ACRO Innovate Advocate Collaborate

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Dat Doan, Center for Drug Evaluation and Research
James Myers, Center for Biologics Evaluation and Research
Paul Kluetz, Oncology Center of Excellence
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 3334
Silver Spring, MD 20993-0002

RE: ACRO comment submission on
Expedited Program for Serious Conditions: Accelerated Approval of Drugs and Biologics
[FDA-2024-D-2033-0002]
Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway
[FDA-2024-D-3334-0002]

Dear Dr. Doan, Mr. Myers, and Dr. Kluetz,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and clinical technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support a majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO thanks the Agency for releasing two draft guidances on accelerated approval:

- *Expedited Program for Serious Conditions: Accelerated Approval of Drugs and Biologics*
- *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway*

Accelerated approval is one of FDA's expedited programs intended to facilitate and expedite development and review of new drugs. Accelerated approval includes four key elements:[1]

- addresses an unmet medical need
- in the treatment for a serious or life-threatening disease or condition
- approval is based on a surrogate endpoint or an intermediate clinical endpoint
- where such endpoints are reasonably likely to predict an effect on irreversible morbidity or mortality (IMM) or other clinical benefit

[1] FDA draft guidance on *Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics*
https://www.fda.gov/media/184120/download
Lines 50-56
Section 506(c) of the FD&C Act, as amended by FDASIA states that accelerated approval may be granted 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.

For drugs granted accelerated approval, confirmatory trials must be completed post-approval to verify and describe the anticipated effect on IMM or other clinical benefit. The confirmatory trial requirement is considered met, and released, if the trial verifies the clinical benefit. Moreover, FDA may impose specific conditions for the required confirmatory trials regarding enrollment targets, the study protocol, milestones, and study completion target date. Accelerated approval may be withdrawn using expedited procedures if the confirmatory trial does not take place; the confirmatory trial fails to verify the anticipated effect; other evidence demonstrates that the product is not shown to be safe or effective under the approved conditions of use; or the sponsor disseminates false or misleading promotional materials. The value of the accelerated approval pathway is in safely expediting products to market for the patients who need them most:

> *This often allows sponsors to obtain approval for products intended to treat an unmet medical need sooner than would be possible under traditional approval . . . Surrogate endpoints or intermediate clinical endpoints have the potential to detect the drug effect that may predict clinical benefit earlier than endpoints showing clinical benefit. For example, accelerated approval has been used extensively in the approval of drugs to treat a variety of cancers where an effect on tumor growth can be assessed rapidly, but demonstrating an effect on survival or other endpoint relevant to show clinical benefit for a particular cancer would need longer and sometimes larger trials because of the duration of the typical disease course.*[2]

Upholding the Gold Standard While Expediting Treatments to Patients

The Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act were signed into law in 1962, granting FDA the authority to require proof of efficacy (rather than just safety) before approving a new drug. This helped establish the FDA approval process as the gold standard for evidence generation for promising new therapies. The accelerated approval pathway exemplifies this gold standard. ACRO thanks FDA for issuing these two draft guidances, which clarify two key elements of the accelerated approval pathway.

First, these draft guidances bolster the accelerated approval pathway's balancing act. A frequently discussed tension in drug development programs are the competing objectives of (1) evidence and (2) access. The accelerated approval pathway enables the successful balancing, and optimization, of these goals by delivering new treatments to patients as quickly as possible while upholding the gold standard for evidence generation on drug safety and effectiveness. This careful balancing act is only possible because of the role of confirmatory trials in accelerated approval as described in the FDA draft guidance on *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway*:

> *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. 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***.[3]

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[2] FDA draft guidance on *Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics* https://www.fda.gov/media/184120/download, Lines 97-107

[3] FDA draft guidance on *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway,* https://www.fda.gov/media/184831/download, Lines 96-103, emphasis added

Second, the draft guidances provide a valuable reminder to stakeholders that accelerated approval does not deviate from traditional approval regarding evidence generation standards. The achievement of the accelerated approval pathway is that it does not tamper with the *dual evidentiary standards themselves*, fully upholding data generation on both safety and effectiveness. Instead, accelerated approval merely modifies and shifts the *timing* of safety and effectiveness demonstrations in a carefully circumscribed manner under statutorily limited circumstances. Indeed, the key sentences in the draft guidance demonstrating the continuity of evidentiary standards between traditional approval and accelerated approval are:

> *Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations. For safety, the standard is having sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.*[4]

Confirmatory Trials and Trial Design

We ask the Agency to consider inclusion of a discussion of decentralized clinical trials in the final guidance on *Expedited Program for Serious Conditions: Accelerated Approval of Drugs and Biologics*. Confirmatory trials may be particularly good candidates for a trial design with decentralized elements for two reasons.

First, confirmatory trials may be amenable to a decentralized trial design due to the nature of the participants. The accelerated approval pathway is limited to drug development programs for the treatment of a serious or life-threatening disease or condition. The flexibilities that trials with decentralized elements offer to patients may be of particular value for patients with serious or life-threatening diseases and conditions who may have limited mobility and other challenges that impact trial participation. These flexibilities include the moving of trial assessments from the central investigator site to the patient's home, local community facility, or mobile unit.

Second, confirmatory trials may be amenable to a decentralized trial design due to the nature of the accelerated approval pathway and potential challenges in participant accrual:

> *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.*[5]

[4] FDA draft guidance on *Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics* https://www.fda.gov/media/184120/download, Lines 284-291

[5] FDA draft guidance on *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway* https://www.fda.gov/media/184831/download, Lines 237-247

The recommendation to "complete all or a significant portion of enrollment prior to accelerated approval" may be more easily achieved in a trial with decentralized elements that offers participants locational flexibilities for assessment procedures. To identify trials which may be suitable for a decentralized design and facilitate their adoption, ACRO has created a DCT Toolkit which contains resources for design and planning of DCTs – including a quality-by-design manual and risk assessment considerations tool.

Thank you for the opportunity to provide feedback on these two draft guidances on accelerated approval. Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions.

Respectfully submitted,

Karen Noonan

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