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FDA to Require Confirmatory Trials Be "Underway" Prior to Accelerated Approval, Per New Draft Guidance

Life sciences companies interested in pursuing accelerated approval should ensure they have a thorough understanding of the complex regulatory landscape and engage in early discussions with FDA regarding their drug development programs.

This week, the U.S. Food and Drug Administration (FDA) announced in draft guidance that, under new authority granted the agency, FDA "generally intends" to require that confirmatory trials be underway prior to approval of drugs under the accelerated approval pathway.[1] Accordingly, sponsors will need to invest significant time and effort up front—and earlier in the development process—to design and initiate confirmatory trials prior to even receiving accelerated approval, a potentially costly and time-consuming prospect.

FDA's Draft Guidance on Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway. The draft guidance describes FDA's interpretation of the term "underway" and discusses policies for implementing this requirement, including factors FDA intends to consider when determining whether a confirmatory trial is underway before accelerated approval. FDA is required to finalize draft guidances before their policies take effect, but, as a practical matter, the agency generally follows the principles set forth in guidance prior to finalization.

Future of the Draft Guidance Under the New Administration. There is some uncertainty as to whether this draft guidance will be finalized or otherwise continue to reflect agency policy under

the incoming Trump administration. During Congressional negotiations on the new authority, some Republican lawmakers and industry stakeholders expressed concerns about granting FDA the authority to require that confirmatory studies be underway at the time of accelerated approval, citing potential delays in approval and challenges related to study enrollment. FDA has provided for certain exceptions to the new proposed policy, including for drugs intended to treat rare diseases, but new FDA leadership may seek to relax the policy further or move to abandon it altogether.

Key Highlights:

- **Law Provides that FDA "May Require" Confirmatory Trials to Be "Underway" Before Approval**: For drugs granted accelerated approval, companies have been required to conduct confirmatory studies post-approval to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. However, some stakeholders have expressed concerns that such post-approval studies were not conducted in a timely manner. Accordingly, in the Food and Drug Omnibus Reform Act (FDORA), enacted in December 2022, Congress amended Section 506(c) of the Federal Food, Drug, and Cosmetic Act to provide FDA additional authorities to help ensure timely completion of such trials. For instance, FDA "may require, as appropriate" a confirmatory trial or trials to be "underway" before approval, or within a specified time period after the date of approval.[3]
- **FDA Generally Intends to Require Confirmatory Trials to Be Underway Before Approval**: FDA's draft guidance clarifies that, under its new authority, the agency generally intends to require that confirmatory trials be underway before granting accelerated approval. According to FDA, this requirement aims to ensure that post-approval studies, which are necessary to confirm clinical benefit, begin without delay. FDA notes that such confirmatory trials would generally be randomized, controlled trials.
- **Definition of "Underway"**: In the draft guidance, FDA outlines its interpretation of the term "underway," specifying that a confirmatory trial is considered to be underway if (1) it has a target completion date consistent with diligent and timely conduct of the trial, considering the nature of the trial design and objectives, (2) the sponsor's progress and plans for post-approval conduct of the trial provide sufficient assurance of timely completion, and (3) enrollment has started.
- **Exceptions**: In certain cases, such as trials dependent on future events (e.g., an infectious disease outbreak), FDA may accept that conducting a confirmatory trial is not feasible before approval.
- **Considerations for Rare Diseases**: For certain rare diseases, FDA may choose not require that a confirmatory trial be underway prior to approval, such as when non-randomized studies are sufficient to verify clinical benefit, given that non-randomized study designs can reduce challenges associated with study enrollment and completion. FDA also may not require a confirmatory trial to be underway in instances in which companies face unique challenges with initiating trials prior to approval, if appropriate justification is provided. The draft guidance notes that this exception is especially pertinent with respect to drugs intended to treat rare diseases with "very small populations with high unmet need."
- **Engagement with FDA**: FDA encourages companies seeking accelerated approval to engage early with the agency. Early discussions about confirmatory trial designs,

timelines, and justifications for the proposed approaches are critical to aligning expectations prior to submission of an application.

- **Comment Period**: The comment period for the draft guidance will close on March 10, 2025.[4] Comments may be submitted to Docket No. FDA-2024-D-3334.
- **Additional FDA Guidance**: This draft guidance follows on the heels of another draft guidance on the accelerated approval pathway that FDA issued in December 2024.[5] That draft guidance focuses on accelerated approval endpoints, evidentiary criteria for accelerated approval, the conduct and design of confirmatory trials, and new expedited withdrawal procedures. The guidance emphasizes the importance of FDA-industry collaboration throughout the development process, especially in navigating accelerated approval eligibility, clinical trial design, study endpoints, and the planning and conduct of confirmatory trials. The comment period for the December 2024 draft guidance closes February 4, 2025; comments may be submitted to Docket No. FDA-2024-D-2033.[6]

Next Steps. Life sciences companies interested in pursuing accelerated approval should ensure they have a thorough understanding of the complex regulatory landscape and engage in early discussions with FDA regarding their drug development programs. Early engagement to clarify the path for accelerated approval, including timing for confirmatory trial initiation, is essential to navigating the accelerated approval pathway effectively.

[1] FDA, Draft Guidance for Industry: Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway (Jan. 7, 2025), available at: https://www.fda.gov/media/184831/download.

[2] 21 U.S.C. § 356(c); 21 CFR Part 314, Subpart H; *id.* Part 601, Subpart E.

[3] Pub. L. No. 117–328, div. FF, title III, §3210(a), 136 Stat. 4459, 5822 (Dec. 29, 2022), codified at 21 U.S.C. § 356(c)(2)(D).

[4] 90 Fed. Reg. 1171 (Jan. 7, 2025).

[5] FDA, Draft Guidance for Industry: Expedited Program for Serious Conditions-Accelerated Approval of Drugs (Dec. 6, 2024), available at: https://www.fda.gov/media/184120/download.

[6] 89 Fed. Reg. 97011 (Dec. 6, 2024).

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Gibson Dunn's lawyers are available to assist in addressing any questions you may have regarding the issues discussed in this update. Please contact the Gibson Dunn lawyer with whom

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