Takeaways From FDA's Updated Confirmatory Trial Guidance

By **Dominick DiSabatino, Audrey Mercer and Julian Klein** (January 23, 2025)

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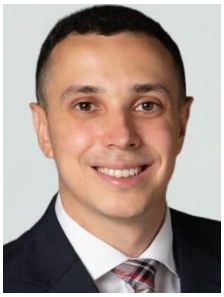

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On Jan. 6, the U.S. Food and Drug Administration released a draft guidance about accelerated approval and considerations for determining whether a confirmatory trial is underway.[1]

The draft guidance responds to the FDA's new authorities and responsibilities in administering the accelerated approval program under the 2023 Consolidated Appropriations Act, which the FDA addressed at a high level in an initial draft guidance.[2]

The new draft guidance narrows in on heightened requirements for confirmatory trials and outlines the granular process for ensuring that confirmatory trials are underway to verify the clinical benefits of accelerated approval drugs. The FDA is inviting comments to the draft guidance, with a deadline set for March 10.

Background

The accelerated approval program balances the urgent need for treatment of certain serious or rare conditions with the equally important need to ensure patient safety by allowing for the conditional approval of drugs for serious or rare conditions before the drug has been fully proven safe and effective under the traditional three-phase clinical study route, based on the identification of a surrogate or intermediate endpoint reasonably likely to predict the drug's ultimate clinical benefit.[3]

As a condition of accelerated approval, sponsors are required to perform post-market confirmatory trials to verify anticipated clinical benefits, i.e., support a complete finding of safety and efficacy that meets the FDA's standard for full market approval. Accordingly, the successful completion of these confirmatory studies converts a drug's accelerated approval to a traditional approval.

New Confirmatory Trial Requirements

In this draft guidance, the FDA provides a detailed explanation of the heightened requirement — established in last month's draft guidance — that confirmatory trials be underway prior to accelerated approval.

Under the heightened requirement, the FDA mandates that confirmatory trials be "well underway, if not fully enrolled" before accelerated approval is granted, with full enrollment required for instances in which post-approval enrollment would be particularly challenging.

The agency explains that a trial is underway if it (1) has a target completion date "consistent with diligent and timely conduct of the trial; (2) "the sponsor's progress and plans for post-approval conduct of the trial provide sufficient assurance to expect timely completion of the trial"; and (3) enrollment of the trial has been, at least, initiated.

The draft guidance goes on to provide considerations for determining the target completion date for a confirmatory trial, which must be supported by "clear and sound justification," as well as other measurable benchmarks that the FDA intends to consider in reviewing confirmatory trial plans, such as recruitment and retention goals, site activation statistics, and accrual rates.

The draft guidance does establish that the FDA may make exceptions to the heightened confirmatory trial requirement for scenarios like unexpected future events or rare diseases with very small populations and high unmet need, where nonrandomized studies may be adequate and appropriate justification is made, but makes clear that such exceptions will likely be few and far between.

Further, as it did in its initial draft guidance last month, the FDA emphasizes the importance in ongoing collaboration with sponsors, and encourages sponsors to engage in early and frequent discussions with the agency to align on clinical trial plans and timelines.

Takeaways

The 2023 Consolidated Appropriations Act served as a clear signal to the FDA to tighten the reins on the accelerated approval program in light of the significant lag time between accelerated approval and full approval of accelerated approval drugs being used to treat patients.

Data shows many drugs lingering on the market for years before confirmatory trials were initiated, if they were ever started at all.

This draft guidance appears to be doing exactly that, but in a more prescriptive manner than last month's high-level framework guidance. Here, the FDA underscores that confirmatory trials are the key to ensuring that balance between urgent access to potentially life-saving drugs and patient safety, and, helpfully, sets out clearer operational expectations for sponsors' execution of such trials.

Although the 2023 Consolidated Appropriations Act gave the FDA until June of this year to develop the draft guidance, the agency put it out just a month after its initial draft guidance — no doubt because the two are meant to work in tandem.[4]

The prior draft guidance introduced the heightened requirements for the accelerated approval program, and the latter honed in on more granular confirmatory trial requirements, clearly defining when the FDA considers a trial to be underway and putting sponsors on notice that the FDA will be monitoring these trials far more scrupulously than in years past.

Specifically, when reviewing accelerated approval applications, the FDA will be monitoring to ensure that sponsors have established a full plan with measurable benchmarks and that the enrollment process has been, at least, initiated.

These heightened requirements communicate that the FDA wants accelerated approval drugs to be as close to traditional approval route as possible at the time of application, without swallowing the purpose of the accelerated approval program in the first place.

The new draft guidance provides actionable steps for sponsors to take in developing and initiating confirmatory trials to support accelerated approval applications, which furthers the overall goal to expedite the period of time that a drug has "accelerated approval" status, as

opposed to traditional approval status.

Moreover, sponsors may also be motivated not only by these new requirements — as the FDA will either reject initial accelerated approval or initiate a post-market withdrawal if its detailed new confirmatory trial requirements are not met — but by forces at play in the greater healthcare landscape.

For example, a Pennsylvania-based insurer, Independence Blue Cross, recently issued a policy excluding nononcology accelerated approval drugs from most benefit plans.[5]

If other payors adopt this approach, and accelerated approval drugs are widely excluded from insurance coverage, sponsors could be financially motivated to complete confirmatory trials to prove full safety and efficacy of their drugs, which may prove to be a much stronger driving force than the regulatory motivation established in the new draft guidance.

Ultimately, whatever the impetus, it appears that the industry may be headed toward more expeditious completion of confirmatory trials for accelerated approval therapies — which, in any case, is probably a good thing for patients.

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[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-and-considerations-determining-whether-confirmatory-trial-underway.

[2] https://www.fdalawblog.com/2024/12/articles/fda/new-accelerated-approval-guidance-underscores-need-for-accountability/.

[3] Section 506(c)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

[4] Not to mention, of course, that FDA may be trying to sure up regulation through guidances in light of uncertainties regarding its authority under the new administration.

[5] See Claim Payment Policy Bulletin — Drugs, Biologics, or Gene Therapies with an Accelerated Approval, Independence Blue Cross (Jan. 1, 2025).