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FDORA Changes to the FDA Accelerated Approval Program

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Enacted on December 29, 2022, the Consolidated Appropriations Act (the year-end omnibus spending bill) includes the Food and Drug Omnibus Reform Act (FDORA), which enhances the Food and Drug Administration's authority in several key areas. One such section addresses recent criticism of the FDA around the accelerated approval pathway. The provisions seek to increase transparency around this regulatory pathway and also grant new authorities to the FDA to ensure that sponsors are complying with post-approval requirements that are essential to ensure that only drugs that are safe and effective for their intended use remain on the market.

What is accelerated approval?

Drugs that treat serious or life-threatening conditions and fulfill unmet medical needs are eligible for review by the FDA under the accelerated approval pathway.[1] This pathway is "accelerated" in that it allows sponsors to seek approval with data that demonstrates efficacy based on a surrogate or intermediate endpoint that is believed to **predict** clinical benefit for the disease or condition, rather than primary clinical endpoints. The pathway has been used primarily for drugs aimed at diseases that progress slowly, such that waiting for trials that demonstrate primary clinical endpoints would result in a yearslong delay before such drugs could be eligible for approval under the traditional pathway.

As a condition of receiving accelerated approval, sponsors are required to conduct post-approval studies to confirm the clinical benefit of the drug. Upon satisfaction of the post-approval requirements, the conditions of accelerated approval are removed. The FDA also can withdraw an accelerated approval if the sponsor fails to conduct the post-approval studies with due diligence, the studies fail to verify the predicted effect or demonstrate that the product is safe or effective under the conditions of use, or if the sponsor disseminates false or misleading promotional material. Prior to FDORA, the law did not provide details of the withdrawal process, except that the drug sponsor must be granted an opportunity for an informal hearing.

The FDA encourages sponsors interested in the accelerated approval pathway to communicate with the agency early in development to discuss proposed surrogate endpoints or intermediate clinical endpoints, plans for confirmatory trials and clinical trial design, among other topics.[2]

Previous critiques of accelerated approval

Since the launch of the accelerated approval pathway in 1992, nearly 300 drugs have been approved through the pathway, including the recent approval of Eisai and Biogen's Leqembi for Alzheimer's disease. In recent years, however, the FDA's standard for accelerated approval has been brought into question, particularly with respect to the agency's decisions to approve Sarepta Therapeutics' Exondys 51 for Duchenne muscular dystrophy and Biogen's Aduhelm for Alzheimer's disease. Exondys 51 was approved despite concerns regarding the reasonable likelihood of clinical benefit, with the head of the Center for Drug Evaluation and Research overruling the findings of an advisory committee and reviewers that evidence of a likely benefit was lacking. Aduhelm was similarly approved under the accelerated approval pathway following unfavorable findings from the FDA's advisory committee and the FDA's Medical Policy and Program Review Council. Based on this, the House of Representatives' Committee on Oversight and Reform and Committee on Energy and Commerce investigated the review process.

The FDA also has come under fire for failing to police sponsors' compliance with post-accelerated approval requirements. An Office of Inspector General (OIG) report issued on September 29, 2022, found that over one-third of drugs granted accelerated approval had incomplete confirmatory trials, and of those studies with incomplete trials, 34% had at least one trial past the original planned completion date. The study also noted that

the multistep process to withdraw products approved through the accelerated approval pathway is lengthy and cumbersome for the agency, which could explain why the FDA has not exercised its authority even when the post-approval data is incomplete.[3]

Changes to accelerated approval program

The key FDORA provisions related to accelerated approval include the following:

Post-approval study elements must be agreed upon pre-approval

FDORA requires the FDA to specify the conditions for any post-approval studies by the date of the accelerated approval and gives the agency much flexibility in setting forth such conditions, which may include enrollment targets, study protocol and milestones – including the target date of study completion.

Timing to start confirmatory studies

FDORA allows, but does not mandate, the FDA to require, as appropriate, that certain post-approval studies already be underway prior to accelerated approval or within a specified time from the date of approval. In other words, certain post-approval studies have to start before the accelerated approval or shortly after it. FDORA leaves it to the agency to explain the standards for setting forth such start date requirements.

Increased transparency for confirmatory studies

If the FDA determines that a post-approval study is not required, the agency must publish the rationale for the determination on its website. FDORA does not specify where the FDA will post this information. Currently, the FDA only posts separately the accelerated approvals and post-market requirements and commitments.

Expedited withdrawal procedure

FDORA creates a formal expedited withdrawal procedure for drugs approved through accelerated approval. The new procedure allows for additional transparency while still affording the sponsor due process. Specifically, the FDA must provide sponsors with notice and an explanation for the proposed withdrawal. The sponsor will have an opportunity to meet with and file a written appeal to the FDA commissioner (or a designee). At the request of the sponsor, an advisory committee also may be convened and consulted on issues related to the proposed withdrawal, if no such committee had previously advised the FDA on the matter. In addition, the FDA must publish the withdrawal proposal for public comments – and later a summary of the comments and the agency's response – on its website.

Previously, the law[4] only required an opportunity for an informal hearing. The regulations[5] provided more details to the withdrawal procedure, including that a hearing would follow Part 15 regulations and that the FDA's withdrawal decision would constitute a final agency action subject to judicial review, if petitioned. The Code of Federal Regulations will be revised to reflect the changes from FDORA.

Post-approval reporting

Pre-FDORA, sponsors were required to submit reports to the FDA annually following approval. FDORA increases the frequency and timing of the reporting period for sponsors to every six months and requires the FDA to publish the reported information on its website.

Enforcement

FDORA amends the prohibited act provisions of the Federal Food, Drug, and Cosmetic Act[6] to include new prohibitions covering the failure to conduct **with due diligence** any post-approval study required by an accelerated approval and the failure to submit timely progress reports for post-approval studies.

Guidance documents

FDORA requires the FDA to issue multiple guidance documents regarding accelerated approval and post-

approval studies, including guidance documents that address the use of novel clinical trial design for post-approval studies, as well as guidance addressing discussion of novel surrogate or intermediate clinical endpoints in early stages with the FDA. All draft guidance must be issued within 18 months of the enactment of FDORA (by June 29, 2024), with final guidance required no later than one year after the close of the public comment period on the draft guidance.

For highly technical issues, including, for example, the development of efficacy endpoints for rare diseases,[7] FDORA directs the FDA to promulgate non-binding guidance (rather than regulations) to provide information to the industry.

Accelerated approval council

FDORA requires the FDA to form an intra-agency coordinating council within one year of the enactment of FDORA. Membership includes the directors of seven specified centers and offices within the FDA, as well as at least three directors of review divisions or offices overseeing products approved under the accelerated approval pathway.[8] The council is tasked with ensuring consistent and appropriate use of accelerated approval across the agency through direct engagement with product review teams. The council also is required to publish an annual report of its activities on the FDA's website.

Putting FDORA in context – What's next for industry and the FDA?

Overall, the new legal requirements attempt to address the concerns that have emerged around the accelerated approval pathway in recent years and may help reverse some of the trends found within OIG's report. The additional requirements around post-approval studies and revised timelines for progress reports are more onerous for sponsors, but the forthcoming agency guidance, formation of the accelerated approval council, and the multiple new reporting and publishing requirements related to the accelerated approval pathway will likely increase transparency and help restore the integrity of the program. Making accelerated approval a viable and credible pathway is in the best interests of the FDA, patients and sponsors and will hopefully help avoid the degree of cost-benefit battle over pricing and reimbursement that Biogen faced with Aduhelm.[9]

Although FDORA establishes multiple new requirements with respect to accelerated approval, the text of the law is relatively sparse, leaving open questions as to how the FDA will implement the new requirements. With respect to confirmatory studies, the law does not contain criteria specifying when it is "appropriate" to require a study to begin – prior to approval or shortly after – leaving the determination up to the FDA.[10] This begs the question as to whether the FDA will make the determination on a case-by-case basis, or whether it will develop guidance or formalize any specific criteria used to make the determination. The law also leaves open what constitutes an adequate rationale to not require a post-approval study and who ultimately is responsible for developing such a rationale.

The expedited withdrawal procedure contained in the law also contains ambiguity as to the sequence and timing for the various reviews and appeals offered to the sponsor. Must a sponsor exhaust all other available avenues before requesting an advisory committee, or may a sponsor avail itself of this option immediately? Is consultation with a withdrawal advisory committee governed by Part 14?[11] When in the decision-making process does the FDA's action constitute final agency action such that a sponsor may petition for judicial review? Given these open questions, as well as the tension now created between FDORA and current regulations,[12] it will be challenging for the FDA to update these regulations and promulgate new guidance consistent with the statutory mandate.

Finally, questions remain as to whether and how the FDA will take advantage of the new enforcement provisions. Given that the accelerated approval pathway aims to fulfill unmet needs for patients dealing with serious or life-threatening conditions, the agency may be hesitant to take actions, such as product seizure, that could adversely impact these patient populations. The FDA also will face oversight pressure to utilize the new enhanced withdrawal and enforcement authorities afforded under FDORA to ensure that the accelerated approval pathway is not abused.

With all of these open questions, as well as the new obligations placed upon the FDA, it will likely be years

before the full effects of the law are felt. Cooley's FDA team will continue to monitor updates in this space. Please reach out to us if you have any questions, including how the improved transparency may benefit your product candidate's potential development pathway.

Senior regulatory analyst Kelly Marco also contributed to this alert.

Notes

1. 21 USC §356(c).
2. *See* Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014, p.16.
3. The study highlights hydroxyprogesterone caproate (Makena), which was approved through the accelerated approval pathway in 2011. Although the sponsor completed the requisite study, it was completed 64 months past the original planned date and failed to demonstrate a clinical benefit. The FDA began the withdrawal process in 2020, which included numerous exchanges between the agency and sponsor, as well as a request for a hearing. A hearing before the commissioner and an advisory committee was held in October 2022, with the committee voting to remove Makena from the market. The drug is currently still on the market, as the final decision from the commissioner is pending.
4. 21 USC §356(c)(3).
5. 21 CFR §314.530.
6. 21 USC §331.
7. Sec. 3208(d) of the Consolidated Appropriations Act.
8. The specified directors include the Directors of the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, the Director of the Oncology Center of Excellence, the Director of the Office of New Drugs, the Director of the Office of Orphan Products Development, the Director of the Office of Tissues and Advanced Therapies and the Director of the Office of Medical Policy.
9. Biogen received considerable criticism to the initial price of the drug following approval, which totaled $56,000 per year for a patient of average weight. *See* Noah Higgins-Dunn, "Biogen's $56K price on Aduhelm 'simply unacceptable,' Alzheimer's Association says after vouching for FDA approval," Fierce Pharma, June 14, 2021. In April 2022, the Centers for Medicare and Medicaid Services (CMS) released a policy announcing that, following completion of a longstanding national coverage determination process, the drug would only be covered for Medicare participants enrolled in a CMS-approved study. *See* Centers for Medicare and Medicaid Services, "CMS Finalizes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease," April 7, 2022.
10. The FDA may be keen to take advantage of this new provision. In a November 2022 meeting of the Friends of Cancer Research, FDA Commissioner Robert Califf stated the agency was considering the idea of **requiring** confirmatory studies to be underway before any accelerated approval. *See* Angus Liu, "JPM23: Is GSK's 15-day accelerated approval withdrawal the new normal? Hear FDA Commissioner Robert Califf's response,"Fierce Pharma, January 11, 2023.
11. 21 CFR §314.530(e)(1).
12. 21 CFR §314.530.

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