

March 29, 2023

Oncology Drug Development in Focus: FDA Offers Recommendations for Clinical Trial Designs to Support Accelerated Approval

On March 24, 2023, FDA published a draft guidance entitled “[Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics](#)” that describes recommendations to promote quality data and efficiency of clinical trials for novel oncology drugs. Notably, the guidance places renewed emphasis on the use of randomized controlled trials (“RCTs”) in lieu of single-arm trials that have commonly been used to support accelerated approvals in the past. This Alert summarizes FDA’s recommendations in the new draft guidance for the design and analysis of clinical trials and the implications for sponsors developing oncology drugs under the accelerated approval pathway.

Attorneys
Joshua Oyster
Rebecca H. Williams

Recent Developments Related to Accelerated Approval

The new draft guidance is the latest action in a series of efforts to reform the accelerated approval program, which has been scrutinized in recent years due to a number of accelerated approval drugs for which FDA subsequently withdrew approval after confirmatory studies failed to verify clinical benefit as well as significant delays in sponsors completing required confirmatory studies in the first place. Since 2020 alone, FDA has withdrawn the accelerated approvals of 16 cancer drug indications.¹

In October 2021, FDA’s Oncology Center of Excellence (“OCE”) launched the “Project Confirm” initiative to promote the transparency of outcomes related to accelerated approval for oncology indications. Through this initiative, OCE has, among other things, published summary information on FDA’s website regarding which accelerated approvals are the subject of ongoing confirmatory studies, which have been withdrawn, and which have completed confirmatory studies that verified clinical benefit.

In December 2022, Congress enacted amendments to the accelerated approval program as part of the Food and Drug Omnibus Reform Act (“FDORA”), expanding FDA’s authority to, among other things, use expedited withdrawal procedures if a sponsor fails to conduct a confirmatory clinical trial with due diligence and require a confirmatory trial be underway prior to granting an accelerated approval. See Ropes & Gray’s prior [Alert](#) for additional details.

Recent attention to the accelerated approval program has also come from the Centers for Medicare & Medicaid Services (“CMS”) in the drug pricing context. In February 2023, CMS announced a new drug pricing model for testing—the accelerating clinical evidence module—that, if implemented, would adjust the Medicare Part B payments for drugs subject to accelerated approval that have not yet completed their confirmatory trials.² CMS stated it intends to consult with FDA to explore the feasibility of such a model and, if the agency determines the model is appropriate, would continue its development thereafter.

These efforts, together with FDA’s new draft guidance, seek to facilitate the timely completion of confirmatory studies and ensure that clinical data to support FDA approval are sufficiently robust.

Key Clinical Trial Considerations

FDA’s accelerated approval program allows for earlier approval of drugs that treat serious or life-threatening conditions, provide a meaningful advantage over available therapies, and have an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.³ For drugs that receive accelerated approval, FDA generally requires the sponsor conduct a confirmatory study to verify and describe the clinical benefit as a condition of continued approval.

The majority of drugs that receive accelerated approval are oncology drugs where traditional efficacy endpoints, such as overall survival (“OS”) and progression-free survival (“PFS”), require substantial follow-up time. FDA’s draft guidance

explains that for these drugs, accelerated approval commonly is based on results from a single-arm trial evaluating tumor response endpoints like objective response rate (“ORR”). These single-arm trials, however, come with significant limitations that can impact the strength and quality of the safety and efficacy data, particularly in comparison to RCTs. For example, the lack of a control arm makes it difficult to generate clinically meaningful data on time-to-event efficacy endpoints such as tumor progression or OS, to attribute adverse events to the study drug, or to demonstrate that the study drug provides an improvement over available therapy. In contrast, RCTs provide a more robust efficacy and safety assessment, particularly for biomarker-directed therapies, allow for a direct comparison to available therapy, and may enable assessment of the drug in earlier lines of therapy.

FDA has long contended—including in a December 2018 [guidance](#) on clinical trial endpoints for oncology drugs—that RCTs are the “most reliable method for demonstrating efficacy.” In the new draft guidance, FDA strengthens this position and states that, when feasible, RCTs are the “preferred approach” to support applications for accelerated approval and verification of clinical benefit.

As discussed in more detail below, RCTs can be conducted as separate trials or as a single trial that is powered for both an earlier endpoint, such as response rate, and a longer-term endpoint to verify clinical benefit. Although the guidance articulates a preference for RCTs, FDA notes that a single-arm trial may continue to be appropriate where there are significant concerns regarding feasibility, such as for trials conducted in a limited patient population. The guidance addresses considerations for the design, conduct, and analysis of each of these trials but emphasizes that sponsors should engage with FDA early in the development process to gain alignment on study design and execution.

Considerations for the One-Trial Approach

The guidance outlines recommendations for a one-trial approach that would permit a single trial to support accelerated approval with a longer follow-up period to verify clinical benefit. This approach has the potential to increase efficiency and reduce enrollment issues in confirmatory trials.

A one-trial approach should be designed, executed, and analyzed in a manner that permits a robust assessment of efficacy. In designing the trial, FDA emphasizes the importance of selecting an endpoint for accelerated approval that is clinically meaningful, of sufficient magnitude to be reasonably likely to predict clinical benefit, and feasible to evaluate earlier in the study considering factors such as disease progression and the drug’s mechanism of action. Although response rate is most commonly used to support accelerated approval, the guidance notes that other endpoints may also be appropriate depending on the intended patient population and disease course.

Additionally, the trial should select a sample size that is adequately powered to detect a clinically meaningful benefit in both the endpoint supporting accelerated approval and the endpoint supporting verification of clinical benefit. For the accelerated approval endpoint, the analysis for response-based endpoints may be based on a pre-specified number of initially randomized patients and the analysis for time-to-event endpoints may be based on a pre-specified number of events. FDA recommends that the analysis of efficacy to support accelerated approval be delayed until the trial is close to or fully enrolled to mitigate potential challenges in patient enrollment if FDA grants accelerated approval.

FDA notes that the one-trial approach has increased the potential to introduce bias, and sponsors should assess the potential for and take steps to mitigate such bias. For example, sponsors should maintain blinding for the data used to support verification of clinical benefit until the protocol-specified analysis time point is reached.

The guidance emphasizes that the data used to support accelerated approval must demonstrate a statistically significant and clinically meaningful treatment effect on the efficacy endpoint and that the sponsor must demonstrate why the observed effect is likely to predict clinical benefit. Additionally, the data must demonstrate that the drug provides a significant advancement over the therapies available at the time that the application is approved.

The guidance also memorializes FDA’s long-standing practice of requesting OS data to support the agency’s review of an accelerated approval application. Specifically, the guidance states that FDA may request summary results of the OS

data analysis at the time of application submission as well as updated results during the course of review. Although OS data will be immature for purposes of the efficacy evaluation, detrimental effects on OS may suggest a potential harm for treatment and FDA may rely on such data as part of its safety assessment. Any detrimental effects on OS may result in FDA denying the accelerated approval application, regardless of the results for the surrogate endpoint.

Considerations for the Two-Trial Approach

Although the one-trial approach may increase efficiency, FDA notes that a sponsor may choose to conduct two RCTs: one study to support accelerated approval and one confirmatory study to verify clinical benefit and support traditional approval. FDA explains that to facilitate enrollment in the confirmatory trial, it may be acceptable to evaluate the drug in earlier lines of therapy than those for which accelerated approval was granted. In addition to facilitating enrollment, this would provide an opportunity for sponsors to assess the safety and efficacy of the drug in patients at an earlier stage of the disease at which the clinical benefit may be greater and could therefore support approval for its use in an expanded patient population. If the sponsor chooses to conduct two RCTs, FDA has long recommended that the confirmatory trial be underway at the time of application submission,⁴ and the new draft guidance now recommends that the confirmatory trial be near full enrollment at the time of the accelerated approval.

Considerations for Single-Arm Trials

Although the guidance expresses a preference for RCTs, it also provides recommendations for the design and conduct of single-arm trials in circumstances in which they are appropriate to support accelerated approval. FDA recommends that a response-based endpoint be selected as the primary endpoint and assessed using established criteria such as Response Evaluation Criteria in Solid Tumors for ORR. FDA recommends that the response rate assessment be performed by a blinded independent central review to mitigate variance in assessment and reduce the potential of introducing bias. The response rate generally should be defined as the sum of partial and complete responses—but not stable disease—and the ability of response rate data to support accelerated approval will depend on the magnitude and duration of response.

For single-arm accelerated approval trials, FDA states that both the sample size and analysis population should be pre-specified and that the selected sample size should include a sufficient number of patients to provide a robust estimation of the duration of response and establish an adverse event profile. FDA generally expects that all patients who have received at least one dose of the study drug will be included in the analysis population, regardless of whether they have had an opportunity to respond, and FDA recommends sponsors allow sufficient follow-up time to characterize the response rate and durability of disease, noting that in most cases, a minimum follow-up period of six months post-response will be necessary.

Additionally, because single-arm trials do not include an active comparator, FDA recommends sponsors pre-specify historical trials that may serve as a basis for comparison. When no trials have been conducted in the applicable patient population, such as biomarker-specific populations, FDA recommends the sponsor provide data demonstrating the magnitude of treatment effect in this population compared to historical results.

Implications for Oncology Drug Developers

FDA's express preference in the new guidance for RCTs and emphasis on endpoint selection echoes recent concerns FDA has raised regarding the ability of surrogate endpoints to predict clinical benefit for oncology drugs. Earlier this month, a group of FDA officials, including several from OCE, published a research article highlighting concerns regarding the ability of ORR and PFS to serve as surrogate endpoints for OS.⁵ While the article acknowledges that ORR and PFS continue to have utility in drug development, there may be discordance between these earlier endpoints and OS due to, among other things, significant toxicity issues or inadequate exploration of dose optimization in earlier trials. The article emphasizes that the results and maturity of OS data may impact a sponsor's ability to seek accelerated approval. Moreover, any detrimental effect on OS may cause FDA to reassess the risk-benefit profile of the product. The authors conclude that "when [risk-benefit is] unfavorable, both parties should honor the regulatory pre-nuptial agreement of drug approval and seek expedited withdrawal of the indication."⁶

These recent actions potentially suggest a broader shift in FDA’s approach to accelerated approval drugs. FDA plans to hold a series of workshops this year to discuss the role of surrogate efficacy endpoints, their ability to predict OS, and the information necessary to make a risk–benefit determination for novel oncology drugs.

Comments on the draft guidance are due by May 26, 2023. Ropes & Gray will continue to monitor developments in this area. If you have any questions, please contact any member of our [FDA regulatory practice](#) or your usual Ropes & Gray advisor.

1. FDA, “Withdrawn | Cancer Accelerated Approvals,” <https://www.fda.gov/drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals> (last updated Dec. 6, 2022).
2. CMS, “HHS Secretary Responds to the President’s Executive Order on Drug Prices” (Feb. 14, 2023), <https://www.cms.gov/newsroom/press-releases/hhs-secretary-responds-presidents-executive-order-drug-prices>.
3. 21 U.S.C. § 356(c).
4. See FDA, *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014), available at <https://www.fda.gov/media/86377/download>.
5. M. Merino *et al.*, Irreconcilable Differences: The Divorce Between Response Rates, Progression-Free Survival, and Overall Survival, *J. of Clinical Oncology* (Mar. 17, 2023), <https://ascopubs.org/doi/10.1200/JCO.23.00225>.
6. *Id.* at 5