July 30, 2026

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

RE: Docket No. FDA-2026-D-2839; Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products; Draft Guidance for Industry

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 1 in 19 people that will be diagnosed with lung cancer in their lifetime, including the more than 229,000 Americans diagnosed with lung cancer last year[i] and the 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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products**".

The product classes addressed by this draft guidance are central to the modern treatment of lung cancer. PD-(L)1 inhibitors are a therapy backbone across non-small cell lung cancer (NSCLC), antibody-drug conjugates (ADCs) are a rapidly expanding class for patients with lung cancer, and CD3 bispecific T-cell engagers are now part of the treatment landscape in small cell lung cancer (SCLC). Because these therapies play such a vital role in lung cancer treatment, the adequacy of their nonclinical safety characterization is of direct importance to the patients we serve.

LUNGevity supports efforts to improve the efficiency of oncology drug development and to reduce unnecessary animal use, provided that the rigorous standards of safety and efficacy of therapies for patients are maintained. We applaud the FDA for advancing approaches intended to streamline nonclinical programs without compromising the protection of patients who participate in clinical trials or receive approved therapies. To help ensure that streamlined programs continue to adequately characterize the safety risks most relevant to patients with lung cancer, we offer the following comments where additional clarification or guidance from the Agency would be valuable as the guidance is finalized.

Antibody-Drug Conjugates: Defining a "Well-Characterized" Payload and Addressing Conjugate- and Target-Specific Toxicities

The draft guidance recommends that, for antibody-drug conjugates (ADCs) with cytotoxic payloads, "when the safety of the payload is well-characterized and the payload is the main driver of toxicities, the 3-month toxicology study may be conducted in rodents only, irrespective of ADC binding to the target antigen". LUNGevity supports leveraging accumulated knowledge of payload characterization to avoid duplicative animal studies. We note, however, that emerging literature indicates that ADCs sharing the same payload do not necessarily share the same toxicity profile, and that toxicity can be shaped by the linker, the drug-to-antibody ratio, conjugation chemistry, the bystander effect, and the antibody target. Interstitial lung disease (ILD)/pneumonitis is a particularly salient example for patients with lung cancer, as ILD has been observed across deruxtecan-based ADCs regardless of target antigen, consistent with a payload-associated mechanism[iii]. While this alone may imply the payload as "the main driver of toxicities", reported ILD incidence varies substantially among agents that share the same topoisomerase I inhibitor payload and differs by target and indication.[iv] This variability suggests that payload precedent alone may not fully predict the risk of serious, potentially fatal toxicities such as ILD.

Accordingly, we request that the FDA define the criteria by which a payload is considered "well-characterized" and the basis for concluding that the payload is the "main driver of toxicities." We also recommend clarifying that when an ADC's linker, drug-to-antibody ratio, conjugation chemistry, or target differs from the reference approved ADC, the weight-of-evidence (WoE) assessment or study design should specifically evaluate conjugate-level and target-mediated toxicities rather than relying on payload precedent alone.

Relatedly, the guidance provides that when the antibody target is novel and does not bind in the rodent species, a WoE assessment should also be submitted. Because a payload-only or non–target-binding rodent study will not characterize on-target, off-tumor toxicity arising from antibody binding to antigen in normal tissues, and as the literature-based component of a WoE is inherently limited for a novel target, we encourage the Agency to specify the methods it expects sponsors to use to characterize target-mediated toxicity in the absence of a pharmacologically relevant rodent model (e.g., human tissue cross-reactivity studies, fit-for-purpose new approach methodologies (NAMs), or a relevant non-rodent species).This will help ensure that streamlining to a rodent-only study does not leave antigen-driven risks uncharacterized before first-in-human exposure.

CD3 Bispecific T-Cell Engagers: Robust First-in-Human Dose Selection and Cytokine Release Risk Assessment

The draft guidance provides that, for CD3 bispecific T-cell engagers, an "assessment of a product's chronic effects may be based on a WoE risk assessment in lieu of a 3-month toxicology study." We agree that the conventional value of animal toxicology studies is limited for this class, as animal models have not reliably predicted cytokine release syndrome (CRS), the dominant acute safety concern for T-cell engagers, and there is currently no validated method to predict CRS from preclinical data.[v]

Because reducing reliance on animal studies places greater weight on human-relevant methods, we encourage the FDA to clarify, within the WoE framework, its expectations for first-in-human starting-dose justification and CRS risk characterization for CD3 bispecifics, including the role of *in vitro* cytokine-release assays, minimal anticipated biological effect level (MABEL) approaches, and quantitative systems pharmacology or translational modeling, as well as risk-mitigation strategies such as step-fractionated or priming dosing. Clear expectations will help ensure that the move away from animal studies is paired with rigorous, fit-for-purpose approaches that protect participants in early-phase trials.

PD-(L)1 Antibodies: Accounting for Product-Specific Features in the Weight-of-Evidence Approach

The draft guidance provides that, for PD-(L)1 blocking monospecific antibodies, the "assessment of chronic effects may be based on a WoE assessment in lieu of a 3-month toxicology study". PD-(L)1 inhibitors are foundational to the treatment of lung cancer, and their characteristic immune-related adverse events, including pneumonitis, colitis, hepatitis, endocrinopathies, and myocarditis, are generally not well predicted by animal toxicology studies. This supports a WoE approach grounded in the substantial clinical experience accumulated with approved agents in this class.

We request that the FDA clarify how the WoE approach applies to PD-(L)1 agents whose engineering differs from approved products in ways that could alter the immune-toxicity profile and where class precedent may not fully apply. Additionally, given that pneumonitis is of heightened concern for patients with lung cancer, who may have limited pulmonary reserve or prior thoracic radiation, the final guidance should make clear that the WoE for a given PD-(L)1 product accounts for product-specific and indication features rather than relying solely on the class as a whole.

Streamlined Approaches in the Context of Combination Regimens

Contemporary lung cancer treatment is predominantly combination-based. The draft guidance currently addresses the nonclinical safety assessment of individual products and does not address whether or how the streamlined approaches and WoE framework apply when products are developed in combination, where additive or synergistic toxicities (such

as overlapping pneumonitis or hepatotoxicity) may emerge that neither a single-agent program nor existing literature precedent would capture. We encourage the FDA to clarify its expectations for nonclinical characterization of combination regimens, so that efficiencies gained for single agents do not inadvertently reduce the characterization of combination-specific risks that are highly relevant to patients with lung cancer.

New Approach Methodologies: Clarifying Validation and Context-of-Use Expectations

The draft guidance identifies fit-for-purpose NAMs as a component that may supplement a WoE assessment and cross-references the Agency's March 2026 draft guidance on NAMs[vi]. LUNGevity strongly supports the development and qualification of NAMs as a path to reducing animal use while maintaining, and potentially improving, the human relevance of safety assessment. To ensure that increasing reliance on NAMs strengthens rather than weakens safety characterization, we encourage the FDA to clarify the level of validation or qualification, and the basis for establishing context-of-use, that the Agency expects before a NAM may substitute for, as opposed to supplement, an animal study within a streamlined program.

LUNGevity appreciates the opportunity to comment on this important draft guidance. We support the Agency's goals of facilitating more efficient oncology drug development and reducing unnecessary animal use, and we share the FDA's commitment to achieving these efficiencies without compromising the safety of patients. With the proposed additional clarifications and considerations, we support this draft guidance. Please feel free to reach out to me at bmckelvey@lungevity.org with any questions.

Sincerely,

Brittany McKelvey

Brittany Avin McKelvey
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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] Shigehiro Koganemaru, Hirobumi Fuchigami, Chihiro Morizono, Hiroko Shinohara, Yasutoshi Kuboki, Keiji Furuuchi, Toshimitsu Uenaka, Toshihiko Doi, Masahiro Yasunaga; Potential Mechanisms of Interstitial Lung

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[iv] L. Maurier, A.-L. Chéné, P. Hulo, J. Chen, C. Sagan, E. Pons-Tostivint. Diffuse interstitial lung disease induced by antibody-drug conjugates. *Revue des Maladies Respiratoires* **42,** 5: 274-285 (2025). https://doi.org/10.1016/j.rmr.2025.03.003.

[v] Lefèvre, A., Parra-Guillen, Z.P., Trocóniz, I.F. *et al.* Leveraging *in vitro* Tumor Cell Killing and Cytokine Release to Predict Cytokine Release Syndrome Associated with CD3 T-cell Bispecifics in Oncology: a Retrospective Analysis. *AAPS J* **28**, 20 (2026). https://doi.org/10.1208/s12248-025-01177-9

[vi] Draft guidance for industry titled “General Considerations for the Use of New Approach Methodologies in Drug Development”, available at https://www.fda.gov/media/191589/download (March 2026).