Biotechnology Innovation Organization
1201 New York Ave., NW
Suite 1300
Washington, DC, 20005
202-962-9200

May 25, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2023-D-0110: Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics.[1] A majority of products granted accelerated approval (AA) are in oncology and therefore this guidance is extremely important to ensure innovations and progress in cancer drug development can continue to benefit patients, and BIO commends the agency on issuing this draft guidance describing how the AA pathway may be applied to modern oncology drug development.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

GENERAL COMMENTS

Accelerated approval is an important regulatory pathway that allows patients with serious and life-threatening illnesses such as cancer to have earlier access to promising therapies that provide a meaningful advantage over available therapies. As of March 31, 2023,[2] FDA has granted AA to 295 drugs and biologics, extending and in many cases saving the lives of patients

[1] FDA, Guidance for Industry - Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics. Available at: https://www.fda.gov/media/166431/download

[2] FDA CDER. "Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint." March 31, 2023. Available from: https://www.fda.gov/media/151146/download

who otherwise would have had no effective therapeutic options. A recent analysis found that more than half of the products granted AA have verified clinical benefit and were converted to traditional approval in a median time of 3.2 years from the time that AA was granted, twelve percent had been withdrawn, and of the remaining 38%, only 30 had been pending for more than 3.2 years, with only eight dangling or delinquent.[3] These figures underscore the effectiveness of the AA pathway and the continued promotion, utilization, and acceptance of it will be imperative to addressing the many unmet medical needs of patients with serious and life-threatening diseases. In addition to being an important regulatory pathway, AA also encourages scientific and medical advancement by advancing the use of surrogate endpoints to predict longer-term benefit.

Last year, Congress passed the Food and Drug Omnibus Reform Act (FDORA),[4] which included important improvements to the AA pathway and provided FDA with the tools it needs to ensure the program is available, reliable, and predictable. The legislation provides greater certainty on when clinical trials conducted as part of a post-marketing requirement are commenced and completed, and it clarifies and expedites the withdrawal process for AA approved products where necessary. There are also more robust reporting requirements that will create enhanced transparency for all stakeholders. Collectively, these provisions ensure there will be the appropriate confidence in the process and pathway, for FDA, industry, payers, and patients.

The FDORA legislation also confirms that FDA "may require, as appropriate, a study or studies to be underway prior to approval, or within a specified time period after the date of approval, of the applicable product."[5] However, the current draft guidance uses inconsistent terminology

when addressing this issue, requesting confirmatory studies be "underway," "well underway," or "fully enrolled" before the AA action.[6] BIO recommends that FDA uniformly use the statutory language set forth within FDORA throughout the guidance to ensure clarity and consistency for both sponsors and FDA reviewers. BIO believes that the FDORA language will enable consistent interpretation of the draft guidance and will ensure that sponsors have the flexibility needed to design and conduct trials specific to an intended drug and patient population.

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[3] Beakes-Read G, Neisser M, Frey P, Guarducci M. "Analysis of FDA's Accelerated Approval Program Performance December 1992-December 2021". Ther Innov Regul Sci. 2022 Sep;56(5):698-703.
[4] Public Law …, "Omnibus Appropriations Act of 2022," https://www.appropriations.senate.gov/imo/media/doc/JRQ121922.PDF
[5] FDORA Section 3210, "Modernizing Accelerated Approval"
[6] FDA, Guidance for Industry - Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics, at Lines 99, 137, 150, 322. Available at: https://www.fda.gov/media/166431/download.

Additionally, while the guidance is focused on oncology products, BIO recognizes that many of the concepts outlined in this draft guidance may have applicability to other disease areas. BIO urges the Agency to ensure a coordinated approach to the development of additional therapeutic-area-specific draft guidances to advance the consistent use of accelerated approval across the Agency.

SPECIFIC COMMENTS

1. One-Trial Approach

The "one-trial" approach proposed in the draft guidance is intended to promote investigation in earlier lines of therapy and aligns with the goals and objectives of FDA's Oncology Center of Excellence (OCE) Project FrontRunner[7]. We applaud the agency's forward-thinking guidance in encouraging this study design as it will allow intervention earlier in disease which may enhance chances of complete response and OS. We agree with this patient-centric approach and are eager to adopt it in practice, though we anticipate challenges with enrollment in some cases, depending on the available therapies or standard of care.

The draft guidance discusses the need to evaluate OS from a safety perspective to ensure that there is no detrimental effect of the investigational agent. It also makes a reference to assessing the potential for bias from crossover "if permitted." BIO recognizes that FDA considers OS to be the gold standard for oncology drug approvals, and we appreciate FDA's concern with ensuring trial integrity such that OS can be evaluated. However, the language in the guidance could be misinterpreted as not allowing crossover in certain cases, and we have concerns with the ethical implications of not allowing crossover in certain cases. Furthermore, we note that early-stage patients are likely to seek subsequent therapeutic options if they progress during the trial. Crossover and use of subsequent therapies are important to address patient needs, but both will confound interpretation of survival results. We urge FDA to revise the language in the guidance to further clarify that crossover is not prohibited.

The draft guidance emphasizes the need to maintain study blinding for the endpoint supporting verification of clinical benefit, until the protocol-specified analysis, to preserve trial integrity. However, the premise of the one-trial approach includes unblinding for interim assessment of the surrogate endpoint which would make it impossible to maintain blinding until the confirmatory endpoint. We therefore request the agency clarify how sponsors may utilize the one trial approach while maintaining blinding for the confirmatory endpoint and simultaneously

[7] FDA OCE. Project FrontRunner. Available from: https://www.fda.gov/about-fda/oncology-center-excellence/project-frontrunner

assess interim or surrogate endpoints which will, by design, be achieved at an earlier time point and necessitate unblinding.

Furthermore, previous OCE guidance[8] states that patients and investigators should be unblinded in the event of safety events or disease progression to allow informed decision-making about additional treatment options. BIO agrees with this statement as patient safety is our paramount concern. However, as a practical matter, this poses challenges for sponsors and investigators; therefore, we urge the FDA to provide additional details regarding how to manage unblinding in the setting of a one-trial approach.

2. Single-Arm Trials

BIO recognizes the relative strengths and limitations of single arm trials (SATs) vs. controlled studies, as outlined by the FDA in the draft guidance. BIO notes that in some situations, single arm trials are necessary, however, the draft guidance does not seem to adequately describe these scenarios BIO strongly recommends that the guidance recognize and provide examples of such scenarios.

3. Surrogate Endpoints

BIO notes that the guidance provides no mention of specific surrogate or intermediate clinical endpoints that could support AA other than RECIST-based response rate beyond a brief reference to complete remission rate and major molecular response. We point to the substantial efforts in the oncology community to identify, develop, and validate novel surrogate endpoints that have the potential to address unmet needs for patients, and ask FDA to note these efforts. For example, the ongoing ctMonitor project,[9] a multistakeholder collaboration involving oncology researchers, drug developers, patient advocates and FDA is evaluating the role of ctDNA as a potential surrogate endpoint which may be fit-for-purpose for investigations in early stages of disease. Similar efforts have led to FDA acceptance of progression free survival

[8] FDA CDER & CBER. "Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products. Guidance for Industry." FDA CDER & CBER. August 2019. Available from: https://www.fda.gov/media/130326/download

[9] Friends of Cancer Research. ctDNA for Monitoring Treatment Response Project. Available from: https://friendsofcancerresearch.org/ctdna/

(PFS), and in certain cases, pathological complete response (pCR)[10] and minimal residual disease (MRD)[11].

Finally, we note with concern the lack of mention or reference to patient-reported outcomes (PROs) in the draft guidance. Given the clear importance of PROs to patients[12,13] and the potential for PROs to measure clinically meaningful effects on how patients feel and function, we urge the FDA to include considerations for how PROs might inform safety or efficacy assessments and verification of clinical benefit. This is particularly important in early disease settings where there may be few OS events, or in which it may not be feasible or ethical to rigorously assess OS, as discussed earlier.

4. Use of Drug Development Tools

BIO commends the agency for its willingness to proactively engage with the sponsor, patient, and advocacy community and encourage innovative drug development tools and methods, including the use of Real-World Data (RWD) and Real-World Evidence (RWE). Thus, we believe that the use of these tools and methods should be noted in the draft guidance. For example, the discussion on external controls in the section of SATs to support AA is limited to historical trials. While we appreciate the FDA's willingness to consider SATs in some settings, we believe this section should also acknowledge the potential use of other sources of RWD, such as natural history studies, to support AA.[14] Likewise, we request that FDA address considerations for when use of RWD may be appropriate to verify clinical benefit

[10] FDA OCE, CDER, CBER. "Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. Guidance for Industry." Available from: https://www.fda.gov/media/83507/download

[11] FDA OCE, CDER, CBER. "Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment. Guidance for Industry." Available from: https://www.fda.gov/media/134605/download

[12] Lungevity. "Patient Reported Outcomes Scientific and Clinical Research Roundtable. March 23, 2018 Public Meeting Summary." Available from: https://www.lungevity.org/sites/default/files/general/LUNGevity-Scientific-Roundtable-032318.pdf.

[13] Friends of Cancer Research. "Enhancing use of patient-centered data in regulatory decision-making." November 2015. Available from: https://friendsofcancerresearch.org/enhancing-use-patient-centered-data-regulatory-decision-making/.

[14] FDA CDER, CBER, OCE. "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. Draft Guidance for Industry." Available from: https://www.fda.gov/media/164960/download

LINE-BY-LINE RECOMMENDED EDITS

SECTION	ISSUE	PROPOSED CHANGE
Lines 42-43	The draft guidance states: "Safety databases are typically small and may not allow for the identification of rare, potentially serious adverse events. For identified serious adverse events, attribution of adverse events to the drug under study can be limited in the absence of a comparator arm." With respect to the size of the safety database, if a SAT is conducted in the context of a follow-on indication, there may be a sizeable safety database from the originally approved indication that can inform the safety profile for the new indication. In this case, the totality of the data would be a key consideration. In addition, sample size and adequacy of the safety database for AAs is not defined.	1.BIO recommends that the draft guidance be updated to include the bold language, as follows: "***For new molecular entities***, safety databases are typically small and may not allow for the identification of rare, potentially serious adverse events. For identified serious adverse events, attribution of adverse events to the drug under study can be limited in the absence of a comparator arm. ***For approved products seeking supplemental indications, the totality of safety data from previous studies can be used to inform the safety profile."***
Lines 58-64	It is unclear how this guidance aligns with the recently published guidance on Externally Controlled Trials (February 2023)[16] Lines 58-63 seem to point out many of the problems with external control arms, but the other guidance clarifies best practices for choosing a historical control arm, so it might be helpful to have some clarity and consistency.	BIO recommends adding a summary of recommendations when choosing an external control arm or adding a reference to the draft Guidance Externally Controlled Trials (February 2023), for further details.
Lines 105-109	The guidance states, "Given the limitations of single-arm trials, a randomized controlled trial is the preferred approach to support an application for accelerated approval. Sponsors can, as appropriate, elect to conduct a single randomized controlled trial to support an accelerated approval and to verify clinical benefit (i.e., follow a "one-trial" approach) or, they can conduct separate trials – one to support the accelerated approval and another, a confirmatory trial, to verify clinical benefit."	BIO recommends that the guidance and this passage instead focus on the benefits and limitations of each approach and describe the characteristics of the circumstances when each approach could be appropriate, rather than stating a general preference without detailing these considerations.

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Line 131	The Section "Considerations for Two Randomized Controlled Clinical Trials" The considerations and advantages outlined in this section are largely appliable for a scenario when a SAT is used to support AA followed by RCT as confirmatory (including advantage to move to earlier line with confirmatory RCT). In addition, the value of pointing out two RCTs in this section is not clear.	1.BIO recommends that the FDA consider adding to the guidance a scenario describing where single arm trials to support AA in refractory settings are followed by confirmatory RCT in an earlier line (one of the scenarios outlined in Friends of Cancer Research 2022 Whitepaper Accelerating Investigation Therapies Earlier Metastatic Treatment Settings.pdf (friendsofcancerresearch.org)). 2. BIO recommends renaming the section ***"Considerations for ~~Two~~ Randomized Controlled Clinical Trial Following Accelerated Approval"***
Lines 133-138	Since a confirmatory RCT can be in a different setting (e.g., an earlier setting (see lines 140-146)), challenges in enrollment after an AA are heightened in the approved target population but may not exist for the confirmatory RCT.	BIO recommends adding the following text in bold: Waiting to initiate a randomized controlled confirmatory trial until after an accelerated approval has been granted can create challenges in enrolling participants ***in confirmatory trials in the same indication,*** due to the availability of the drug in clinical practice.
Line 141	The guidance states, "To facilitate completion of the confirmatory trial, it may be acceptable to evaluate the drug in the same cancer type but in another line of therapy. For instance, for an accelerated approval granted for an indication in a refractory cancer setting, the confirmatory trial could be conducted in an earlier disease setting."	BIO recommends addition of the following language in bold: To facilitate completion of the confirmatory trial, it may be acceptable to evaluate the drug in the same cancer type ***or a closely-related tumor*** type but in another line of therapy. For instance, for an accelerated approval granted for an indication in a refractory cancer setting, the confirmatory trial could be conducted in an earlier disease setting. *Such confirmatory trials may include combination regimens or other approaches to demonstrate clinical benefit.*
Line 143	Since the earlier disease setting may require combination therapy, suggest clarifying the statement that the confirmatory study in earlier disease may be conducted with monotherapy or in combination with standard of care.	BIO recommends adding the bolded text: "For instance, for an accelerated approval granted for an indication in a refractory cancer setting, the confirmatory trial could be conducted in an

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		earlier disease setting ***with monotherapy or in combination with standard of care.***"
Lines 166-172, and 230-233	The guidance outlines considerations to address the potential data integrity issues of having a "one-trial" approach, but it would be helpful to give more instructive points to maintain the integrity. There is one example listed on line 230 for a double-blind trial design, but additional examples, including for open-label RCT designs, would be helpful.	BIO recommends that FDA should: 1.Provide examples and/or more instructive guidance on maintaining data integrity using a "one-trial" approach, and 2. Provide guidance addressing crossover, as it is expected that many patients in the control arm would need to be crossed over to therapy with demonstrated efficacy, particularly in later line settings. This will impact the ability to demonstrate any benefit in OS.
Lines 169-172	Please clarify how bias should be assessed based on a drug's efficacy and safety profile approved in the AA setting.	BIO recommends that FDA consider adding the additional text, in bold: In assessing the potential for bias, sponsors should consider factors such as the anticipated impact of crossover (if permitted); the preliminary data on the drug's effects, including the toxicity profile, the treatment landscape, and the treatment used in the control arm, among other factors. ***In addition, when crossover is not permitted, FDA suggests the following approach(es) <<FDA to share insight on potential approaches here>>. Furthermore, the following examples illustrate examples of the types of adjustments made based on the preliminary data:*** • ***Adjusting safety assessments if a safety signal emerged;*** • ***Adding another SOC option to the investigator choice control arm due to change in treatment landscape;*** • ***Modifying the timing of the efficacy assessment to align with emerging consensus.*** • ***<<FDA to share examples here>>***

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Lines 230-241	The Agency states "in reviewing an application for accelerated approval, FDA's safety assessment may include evaluating whether the available data suggest a potential for harm from treatment on the investigational arm (e.g., detrimental effects on clinical endpoints such as OS). FDA may request summary results of the analysis on survival data to support such an assessment as part of an application submission and may request updated survival results during the course of the review of the application. Sponsors should specify a plan that describes measures to maintain study blind for such an analysis."	1.BIO recommends clarifying/modifying "blinding of data for the endpoint supporting verification of clinical benefit should be maintained until the endpoint's protocol specified analysis time point is reached to ensure a robust assessment of this endpoint." Often it is appropriate, and FDA requests for an interim analysis to be provided on the confirmatory endpoint at the time of submission for AA (e.g., if OS is the confirmatory endpoint the next paragraph referencing ruling out a detrimental effect on OS). In this case the sponsor, FDA, etc. would be unblinded to summary level data and in many cases patient level data; however, investigators and participants could remain blinded to individual treatment assignments. We recommend the following edit: "~~blinding of data~~ **appropriate blinding (e.g. blinding of investigator and participants to individual treatment assignments)** for the endpoint supporting verification of clinical benefit should be maintained until the endpoint's protocol specified analysis time point is reached to ensure a robust assessment of this endpoint." 2. BIO recommends the Agency either to remove sentence (231-233) or rewrite it to include that measures should be put in place to ensure integrity of the trial, as a descriptive analysis of the late endpoint will be provided with the early endpoint for AA. The rationale is based on the language at lines 235- 237, "In reviewing an application for accelerated approval, FDA's safety assessment may include evaluating whether the available data suggest a potential for harm from treatment on the investigational arm (e.g., detrimental effects on clinical endpoints such as OS)," which implies FDA is going to want to see at least a descriptive analysis of OS with the response rate data to support AA.
Line 267	The guidance states, "To facilitate the demonstration of advantage over available therapies, sponsors should pre-specify the historical	BIO recommends the following edit in bold: "To facilitate the demonstration of advantage over available therapies, sponsors should pre-specify the historical trial(s) ***and/or the Real World***

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	trial(s) that will serve as the basis for the comparison, and the rationale for the selected trial(s)."	***Evidence*** that will serve as the basis for the comparison, and the rationale for the selected trial(s)."
Lines 324-327	Since the accelerated approval and post marketing confirmation can be from the same trial, two potential issues may arise: • How to maintain the blind for the confirmatory portion of the trial? • If we believe the response rate can predict the outcome of the confirmatory endpoint, will the unblinded result of the accelerated approval introduce bias into the confirmatory result?	BIO asks for FDA's recommendations for both potential issues.

Respectfully Submitted,

/s/
Leslie Harden, PharmD
Director, Science and Regulatory
Biotechnology Innovation Organization