March 10, 2025

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

RE: Docket No. FDA-2024-D-3334; Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway—Draft Guidance

To Whom It May Concern:

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each year[i] and over 600,000 Americans living with the disease,[ii] we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway**."

The accelerated approval pathway is an invaluable means of speeding the delivery of novel therapeutics to patients. Over 60% of accelerated approvals have been granted for oncology indications, facilitating access to effective anti-cancer therapies for patients an estimated median of 3.1 years sooner than they would otherwise be made available through traditional approval.[iii] Patients diagnosed with lung cancer have greatly benefitted from this pathway, with 28 drugs indicated for the treatment of lung cancer receiving accelerated approval since the pathway's inception, with 18 of the accelerated approvals converted to full approval and only four withdrawals.[iv]

The majority of oncology accelerated approvals are based on demonstration of efficacy by assessment of tumor dynamics (e.g., objective response rate), which may not always translate to long-term clinical benefit, such as overall survival (OS). Timely conduct of postapproval studies assessing time-to-event endpoints like OS or progression-free survival (PFS) is critical to instilling confidence in patients and their providers that the treatments will provide meaningful clinical benefits. We applaud the FDA for issuing this draft guidance, in compliance with and expanding on The Consolidated Appropriations Act, 2023, to clarify the Agency's interpretation of confirmatory trials being "underway" and the factors the FDA will consider to determine appropriate requirements for when and how the trial should be underway.

Determination of Considerable Toxicity

The draft guidance highlights that confirmatory trials being underway is "especially important when the drug has considerable toxicity." We appreciate that patients should not be needlessly exposed to toxicities without verification of clinical benefit. However, as drugs receiving accelerated approval are for serious or life-threatening diseases, the risk-benefit of the therapy, and therefore tolerance for toxicity, must be considered. Further clarification is needed on how the Agency defines "considerable toxicity" in relation to determination of when and how far a confirmatory trial must be underway.

Factors to Determine When a Confirmatory Trial Should be Underway

As having a confirmatory trial underway prior to an initial approval presents inherent risks and may demand substantial resource investments for clinical trial sponsors, regulatory expectations around the timing of confirmatory trial initiation should be communicated as clearly as possible. The draft guidance highlights conflicting expectations for similarly-described circumstances: (1) the FDA may require enrollment to be complete at the time of accelerated approval if the Agency "determines that continued enrollment/retention after the drug product is on the market is likely to be especially challenging," and (2) having a confirmatory trial underway may not be required when a sponsor "faces unique challenges with initiating postapproval confirmatory trials prior to approval." We request additional clarity in the final guidance on the FDA's expectations for timing of confirmatory trials, particularly in cases where sponsors may face challenges to trial initiation, accrual, and retention. This could involve more clearly differentiating, through examples or listing general considerations or factors, the circumstances that would require a confirmatory trial be fully enrolled versus those in which a trial may not be required to be underway prior to accelerated approval. Additionally, defining factors for when a trial is "likely to be especially challenging" would be helpful.

Communication on Accelerated Approval

The draft guidance document notes that the FDA and sponsor should agree on the confirmatory trial design and timeline "as soon as practicable". As there is no formal process for product development through the accelerated approval pathway, further guidance from the Agency on how and when (e.g., formalizing what "early" means) sponsors should engage with the Agency in the development process to enhance the effective use of the pathway would be valuable.

LUNGevity appreciates the opportunity to comment on this important guidance. While the accelerated approval pathway has played an impactful role in expediting the approval of life-saving therapies, postapproval trials to confirm such treatments convey meaningful clinical benefits to patients are critical. Refinement and finalization of this draft guidance to industry on the regulatory expectations for initiation and conduct of confirmatory trials after accelerated approval will help ensure their timely and efficient completion. Please feel free to reach out to me at bmckelvey@lungevity.org with any questions.

Sincerely,

Brittany Avin McKelvey
Senior Director, Regulatory Policy
On Behalf of LUNGevity Foundation

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[i] Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
[ii] Centers for Disease Control and Prevention. United States Cancer Statistics. Available at https://gis.cdc.gov/Cancer/USCS/#/Prevalence/
[iii] Gautam U. Mehta et al., Oncology Accelerated Approval Confirmatory Trials: When a Failed Trial Is Not a Failed Drug. JCO 42, 3778-3782(2024). DOI:10.1200/JCO-24-01654
iv Friends of Cancer Research. Accelerated Approvals in Oncology Dashboard. Accessed February 10 2025. Accelerated Approvals in Oncology (1992 – Present) - Friends of Cancer Research

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[i] Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
[ii] Centers for Disease Control and Prevention. United States Cancer Statistics. Available at https://gis.cdc.gov/Cancer/USCS/#/Prevalence/