approval
	• Outlines reasons an accelerated approval can be withdrawn using expedited procedures
	  ○ failure to conduct any required post-approval study of the product with due diligence
	  ○ post-approval studies fail to verify or show reduction in morbidity/mortality or other clinical benefit
	  ○ other evidence showing the product is not safe or effective under conditions of use
	  ○ dissemination of false or misleading promotional material

Appendix	
Accelerated Approval Integrity Act of 2022 (H.R. 6963)	Accelerating Access for Patients Act of 2022 (H.R. 6996)
Automatic Expiration • Accelerated approval automatically expires one year after post-approval studies are scheduled to be completed, and in *no case later than five years after approval*, unless the post-marketing study has been completed and verified the clinical benefit OR the Secretary of Health and Human Services determines that adequate progress has been made and that the study may continue	

Labeling
• Requires additional information in accelerated approval drugs' labeling
  ○ Statement it was approved under accelerated approval
  ○ Statement that continued approval is subject to post-marketing studies to verify clinical benefits
  ○ Identification of clinical endpoints that are under study and known limitations of that surrogate or intermediate endpoint in determining benefit
  ○ Succinct description of product and uncertainty about anticipated clinical benefits and discussions of available evidence
  ○ Any other information required by HHS Secretary	

Report on Post-marketing Studies • Drug sponsor must submit to the Secretary a report of the progress of any study required under section 506(c), including progress toward any agreed-upon enrollment targets, milestones, and other information as required by the Secretary, not later than 90 days after the approval of such drug and not less frequently than every 90 days thereafter	

Appendix	
Accelerated Approval Integrity Act of 2022 (H.R. 6963)	Accelerating Access for Patients Act of 2022 (H.R. 6996)
Enforcement • Makes failure to submit reports or act with due diligence on post-approval studies prohibited acts subject to penalties.	

	HHS Reporting
	• Not later than 180 days after enactment, and annually thereafter, HHS Secretary must submit to House Energy and Commerce Committee and Senate HELP Committee a report describing
	  ○ Circumstances and number of applications submitted for accelerated approval for which real world evidence was deemed appropriate to support or fulfill post-approval studies
	  ○ Circumstances and number of applications submitted for approval for which real world evidence was submitted for post-approval studies

	Guidance • Requires issuance of FDA draft guidance not later than 18 months after enactment • Requires issuance of FDA final guidance not later than 18 months after close of public comments on draft guidance • Allows FDA to grant accelerated approval prior to issuing initial draft or final guidance