March 6, 2025

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

RE: Docket No. FDA-2024-D-2033; Accelerated Approval – Expedited Program for Serious Conditions, Guidance for Industry—Draft Guidance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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Accelerated Approval – Expedited Program for Serious Conditions**."

The accelerated approval pathway is critical to provide lifesaving treatments to patients sooner, oftentimes years (median 3.1 years) before they would have access through traditional approval. This crucial pathway has been beneficial particularly in oncology (over 60% of accelerated approvals have been granted for oncology indications)[iii], and particularly for patients diagnosed with lung cancer. Since the pathway's inception, 28 accelerated approvals have been granted for lung cancer indications, with over half (64%) converted to full approval and only four accelerated approvals withdrawn.[iv] Furthermore, the median time from accelerated to full approval in this indication is only 2.8 years, and only a median 2.6 years to withdrawal of accelerated approval.

For oncology, the Agency's March 2023 draft guidance, "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics[v]," has been instrumental to promoting a clinical development program that supports accelerated approval of anti-cancer therapies while ensuring robust evidence of safety and efficacy. The Agency's new draft guidance further supports this goal across disease indications. It is imperative to continue to support the accelerated approval pathway to benefit patients, while continuing to encourage completion of confirmatory trials to verify patient safety and benefit. We applaud the Agency for providing draft guidance in fulfillment of The Consolidated Appropriations Act, 2023 and providing additional clarification on the pathway's

procedures. We have a few areas to elicit further clarification as the Agency works to finalize this draft guidance.

Communication on Accelerated Approval

In Section III, the guidance notes "communication between the sponsor and Agency is critical," and recommends that the sponsor "communicate with the Agency early in development". Currently, there is no formal process for product development through the accelerated approval pathway, which can lead to inefficiencies in trial planning and confusion around the optimal approach to using this 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. A formalized framework which allows for focused discussions on trial design, endpoints, and plans for confirmatory trials could ensure timely development and review.

Novel Endpoints for Accelerated Approval

We appreciate the draft guidance's inclusion of Section IV.B on evidentiary criteria for accelerated approval, including important factors to consider when assessing the likelihood of surrogate or intermediate clinical endpoints to predict clinical benefit. However, further guidance is needed on the evidentiary requirements for use of novel surrogate or intermediate clinical endpoints in regulatory decision-making. While the Agency has provided guidance on the potential for use of specific novel intermediate endpoints (e.g., pathologic complete response in breast cancer, ctDNA in early-stage solid tumors), a standardized process for validating intermediate clinical endpoints for regulatory purposes has not been established. This potentially hinders the ability to use relevant novel endpoints to support accelerated approvals. A defined process could provide greater predictability in generating evidence to support the use of surrogate and intermediate clinical endpoints, encourage collaborative data collection efforts, and support the rigorous validation required to advance their use in regulatory decision-making. For example, the finalized guidance on use of ctDNA in early-stage solid tumors as an early endpoint[vi] notes specific requirements for trial-level and patient-level associations with long term outcomes through meta-analyses. This draft guidance does not include language around required associations or meta-analyses, and an aligned position on processes and principles for validation across guidance documents and the Agency would help prevent confusion on the evidentiary requirements.

Confirmatory Trials and Innovative Trial Approaches

The draft guidance notes the acceptability of the confirmatory trial being conducted in a "different but related population", providing the example of an oncology accelerated approval in late-stage disease and the confirmatory trial being conducted in an earlier-stage disease. Differences between early-stage and late-stage cancer populations may complicate interpretation of disparate results between the trial supporting accelerated approval and the confirmatory trial. If clinical benefit is not confirmed in the earlier setting by the confirmatory trial, would the accelerated approval in the late-stage setting be revoked, when there may be clinical benefit in this population? Additional guidance on when conducting a confirmatory trial in a different population is appropriate is needed.

The draft guidance document highlights the use of a single trial to support an accelerated approval and later fulfill the demonstration of clinical benefit. This approach holds greater risk and higher investment of resources that may be prohibitive to some sponsors. The one-trial approach requires a much larger number of patients to be appropriately powered to conduct statistical analyses for both the intermediate and long-term clinical endpoints. Early communication with the Agency will be crucial in planning a one-trial approach to ensure the appropriateness of the trial design and endpoints given the undertaking, which the guidance should note.

The draft guidance also highlights the possibility for confirmatory trials to leverage novel trial designs, specifically naming pragmatic and decentralized trial designs. We appreciate the recommendation to leverage novel trial designs such as pragmatic and decentralized trials, which could enroll and retain a more representative patient population and lessen patient, investigator, and site burden. However, additional guidance on the use of these trial designs for confirmation of clinical benefit for accelerated approval is needed. As stated in the "Integrating Randomized Controlled Trials for Drug and Biological Products into Routine Clinical Practice"[vii] draft guidance, drugs that are already approved with well-characterized safety profiles are most suitable for these designs. This seems contradictory with the present draft guidance which highlights safety risks after an accelerated approval owing to "less information available at the time of accelerated approval about the occurrence of rare or delayed adverse events." Guidance on when pragmatism may be appropriate for confirmatory trials is needed.

Lastly, the draft guidance does not include mention of real-world data (RWD) and the role it may play in confirmation of benefit, particularly in cases where it may be challenging to conduct clinical trials after accelerated approval. Past FDA Commissioner Robert Califf in a September 2023 public Friends of Cancer Research meeting[viii] highlighted confirmation of clinical benefit after accelerated approval as an example of where RWD could be easily

leveraged, providing example indications in Alzheimer's and obesity therapeutics. Guidance from the Agency on how RWD may be used to help satisfy postmarketing requirements for confirmation of clinical benefit is needed.

LUNGevity appreciates the opportunity to comment on this important guidance. The accelerated approval pathway has played a critical role in the treatment of lung cancer by speeding the delivery of effective therapeutic options to patients. The continued use of this pathway is critical for patients, and the continued refinement on supported endpoints, confirmatory trials, and processes for withdrawal are necessary to ensure the robust use of this pathway. 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

---

[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 January 16 2025. Accelerated Approvals in Oncology (1992 – Present) - Friends of Cancer Research

[v] US FDA, Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics Guidance for Industry

[vi] US FDA, Use of Circulating Tumor ctDNA for Curative-Intent Solid Tumor Drug Development Guidance for Industry

[vii] US FDA, Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice Draft Guidance for Industry

[viii] US FDA Commissioner Pushes Real-World Evidence To Guide Use Of Alzheimer's, Obesity Drugs