March 10, 2025

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: FDA-2024-D-2033 ("Accelerated Approval – Expedited Program for Serious Conditions") and FDA-2024-D-3334 ("Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway")

The Alliance for Aging Research, the Partnership to Fight Chronic Disease, and the Global Alzheimer's Platform Foundation appreciate the opportunity to comment on both of the recently issued draft guidances on accelerated approval—*Expedited Programs for Serious Conditions—Accelerated Approval of Drugs and Biologics* (hereafter the "Programmatic Guidance")[1] and *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway* (hereafter the "Confirmatory Trial Guidance").[2] Together the draft guidances describe FDA policies and procedures for the accelerated approval program, including implementation of new authorities enacted by Congress through the Food and Drug Omnibus Reform Act of 2022 ("FDORA").[3]

Accelerated approval is a vital pathway to expedite the availability of drugs to address unmet medical need in the treatment of serious or life-threatening diseases or conditions, including many that disproportionately impact older Americans. We appreciate FDA's work to ensure the success of the accelerated approval pathway. In particular, once finalized, these guidance documents will provide additional programmatic transparency, predictability, and consistency for drug sponsors, in turn facilitating investment in development programs for novel therapies that treat patients with unmet medical needs.

Our organizations offer the following general comments to underscore features of the guidance that we found particularly informative and helpful, as well as a few specific comments on ways in which the guidances could be further refined as they are finalized.

General Comments

Prior to FDORA, the accelerated approval program, although successful, had been criticized for uncertainties regarding whether a therapy's effect on a surrogate endpoint would ultimately show clinical benefit (with questions raised as to whether the accelerated approval provisions were being applied uniformly throughout the Agency), and for delays in confirmatory trials.[4] In 2023, Congress

[1] FDA, "Expedited Programs for Serious Conditions—Accelerated Approval of Drugs and Biologics," Dec. 6, 2024 (Docket no. FDA-2024-D-2033).
[2] FDA, "Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway," Jan. 7, 2024 (Docket no. FDA-2024-D-3334).
[3] *See* section 3210 of FDORA, included as part of the Consolidated Appropriations Act, 2023 (Public Law 117-328).
[4] *See, e.g.*, Jeff Craven, "Study: Accelerated approval pathway working as intended in most cases," Regulatory Focus (Aug. 10, 2022), available at https://www.raps.org/news-and-articles/news-articles/2022/8/study-accelerated-approval-pathway-working-as-inte; HHS Office of the Inspector General, "Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns," report no. OEI-01-21-00401 (Sept. 29, 2022), available at https://oig.hhs.gov/reports/all/2022/delays-in-confirmatory-trials-for-drug-applications-granted-fdas-accelerated-approval-raise-concerns/.

acted to strengthen the program in three key respects by providing FDA with authority to: (1) specify conditions and procedures for confirmatory trials, (2) help expedite the withdrawal of approval of a drug or biologic approved through the accelerated approval pathway, and (3) require, as appropriate, that confirmatory trials be underway at the time of approval or within a specified time period thereafter.[5] Congress also directed FDA to issue draft and final guidance documents to describe its implementation of the new provisions.[6]

The Programmatic Guidance helpfully addresses the statutory requirements. In addition, the guidance underscores the rigorous standard that sponsors must meet for approval under the accelerated approval pathway, noting that "[d]rugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval."[7] We urge FDA to continue emphasizing this point. Although accelerated approval is an important mechanism for FDA to allow earlier approval of drugs that treat serious and life-threatening illnesses than would occur through traditional approval, this pathway does not compromise FDA's gold standard review of a product's safety and effectiveness.

Our organizations appreciate the transparency and detail provided in the guidance documents, which will help enable consistent application across components of FDA. In particular, we note that the Programmatic Guidance provides clarifying detail regarding the evidentiary criteria for surrogate endpoints and intermediate clinical endpoints and when they will, or will not, support accelerated approval. Helpfully, however, in describing the evidentiary criteria for accelerated approval, the Programmatic Guidance also includes flexibility for FDA to consider case-specific context as appropriate. The guidance acknowledges that "[d]etermining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend upon the biological plausibility of the relationship between the disease, the endpoint, the desired effect, and the empirical evidence to support that relationship."[8] While the guidance provides an overview of the factors that FDA will consider identifying and assessing whether surrogate endpoints or intermediate clinical endpoints are reasonably likely to predict clinical benefit, the guidance is not overly rigid—for instance, by noting that FDA "may" utilize an advisory committee (rather than stating categorically that FDA "will" do so in every case) or describing a variety of sources of information that FDA may consider to determine if "the convergence of evidence" supports a surrogate as reasonably likely to predict intended clinical benefit.[9] We support these flexibilities as a means to help enable patients with unmet medical needs to benefit from earlier access to novel therapies.

Finally, we support the procedures outlined in the Programmatic Guidance and the Confirmatory Trials Guidance to help ensure that confirmatory trials are a meaningful aspect of the accelerated approval process and that expedited withdrawal procedures operate efficiently. Implementation of these robust procedures will help address concerns (noted above) that emerged about the accelerated approval pathway in recent years and led to the FDORA amendments. Strengthening these aspects of the accelerated approval pathway will further bolster public confidence in therapies approved under this pathway, helping to ensure the long-term success of the pathway and continued patient access to novel therapies for unmet medical needs.[10]

---

[5] *See* FDORA § 3210(a).
[6] *See id.* § 3210(d).
[7] Programmatic Guidance, lines 284-285.
[8] Programmatic Guidance, lines 293-295.
[9] Programmatic Guidance, lines 303-304 and 331-334.
[10] The Alliance is aware that some health insurance providers have taken the position that they will not immediately cover some therapies approved under accelerated approval in order to provide time for the confirmatory trials to be completed. *See, e.g.*, https://provcomm.ibx.com/pnc-ibc/news/Pages/Coverage-for-certain-drugs-biologics-and-gene-therapies-with-FDA-

Additional, Specific Comments

We offer the following additional, specific comments for consideration as the Agency works to finalize the guidance documents.

In the Programmatic Guidance, we appreciate the examples that FDA provides throughout the guidance—in particular, to illustrate reasonably likely surrogate endpoints and intermediate clinical endpoints.[11] To the extent feasible, we urge FDA to provide additional examples in the final guidance, particularly with respect to diseases that disproportionately affect older Americans. FDA helpfully includes a footnote to the Agency's webpage "Surrogate Endpoint Resources for Drug and Biologic Development,"[12] but the guidance would be further strengthened if FDA incorporated additional examples from among the cases listed on the website.

We appreciate that FDA acted expeditiously to issue the draft guidance documents. Recognizing that change in political leadership in the Administration, including at HHS and FDA, may impact FDA's processes for issuing guidance documents going-forward, we nevertheless urge the Agency to issue final guidance not later than 1 year after the close of the comment period, as per the FDORA requirement.[13] Final guidance will enable FDA and sponsors to operationalize new aspects of the accelerated approval program efficiently and consistently.

Finally, we note that, given the synergy in topics between the two draft guidance documents, sponsors and other members of the public would benefit from combined final guidance. The information about when FDA will consider a confirmatory trial to be "underway" could be consolidated into the section of the Programmatic Guidance pertaining to confirmatory trials. Having one final guidance will reduce redundancy and provide a more streamlined resource for public use.

Conclusion

The accelerated approval pathway is a critical tool to enable FDA to expedite availability of drugs and biologics to address unmet medical need in the treatment of a serious or life-threatening diseases or conditions. We applaud the Agency for continuing to strengthen the operation of this pathway through implementation of the FDORA amendments. Please contact Sue Peschin, President & CEO at the Alliance for Aging Research at speschin@agingresearch.org with any questions. Thank you for considering our recommendations as you finalize these guidance documents.

Sincerely,

Alliance for Aging Research
Global Alzheimer's Platform Foundation
Partnership to Fight Chronic Disease

---

accelerated-approval.aspx. The Alliance strongly disagrees with such positions. However, we believe that timely implementation of the confirmatory trial and withdrawal procedures will help combat ongoing skepticism about the strength of the accelerated approval process.

[11] Programmatic Guidance, lines 208-226 and 239-253

[12] Programmatic Guidance, footnote 26.

[13] *See* FDORA § 3210(d)(2)(B).