



May 26, 2023

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

Re: FDA-2023-D-0110, Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics

Filed electronically at <http://www.regulations.gov>

Dear Commissioner Califf,

Thank you for the opportunity to provide comments to the Food and Drug Administration (FDA) on the following draft guidance issued in March 2023:

- *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics*

Arnold Ventures is a philanthropy dedicated to investing in evidence-based policy solutions that maximize opportunity and minimize injustice. Our work within the health care sector is driven by the recognition that the system costs too much and fails to adequately care for the people it serves. Our work spans a range of issues including commercial-sector prices, provider payment incentives, prescription drug prices, clinical trials, Medicare sustainability, and complex care.

We appreciate FDA's commitment to facilitating the development and execution of randomized controlled trials that support applications for accelerated approval and subsequent confirmatory trials that verify meaningful clinical benefit to patients. Confirmatory trials must be conducted with due diligence and in accordance with prespecified trial conditions that validate the use of a particular surrogate endpoint including enrollment targets, milestones, and target date of study completion.

To assure confirmatory studies are underway at the time of accelerated approval, FDA suggests one randomized controlled trial to support and verify clinical benefits to patients. Given the limitations of single-arm trials, we see the Agency's guidance to industry as recognizing that a randomized controlled trial is the preferred approach to support an application for accelerated approval. Confirmatory randomized controlled trials should be underway when the marketing application is submitted to verify the clinical benefits to patients, rather than to verify, confirm, or otherwise validate the context of the surrogate endpoint itself.¹

The proposed guidance should also fulfill requirements in the Food and Drug Administration Modernization Act of 1997 (FDAMA)² that all clinical investigations supporting effectiveness be of appropriate design and of high quality (i.e., adequate, and well-controlled). This includes a confirmatory trial to verify clinical benefits to patients. Therefore, we ask that the Agency finalize clearer guidance for industry about how to (1) meet these requirements and (2) develop

¹ <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2733561>

² <https://www.govinfo.gov/content/pkg/PLAW-105publ115/html/PLAW-105publ115.htm>



processes to withdraw those products that do not confirm clinical benefit to patients alongside the new Section 506(c) of the Federal Food, Drug, and Cosmetic Act.³

Additionally, we recommend that FDA provide further clarification on the following policy areas in final guidance to ensure strong pre and post market evidence collection:

1. Define which settings are consistent with the use of surrogate endpoints for accelerated approvals, namely chronic diseases where the surrogate is measured far in advance of the direct patient outcome;
2. Delineate what evidence supports the “reasonably likely to predict clinical benefit” criteria to make clear that, at a minimum, the evidence supports the determination that the surrogate is a valid correlate of patient outcomes at the patient level independent of treatment and generalizes to the relevant population;
3. Describe how confirmatory trials are designed to confirm the benefits of the labeled indication, not to expand into new indications;
4. Limit the use of “crossover” designs, which obviate continued follow-up of enrolled participants and the use of single trials to both initiate and confirm clinical patient benefit;
5. Clarify that regulatory approval decisions are based on the best available therapy at the time clinical trial results are under review; and
6. Publish changes to surrogate endpoint definitions with analysis that clarifies their effects on surrogate validity and inferences regarding direct clinical patient benefit.

The draft guidance outlines specific considerations when (1) designing, (2) conducting, and (3) analyzing clinical trials intended to support accelerated approval and to verify the clinical benefits of accelerated approval drugs to patients. The following sections detail our recommendations within the context of each of the three considerations outlined by FDA.

1. Design Considerations

The draft guidance recognizes that confirmatory clinical trials for drugs and biological products approved under the accelerated approval pathway help address the lack of evidence of their clinical benefits to patients. As a result, design considerations for confirmatory studies at the outset should propose relevant clinical questions about safety and efficacy. Additionally, design considerations of confirmatory trials enrolled at the time of accelerated approval must verify labeled claims of clinical benefit to patients.

Design considerations should also include enrolling relevant types of patients who would use the drug in clinical practice. Patients and providers often lack information about whether a cancer drug or biological product under further investigation through confirmatory trials improves survival or quality of life. In order for patients and providers to have better information, FDA should validate the surrogate endpoint for use while confirming clinical benefit for patients from the accelerated approval indication.

While accelerated approval can be based on demonstration of an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, it is expected that patients, prescribers, providers, and payers have confidence that FDA uses empirical evidence in this prediction. The evidence standards underlying this prediction of treatment effect at the time of drug approval was not addressed in draft guidance. Arnold Ventures recommends that FDA clarify in final guidance

³ <https://www.govinfo.gov/content/pkg/COMPS-973/pdf/COMPS-973.pdf>



how Agency staff identify surrogate endpoints that are reasonably likely and appropriate for conducting trials under the accelerated approval pathway. Without this information, it remains unclear to what extent a drug or biological product's indication remains an investigational use in clinical practice.

Furthermore, appropriate use of surrogate endpoints for accelerated approval indications requires an appreciation for how the validity of a surrogate can vary from one indication and patient population to another. Therefore, we recommend that FDA seek medical and scientific consensus in public meetings or through updates to federal regulations with formal notice and public comment regarding the use of a surrogate endpoint before it is applied to a trial's design. Consensus on surrogate endpoint selection and what features allow them to serve as the basis for accelerated approval has been piloted by the Agency previously⁴ and can ensure that the surrogate endpoint is a strong candidate for trial level surrogacy.⁵

2. Conduct Considerations

Arnold Ventures recommends that FDA make clear in final guidance to industry that crossover is problematic for studies of accelerated approval indications and confirmatory trials when the efficacy of the experimental agent has not been previously established. We appreciate the Agency's attention to preserving the integrity of trials to determine clinical benefits to patients of accelerated approval indications for drugs and biological products. There are many ways bias can be introduced as outlined by Agency staff in this guidance and recognized in scientific and medical literature. In assessing the potential for bias, we agree that the Agency should hold product sponsors responsible for considering factors such as the impact of crossover,⁶ the drug's toxicity profile, the treatment landscape, and the treatment used in the control arm, among other factors. However, when dealing with crossover in trial conduct for this specific guidance, the Agency has provided little information to make clear situations in which crossover is either desirable or problematic.

Arnold Ventures also recommends that the Agency either make clear the distinction between "best available therapy" and standard of care or provide explanation as to whether the accelerated approval pathway and confirmatory trial conduct fulfills unique regulatory requirements that are separate and distinct from subsequent provider, prescriber, and payer decisions. We support the Agency's assertion that the determination of what constitutes "best available therapy" must be made at the time the regulatory decision is made rather than at the time the trial was initiated.

We appreciate that the Agency expects confirmatory trials to be well underway and fully enrolled at the time of accelerated approval action. The Agency recognizes that even the "best available therapy" for conditions with serious unmet medical need evolves rapidly. We also observe that there is much confusion in clinical trial conduct as to how the "best available therapy" inside a trial relates to the standard of care outside a trial. The consequence of this disconnect raises significant concern as to whether a controlled trial provides at a minimum the current standard of clinical care for cancer patients in the United States.

⁴ <https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-S>

⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3551627/>

⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981898/>



Finally, we recognize that trial conduct will change over time; for example, trials are increasingly global and decentralized. As trial conduct evolves, FDA should consider as part of finalizing this guidance to industry a method for publicly reporting the status of confirmatory trials at least annually. Additionally, when the confirmatory trial is completed, FDA should require that trial findings be promptly released.

3. Analysis Considerations

Arnold Ventures recommends that FDA detail in final guidance the appropriate trial analysis considerations beyond the acknowledgement that the analysis population should be pre-specified. For example, FDA could provide a framework for analysis or state plainly that studies with (1) multiple increases to the sample size, (2) analysis combined from multiple studies, or (3) a single study that has had repeated analysis of the assessment data likely introduces bias in the assessment of efficacy and should be avoided. We also request that the analysis considerations published in final guidance include explanations for handling changes to surrogate endpoint definitions. We request this because FDA has previously noted⁷ some clinical trial endpoints' definitions vary among studies and therefore may require more confirmatory evidence from multiple randomized controlled trials.

We appreciate that FDA seeks to finalize this guidance to industry while also guarding against switching surrogate endpoint definitions that make studies less comparable. These definitions should be consistent between trials and among trials for transparency and comparability of drugs within oncology. Switching surrogate endpoint definitions makes it likely, for example, that results and effect sizes may no longer reflect patient outcomes. We request that the final guidance include a detailed discussion of key analysis considerations with references to seminal work by the Agency on this matter and offer the general suggestion that the final principles of clinical trial analysis described should be generalizable across the field of oncology.

Conclusion

Arnold Ventures is prepared to assist with any additional information needed to address these comments in final guidance to industry. Comments were prepared by Katherine Szarama, PhD, Director of Health Care at Arnold Ventures, with assistance from John Powers, MD.

Please contact Mark E. Miller, Ph.D. Executive Vice President of Health Care at Arnold Ventures at mmiller@arnoldventures.org or Andrea Noda, MPP, Vice President of Health Care at anoda@arnoldventures.org with any questions.

Thank you again for the opportunity to comment and for your important work ensuring the safety and efficacy of human drugs and biological products.

Sincerely,

Andrea Noda

⁷ <https://www.fda.gov/media/71195/download>