Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (OCE/CDER) Tamy Kim at tamy.kim@fda.hhs.gov or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Procedural

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Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The accelerated approval provisions in section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) provide that FDA may grant accelerated approval to:

> [A] product for a serious or life-threatening disease or condition… upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.[2]

For drugs[3] granted accelerated approval, sponsors have been required to conduct confirmatory studies postapproval to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit.[4] In the Consolidated Appropriations Act, 2023, Congress amended Section 506(c) of the FD&C Act to provide additional authorities to help ensure timely completion of such trials, including that FDA "may require, as appropriate, a study or studies to

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

[3] For the purposes of this guidance, all references to *drugs or drug products* include both human drugs and biological products regulated by CDER and CBER unless otherwise specified.

[4] Section 506(c)(2)(A)(i) of the FD&C Act; see also 21 CFR 314.510 ("Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.").

be underway prior to approval, or within a specified time period after the date of approval, of the applicable product."[5] This 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[6,7] is underway prior to accelerated approval.[8]

FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

At the time a drug product is granted accelerated approval, FDA has determined that an effect on the endpoint used to support approval – a surrogate endpoint or an intermediate clinical endpoint – is reasonably likely to predict clinical benefit. This allows earlier approval of products intended to treat patients with serious and life-threatening conditions than under traditional approval, where evidence of effectiveness is provided by trials that directly measure an effect on the clinical outcome of interest, or on validated endpoints that have been extensively studied, and commonly require more time to complete.

The risks of this approach include the possibility that patients may be exposed to the risks of a drug that eventually fails to verify clinical benefit. In addition, a drug granted accelerated approval is generally supported by smaller or shorter clinical trials than is typical for a drug

[5] Section 506(c)(2)(D) of the FD&C Act; Pub. L. No. 117-328.

[6] For purposes of section 506(c), FDA interprets the term "study" to include a clinical investigation such as a randomized, controlled trial, which is the type of confirmatory study that is typically required to confirm benefit, as well as other types of studies. In this guidance, references to a confirmatory "trial" or "study" should be understood to mean one or more trials or studies, as appropriate for the relevant product. The terms *trials* and *studies* are used interchangeably in this guidance. Policies regarding studies other than those that may be required under section 506(c) are beyond the scope of this guidance. Sponsors are encouraged to discuss with FDA early in the development process what studies should be conducted to verify and confirm benefit, and conditions for any such studies. The fact that this guidance refers to clinical trials as a type of clinical study should not be read to suggest that FDA considers clinical trials to be studies under section 505(o) of the FD&C Act, which authorizes FDA under specific conditions to require postapproval clinical trials and studies.

[7] The terms *postapproval*, *postmarketing*, and *confirmatory* are used interchangeably throughout this guidance to describe the postapproval studies that FDA requires under section 506(c) of the FD&C Act. 21 CFR 314.510 refers to these postapproval studies as *postmarketing studies*, and the term *confirmatory studies* has commonly been used to describe studies that are completed postapproval and are intended to verify clinical benefit.

[8] Other aspects of the accelerated approval program under section 506(c) of the FD&C Act and FDA regulations are beyond the scope of this guidance. For a fuller discussion of the accelerated approval authorities and FDA's implementation of this program, see the draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024), available at https://www.fda.gov/media/184120/download. When final, this guidance will represent the FDA's current thinking on this topic. Note that we update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

receiving traditional approval, which may mean there is less information about the occurrence of rare or delayed adverse events.

Sponsors have therefore been required to conduct postapproval trials to verify clinical benefit of drugs granted accelerated approval. These confirmatory studies protect the public health and the integrity of the drug approval process by balancing earlier approval of drugs with an assurance that studies will be conducted to resolve residual uncertainty about benefit. Confirmatory trials must be completed with due diligence.[9] It is critical that such studies are promptly initiated and completed in a timely manner to limit the time that a drug is approved for an indication without verification of clinical benefit. This is especially important when the drug has considerable toxicity because the longer the time between approval and verification of clinical benefit the more patients will be exposed to the toxicity without verification of clinical benefit.

While many confirmatory trials are completed in a timely fashion, some have been slow to initiate or have stalled, resulting in long delays or even uncertainty about whether studies can be completed. In the Consolidated Appropriations Act, Congress provided FDA with additional authorities to help prevent such delays, including that FDA may, when appropriate, require a confirmatory study or studies to be underway prior to approval.[9]

III. POLICY FOR REQUIRING A CONFIRMATORY TRIAL TO BE UNDERWAY PRIOR TO APPROVAL

Randomized controlled trials are commonly required to verify clinical benefit of a drug granted accelerated approval and may be challenging to conduct (especially placebo-controlled studies) if the trial is not underway when the drug is approved. For drug development programs intending to seek accelerated approval, FDA generally intends to require that the confirmatory trial(s) be underway prior to the accelerated approval action.[10] If FDA determines that a confirmatory trial must be underway prior to accelerated approval and the trial is not underway, FDA does not intend to grant accelerated approval until this deficiency is addressed.[11] In some cases, when FDA determines that continued enrollment/retention after the drug product is on the market is likely to be especially challenging, FDA may require enrollment to be complete at the time of approval.

[9] FDA intends to address in other guidance complementary authorities added by the Consolidated Appropriations Act, 2023 to help ensure timely study completion. The Consolidated Appropriations Act authorizes FDA to specify the conditions for the progress of a required postapproval trial, which may include enrollment targets, the study protocol, and milestones, including the target date of study completion. See section 506(c)(2)(C) of the FD&C Act. Failure to conduct a trial with due diligence, including with respect to these conditions, can be grounds for withdrawing approval using expedited withdrawal procedures. See section 506(c)(3)(A). The Consolidated Appropriations Act also requires sponsors to submit reports to FDA on the progress of required confirmatory trials approximately every 180 days. See section 506B(a)(2).

[10] Section 506(c)(2)(A), (C), (D).

[11] Section 506(c)(2)(D).

There may be limited circumstances where FDA may not require the confirmatory trial to be underway prior to accelerated approval. For example, the confirmatory trial may be dependent on a future event, e.g., an infectious disease outbreak that has not yet occurred and at the time of approval it would be infeasible to conduct a trial.

For certain rare diseases, the clinically relevant endpoints and disease natural history may enable postmarketing studies that do not require randomization to verify clinical benefit, and this design could reduce the challenge of enrolling and completing the study if it is not underway prior to approval. FDA also recognizes that sponsors seeking approval for drugs intended to treat some rare diseases, especially those with very small populations with high unmet need, may face unique challenges with initiating postapproval confirmatory trials prior to approval. In these circumstances, if appropriate justification is provided, FDA may not require that the confirmatory trial is "underway" prior to accelerated approval.

We encourage sponsors to have early discussions with FDA on the plan and timeline for a postapproval trial. This includes a proposed study design to verify benefit, timing for initiation of the confirmatory study, and appropriate justification for the plan and timeline, so that plans can be agreed upon prior to submission of an application.

IV. UNDERWAY DETERMINATION

Soon after sponsors and FDA reach preliminary alignment that a development program could support accelerated approval, sponsors should request a meeting with FDA to discuss a comprehensive drug development program, which includes plans for confirmatory trial(s), if such plans are not already completed and agreed to. As soon as practicable, and generally soon after the End-of-Phase 2 meeting, there should be agreement between FDA and the sponsor on the design of the confirmatory trial(s) intended to verify and describe clinical benefit, including FDA's review of draft protocol(s). The trial must be feasible to conduct and appropriately designed to verify and describe clinical benefit.

FDA generally intends to consider a confirmatory trial to be "underway" prior to accelerated approval if (1) the trial has a target completion date that is consistent with diligent and timely conduct of the trial, considering the nature of the trial's design and objectives, (2) the sponsor's progress and plans for postapproval conduct of the trial provide sufficient assurance to expect timely completion of the trial, and (3) enrollment of the confirmatory trial has been initiated.

The discussion below provides more information about how target completion dates may be set for the trial and factors that FDA intends to consider in deciding whether a trial is "underway" prior to approval.

A. *Confirmatory Trial Target Completion Date*

The timelines for the confirmatory trial – and in particular, the expected completion date – should be discussed with FDA prior to the submission of the application for accelerated approval. The timeline for confirmatory trial completion should reflect timely completion of the

trial, including diligent conduct of the trial by the sponsor in a manner that limits the amount of time the drug will remain approved without verification of clinical benefit. Considerations to inform the target trial completion date may include:

- Natural history of the disease (e.g., rate of disease progression)
- Availability of alternative treatments (e.g., impact of alternative treatments on study participant recruitment before and after accelerated approval of the drug)
- Anticipated recruitment timeline (including consideration of potential challenges with enrolling or retaining participants in the trial post-accelerated approval, see Section IV.C.)
- Projected timeline for efficacy analysis(es), taking into consideration event rate(s) and/or minimum follow-up required, depending on the outcome(s) of interest

Appropriate target completion dates may differ across therapeutic areas. In oncology, for example, the median time from accelerated approval to verification of benefit is approximately 3 years (including FDA review) and has been decreasing over time.[12] Specific target completion dates for a trial depend on more considerations than can be described here. In all cases, sponsors should provide FDA with a clear and sound justification of the proposed target completion date for the Agency's consideration.

B. *Other Factors that FDA Intends to Consider When Deciding Whether a Trial is Underway*

FDA generally intends to consider a confirmatory trial to be "underway" for purposes of section 506(c)(2)(D) if the sponsor's progress to date and plans for postapproval conduct of the trial (specifically, the trial period intended to provide confirmation of benefit[13]) provide sufficient assurance to expect timely completion of the trial. Considerations include:

- Accrual to date (including the rate of participant accrual), and projected rate of participant accrual. If full enrollment is not expected prior to approval, the sponsor should provide the anticipated timeline for complete enrollment after accelerated approval.
- Number of active sites to date, projected rate of additional site activation

[12] See the November 16, 2023 Oncologic Drug Advisory Committee- FDA Briefing Document at https://www.fda.gov/media/173780/download.

[13] In some cases, a trial design may include more than one phase, e.g., a dosing and run-in study may be conducted with a relatively small number of participants, with protocols that require the results of this phase to be evaluated before initiating the confirmatory phase of the trial (i.e., the phase that is designed to verify the clinical benefit of the drug). For purposes of section 506(c)(2)(D), FDA generally intends to consider enrollment in the confirmatory phase of the trial to be necessary to consider the confirmatory trial to be underway.

(including U.S. and ex-U.S. locations)

The sponsor should propose benchmarks (including, e.g., participant recruitment goal, extent of site activation, proportion of primary endpoint events accrued) consistent with the considerations above that could be assessed at the time of the anticipated accelerated approval to facilitate FDA's determination of whether the trial is underway. Benchmarks should be identified to allow measurement of the sponsor's progress, which if met would provide assurance of the trial's feasibility and allow the Agency to expect timely completion of the trial by an appropriate target completion date. Sponsors should discuss with FDA whether the proposed benchmark(s) is/are acceptable prior to submission of the application. Sponsors are expected to ensure adequate trial resources such that implementation meets benchmark timelines.

If one or more sponsor benchmark(s) have not been met prior to the accelerated approval action date, FDA intends to consider whether accelerated approval is appropriate after taking into consideration the sponsor's justification for the delayed progress and the sponsor's plan to address the delay.[14]

In many instances, including in rare disease development programs, a pre-planned assessment of a surrogate or intermediate clinical endpoint from an ongoing trial may be able to support accelerated approval, with the trial continuing after accelerated approval to verify clinical benefit. Such a trial would be considered underway as long as the trial is expected to complete in a timely manner.

C. *Anticipated Effect of Accelerated Approval on Participant Enrollment and Retention*

In planning the timeline for a confirmatory trial, sponsors should consider factors that may adversely affect accrual, including how an accelerated approval and wider availability of the drug are expected to impact the accrual and conduct of the confirmatory trial. For example, the impact of an accelerated approval may be limited if the confirmatory trial is not being conducted in the approved indication (e.g., the confirmatory trial is to be conducted in an earlier disease stage or different treatment setting). Alternatively, the impact of approval may be greater if the confirmatory trial is in the same population as the approved indication, particularly if the trial is not at full or near full enrollment at the time of accelerated approval. In the latter setting, sponsors should mitigate the anticipated impact of accelerated approval on participant enrollment and retention by completing all or a significant portion of enrollment prior to accelerated approval. Additionally, to ensure the confirmatory trial enrolls and retains sufficient U.S. participants, the sponsor's enrollment strategy should prioritize early U.S. recruitment, and U.S. recruitment should be closer to completion at the time of accelerated approval.

[14] Section 506(c)(2)(D).