February 6, 2025

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

Re: FDA-2024-D-2033, Expedited Program for Serious Conditions - Accelerated Approval of Drugs and Biologics

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

Dear Acting Commissioner Brenner:

Thank you for the opportunity to provide comments to the Food and Drug Administration (FDA) on the following draft guidance issued in December 2024:

- *Expedited Program for Serious Conditions - Accelerated Approval of Drugs and Biologics*

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 Medicaid.

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.

RECOMMENDATIONS

Granting Accelerated Approval

1. *Delineate a clearer framework to ensure more consistent and appropriate use of the accelerated approval program.*

We appreciate FDA's descriptions and examples of potentially appropriate settings and conditions for accelerated approval. However, we are concerned at the lack of clear definitions or standards for certain aspects of accelerated approval. Leaving room for interpretation of when accelerated approval is appropriate is more beneficial to sponsors than it is to patients and providers. The Health and Human Services Office of the Inspector General (HHS OIG) released a report in January 2025 that outlined multiple instances in which FDA deviated from the typical accelerated approval procedure, leading to drugs being inappropriately approved and eventually withdrawn.[1]

To avoid such deviations, we recommend that FDA delineate a clearer framework to ensure more consistent and appropriate use of the accelerated approval program. Specifically, the areas of deviation identified by the OIG report should be standardized in such a framework. We also recommend that FDA make public a standardized accelerated approval review template that includes a structured explanation for why accelerated approval was deemed necessary as well as the justification and evidence for use of the chosen surrogate endpoint.

[1] https://oig.hhs.gov/documents/evaluation/10160/OEI-01-21-00400.pdf

2. *Clearly define the parameters of a positive benefit-risk profile to ensure that the standard for clinical benefit is not left open to interpretation.*

Patients and providers should understand the uncertainty and potential risks associated with a drug approved through the accelerated approval program.

We recommend that FDA further define several terms that are used to determine whether a drug should be approved using accelerated approval. FDA should issue definitions and evidence to support conclusions for "reasonably likely" and "acceptable risk" in the final guidance to avoid overly broad interpretation of these terms that could potentially lead to more patient harm than benefit.

Surrogate Endpoints

3. *Specify scenarios in which surrogate endpoints should not be used, such as in the case of acute disease or in cases in which clinical endpoints are available.*

We are concerned about the lack of clear standards for how surrogate endpoints are chosen and in which specific cases they are appropriate to use. In the final guidance, FDA should specify when it is and is not appropriate to use surrogate endpoints. For example, FDA should discourage the use of surrogate endpoints (1) in cases where clinical endpoints are available, and (2) for drugs and biologics that treat an acute disease, where there is no advantage to using surrogate endpoints due to the rapid progression of the disease.

As we outlined in our prior comment letter on accelerated approval, we recommend that FDA define a clear and consistent framework for identifying surrogate endpoints that are appropriate for conducting trials under the accelerated approval pathway.[2] FDA should also 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.[3,4] We also recommend that FDA revise product labeling to ensure that providers and patients know if a surrogate endpoint was used by FDA to approve the product.[5]

Intermediate Endpoints

4. *Encourage the use of intermediate endpoints that use patient-reported outcomes (PROs) whenever possible and/or where appropriate.*

We urge FDA to include more specificity in the final guidance on the appropriate use of intermediate endpoints. We recommend that FDA encourage the use of direct intermediate endpoints that demonstrate an effect on outcomes using patient-reported outcomes (PROs) whenever possible and/or appropriate. To the extent possible, PROs should be used as intermediate endpoints because, unlike clinician-reported outcomes or lab values, PROs are a more reliable indicator of patient improvement. Other intermediate endpoints, such as measuring the change to a lab value, can indicate improvement despite the patient experiencing no improvement in symptoms or function.[6]

We agree with FDA's statement in section IV. B. of the guidance that "[e]vidence of pharmacologic activity alone is not sufficient. Clinical data should be provided to support a conclusion that an effect on the surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict the intended clinical benefit." The example in the draft guidance that most supports this is a situation in which an intermediate endpoint demonstrates clinical benefit on a less serious or earlier symptom of a serious disease, but the benefit observed is anticipated to predict a favorable disease outcome (see section IV. A.).

Confirmatory Trials

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[2] https://www.arnoldventures.org/resources/arnold-ventures-comments-on-fda-accelerated-approval-draft-guidance
[3] *Ibid.*
[4] https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2782120
[5] https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2782120
[6] https://pmc.ncbi.nlm.nih.gov/articles/PMC3551627/

Arnold Ventures is aware that FDA issued a separate draft guidance describing when a confirmatory trial is considered underway. Here, we reiterate the recommendations we made in our previous comment letter regarding confirmatory trials:[7]

5. *Ensure that confirmatory trials use direct measures of patient outcomes instead of surrogate or intermediate endpoints.*
6. *Clarify that a surrogate endpoint should not be used to confirm a surrogate endpoint.*
7. *Require both final confirmatory trial protocol and patient enrollment into the trial as a condition of accelerated approval.*[8,9,10,11]
8. *Require that manufacturers comply with requirements for post-marketing studies in a timely manner.*[12,13]

Withdrawal of Accelerated Approval

9. *Streamline the expedited withdrawal process to avoid dangerous or ineffective drugs staying on the market for longer than necessary.*

We are concerned that the expedited withdrawal process detailed in the draft guidance is lengthy and cumbersome. Accelerated approval drugs for which confirmatory trials do not demonstrate direct benefits for patients are allowed by FDA to "dangle" on the market despite a lack of evidence that they are effective. These "dangling" approvals, as FDA refers to them, can help sponsors keep their marketing authorization for years. One example of a dangling approval is hydroxyprogesterone caproate (HPC), marketed as Makena, for which FDA ultimately withdrew approval after 12 years on the market. HPC was cited in OIG's January 2025 report as one of three accelerated approval drugs that raised concerns.[14]

We urge FDA to automatically withdraw an accelerated approval drug from the market when the confirmatory trial is negative without the need for voluntary withdrawal by the manufacturer or an advisory committee meeting.[15]

Should the FDA keep in its process the use of an advisory committee, FDA should ensure that the advisory committee tasked with evaluating withdrawal recommendations makes evidence-based decisions. FDA should ask Congress to strengthen the Federal Advisory Committee Act by establishing standardized timing and process of convening advisory committees. Furthermore, we urge FDA to ensure that advisory committee members are free of conflict of interest and discourage the approval of waivers whenever possible.[16]

10. *Automatically withdraw approval of a drug that received accelerated approval but failed to complete a successful confirmatory trial by FDA's deadline.*

FDA has allowed "delinquent" approvals to linger on the market, despite failing to complete their required confirmatory trials by their deadline. In fact, more than half of the drugs granted accelerated approval from 2012 to 2021 did not complete confirmatory trials by FDA's deadline.[17] As of 2020, 11 of the 16 accelerated approval drugs that have been withdrawn from the market had been on the market for 10 years without confirmatory studies demonstrating efficacy.[18]

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[7] https://www.arnoldventures.org/resources/arnold-ventures-comments-on-fda-accelerated-approval-draft-guidance
[8] https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2782120
[9] https://www.nature.com/articles/s41571-018-0066-3
[10] https://jamanetwork.com/journals/jama/fullarticle/2801050
[11] https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2733561
[12] https://www.arnoldventures.org/resources/arnold-ventures-approval-issue-brief
[13] https://www.commonwealthfund.org/blog/2021/reducing-spending-prescription-drugs-limited-clinical-evidence
[14] https://oig.hhs.gov/reports/all/2025/how-fda-used-its-accelerated-approval-pathway-raised-concerns-in-3-of-24-drugs-reviewed/?source=email
[15] https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2782120
[16] https://pubmed.ncbi.nlm.nih.gov/25199895/
[17] https://jamanetwork.com/journals/jama-health-forum/fullarticle/2803074
[18] https://www.commonwealthfund.org/blog/2021/reducing-spending-prescription-drugs-limited-clinical-evidence

These delinquent approvals can be costly to the health of patients as well as to the health care system. For example, eteplirsen, which was identified by OIG in its report concerning accelerated approvals, was approved in 2016 to treat Duchenne muscular dystrophy.[19] As of January 2025, its confirmatory trials remain unfinished, despite an original deadline of November 2020. Eteplirsen can cost more than $1 million per year for a one-time treatment and patients and payers in the U.S. spent $2.6 billion over 2017-2022 period on this drug.[20]

Delinquent approvals can set a precedent for future approvals based on unconfirmed evidence. Eteplirsen's approval, for instance, was referenced in the accelerated approval of three other drugs to treat Duchenne muscular dystrophy.[21] All three drugs used the same surrogate endpoint—which was never validated by confirmatory trial—as was used in the pre-approval trials for eteplirsen. According to the OIG report, the clinical reviewer for one of the three drugs concluded that there was not clear evidence that the drug's effect on the surrogate endpoint met the reasonably likely standard, but the reviewer felt bound by prior FDA approvals, including eteplirsen.[22]

To curb delinquent or dangling approvals and their potentially compounding negative effects, we recommend that FDA automatically withdraw approval of a drug that received accelerated approval but failed to complete a successful confirmatory trial by FDA's deadline.

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 Natilee Festa, Health Care Manager and Andrea Noda, Vice President of Health Care at Arnold Ventures, with assistance from John H. Powers, MD.

Please contact Mark E. Miller, Executive Vice President of Health Care at Arnold Ventures at mmiller@arnoldventures.org or Andrea Noda 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 drugs and biological products.

Sincerely,

Andrea Noda

Vice President of Health Care

Arnold Ventures

[19] https://oig.hhs.gov/documents/evaluation/10160/OEI-01-21-00400.pdf
[20] https://jamanetwork.com/journals/jama/fullarticle/2816420
[21] https://oig.hhs.gov/documents/evaluation/10160/OEI-01-21-00400.pdf
[22] *Ibid.*