Brigham and Women's Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061, Rockville, MD 20852

February 4, 2025

Re: **FDA-2024-D-2033**
Draft Guidance: Expedited Program for Serious Conditions - Acceleration Approval of Drugs and Biologics
Submitted electronically via Regulations.gov

To whom it may concern,

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard ("MRCT Center") appreciates the opportunity to comment on the Food and Drug Administration's ("FDA" or "the Agency") draft guidance document entitled "Expedited Program for Serious Conditions - Acceleration Approval of Drugs and Biologics" published Fed. Reg. On December 6, 2024, by the Department of Health and Human Services. This guidance is timely and necessary, and it helps clarify a number of issues with regard to the accelerated approval pathway.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.[1]

We commend the FDA's commitment to developing pathways and mechanisms for the review of new drugs and biological drug products addressing unmet medical needs for serious or life-threatening conditions. Below are recommendations to enhance the implementation of this draft guidance.

Recommendations

Under Section 506(C) of the FD&C Act, amended by FDASIA, the accelerated approval (AA) pathway was conceived to prioritize and grant access to products for serious or life-threatening conditions. Focused on diseases and conditions currently lacking effective treatment, the AA pathway has been instrumental in bringing innovative therapies to patients

[1]Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, and Harvard University.

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more swiftly. As FDA recognizes, this pathway is not without risk in that less information is known at the time of accelerated approval, and patients might be exposed to safety risks from a product that does not later demonstrate clinical benefit. This risk is balanced by the urgency of providing treatments for patients who have no better options. To strengthen this guidance, we recommend:

1. The draft guidance states that "Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval" (lines 284-5, citing Sections 505(d) and 506(e)(2) of the FD&C Act). But in the AA pathway, it is clear that there is less information about safety (see lines 115-119) and, importantly, the AA pathway only requires demonstration that the drug has a "reasonable likelihood" of benefit. It is hard to resolve these conflicting statements, and we encourage FDA to clarify the difference between AA approval and traditional approval for the general public. This clarification and education will help patients understand why they should consider volunteering for confirmatory studies when the product is already "approved," particularly when the confirmatory study is randomized.

2. Similarly, ethics committees often struggle with whether and how to approve confirmatory trials, particularly randomized trials, when a product is already approved—albeit by the AA pathway—for use in patients without equivalent therapeutic options. If the standards for approval are "the same," can ethics committees reasonably approve randomization? Further, what should be explained to the proposed participants in the informed consent process? Guidance would be helpful.

3. The draft guidance states that sponsors must perform confirmatory trials with "due diligence." The only further clarification of the term "due diligence" is to remind sponsors that "sufficient resources" must be committed to conduct the trial "expeditiously." What other factors should be considered?

4. The draft guidance points to timelines for completion of confirmatory trials, timelines that have historically been prolonged and problematic. We urge FDA to specify acceptable timelines for each product approved under the AA pathway as a condition of approval.

5. We agree that these confirmatory trials should have commenced as a condition of approval. The draft guidance allows for "limited circumstances" in which confirmatory trials would not be needed. We request FDA to clarify, and provide examples of, the kinds of circumstances that would eliminate the need for confirmatory trials.

6. The draft guidance emphasizes the importance of a proposed endpoint surrogate or an intermediate clinical endpoint as a basis for accelerated approval, and it discusses the differentiation between them. What standards are used to establish the correlation of a proposed surrogate with clinical outcome?

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7. Guidance regarding the validation process of surrogates is needed, to clarify what data are needed to move a "proposed endpoint surrogate" to a validated category. We recommend including detailed criteria and examples of validated – and the process of validation of – surrogate endpoints across various therapeutic areas to assist sponsors in understanding their applicability.

8. Relatedly, if in the course of a confirmatory study, a proposed endpoint surrogate is validated, does the confirmatory study nevertheless require completion? Can the confirmatory study be used as a means of validation for future trials, and if so, are there limitations to relying on prior studies?

9. The draft guidance allows for enrollment of a "related population" in a confirmatory trial, but the guardrails around relatedness are not defined. The only example given is one where patients with advanced cancer in the AA trial are substituted for patients with earlier disease in the confirmatory trial. Are there limitations to consider, and what happens if the confirmatory trial with a related but non-identical population fails to show benefit? Will the product be withdrawn, or will another confirmatory trial be required? And what are the expectations for the safety profile and for the choice of control?

10. Engaging patients in the development of meaningful surrogate endpoints (and confirmatory trial designs) is important. What is less clear is the relationship between proposed surrogate endpoints addressing quality-of-life measures (and other patient-reported outcomes) and intermediate clinical endpoints, if any. When must an intermediate clinical endpoint involve prolongation of life and/or an impact on irreversible morbidity and mortality? Are there "other clinical benefit[s]" that would fulfill the requirements for quality-of-life or other patient-reported outcome surrogates to be used? Examples (and expectations) would be helpful.

11. Encouraging early consultation between sponsors and the FDA on novel endpoints is welcome. Providing a structured framework for these consultations, including timelines and required documentation would enhance the efficiency and transparency of this process. Further, we encourage FDA to include certain information in their public disclosures, including NCT numbers, trial timelines, progress updates, and the rationale for any regulatory actions (or lack thereof).

12. Acknowledging the potential of innovative trial designs, such as adaptive trials, decentralized trials, and the use of real-world evidence, is valuable. Providing guidance on acceptable methodologies and statistical considerations for these designs would support sponsors in their implementation.

13. We appreciate the detailed instructions provided by the draft guidance on the processes of drug withdrawal. Any measures to increase the transparency of decision-making, the engagement of the patient population, and the timeliness of withdrawal are welcome.

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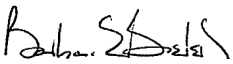
14. Clinical research is global and addressing the applicability of confirmatory trials in multi-regional settings was not addressed. Would the design or conduct of a multi-national confirmatory trial differ if one country had approved the product through an AA pathway or equivalent and another had not? In the same vein, providing guidance on the alignment with other international regulatory standards, such as those from the European Medicines Agency (EMA) and other global counterparts, would help clarify the differences, allow study designs to conform with differing standards, and permit further harmonization.

Thank you for allowing us the opportunity to submit comments. We would be happy to discuss at any time.

Respectfully submitted,
on behalf of the MRCT Center



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