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Helping hematologists conquer blood diseases worldwide

2026
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Food and Drug Administration
5630 Fishers Lane
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Submitted electronically via https://www.regulations.gov

Re: Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products Guidance for Industry

Dear Mr. Diamantas and Dockets Management Staff:

The American Society of Hematology (ASH) appreciates this comment opportunity on the Food and Drug Administration's (FDA) draft guidance for *Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products Guidance for Industry* (FDA-2026-D-2839).

ASH represents more than 18,000 clinicians and scientists committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematology (non-malignant) conditions like sickle cell disease, hemophilia, and venous thromboembolism. In addition, hematologists are innovators in the fields of stem cell biology, transfusion medicine, and gene and cell therapies. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

Thank you for the opportunity to comment on this important and timely draft guidance. We generally support the draft guidance and wish to provide the following comments to strengthen its applicability to the development and innovation of treatments for hematologic cancers.

Overall Impressions of the Draft Guidance:

The Society generally supports the draft guidance and the more flexible, risk-based approach to nonclinical testing it advances. This approach has the potential to accelerate the development of innovative therapies while reducing unnecessary clinical trials that are performed in animals. We note that allowing trial sponsors to propose scientifically justified alternatives on a case-by-case basis may improve the efficiency of drug development without compromising the FDA's ability to evaluate the safety of drugs and therapies under clinical investigation. However, when the final guidance is released, we encourage the agency to clearly emphasize that animal studies remain scientifically necessary, are often critical and therefore animal studies should not be eliminated completely from use in clinical trials. As noted in ASH's comments on FDA's General Considerations for the Use of New Approach Methodologies (NAMs) in Drug Development draft guidance, NAMs are powerful tools but must be interpreted alongside essential systemic data obtained in living organisms.

While NAMs may replace some traditional in vitro and selected in vivo studies, they cannot fully supplant vivo drug metabolism and pharmacokinetics (DMPK) and core systemic toxicology at this time. In vivo animal studies continue to represent the most informative method for evaluating complex, multi-organ biological and toxicological effects and should remain the standard, particularly for clinical studies of immuno-oncology therapies.

ASH recommends that the FDA provide additional scientific rationale to support the specific recommendations contained in the guidance. These examples or explanations of how the FDA came to certain conclusions in the draft guidance will improve stakeholder confidence in the process and provide clear direction to clinical trial sponsors. For example, the draft guidance states that sponsors may rely on a weight-of-evidence (WoE) approach instead of conducting repeat-dose animal toxicity studies. We believe that the FDA should explain the evidence underlying this statement. When applicable, FDA should provide evidence that suggests that WoE approach is sufficient or more effective than animal safety studies in generating useful information to protect human subjects from, for example, checkpoint inhibitors.

Additionally, ASH respectfully requests that FDA clarify the scientific and regulatory rationale for focusing this guidance on PD-1/PD-L1 checkpoint inhibitors, antibody-drug conjugates, and bispecific antibodies. Specifically, why are these therapies singled out, while other potentially high-risk treatment modalities—including genetically targeted therapies such as CAR-T cell therapies, transplantation, and traditional chemotherapies—do not appear to receive comparable attention? The Society also suggests that FDA consider placing an emphasis on pre-malignant conditions such as bone marrow failure syndromes, in order to understand whether the FDA could support and approve drug development workflows based on NAMs, with priority given to ultra-rare diseases and personalized medicine approaches.

Finally, ASH recommends the FDA conduct a reassessment of the final guidance after three years of implementation to assess its impact on drug development timelines, regulatory decision-making outcomes, and any potential reductions in patient safety. If revisions are warranted after three years, the FDA should propose changes and provide the opportunity for public comment.

WoE Risk Assessment

ASH believes the guidance provides trial sponsors with a reasonable framework for developing a weight-of-evidence (WoE) assessment and is clear enough for trial sponsors to at least initiate discussions with FDA regarding drug approvals. The Society believes the guidance appropriately identifies broad categories of evidence that may be used in WoE risk assessment like investigational product data, target biology and literature, drug class effects, and modern alternatives. Although these broad categories appropriately provide flexibility for sponsors given the diversity of products and the need for case-by-case scientific judgment, ASH recommends that FDA include illustrative examples showing how sponsors may apply these categories in practice. Such examples would help clarify FDA's expectations for a sufficient WoE assessment without limiting sponsors' ability to propose scientifically justified, product-specific approaches. In short, we support the flexibility provided by the draft guidance allowing trial sponsors to choose the WoE that is best suited for their clinical trial.

Administrative Burden

We support the FDA's efforts to modernize preclinical safety evaluation and believe the proposed recommendations have the potential to reduce overall administrative burden and associated drug development costs. By allowing greater use of scientifically appropriate NAMs, the guidance can reduce the need for animal studies in cases where alternative approaches provide sufficient evidence.

At the same time, we recognize that the extent of preclinical testing will continue to vary depending on the specific product and development program. Determinations regarding the appropriate level of testing should remain flexible and be informed through early and ongoing discussions between trial sponsors and the FDA.

Although the recommendations are expected to reduce the operational and administrative burden associated with conducting animal studies, these burdens may increase the administrative effort required to prepare supporting documentation, justifying the selection and validation of the NAMs.

ASH also encourages FDA to harmonize this guidance with its guidance on NAMs in Drug Development. Clear

alignment between the two documents, including consistent terminology and expectations for the use and validation of NAMs, would minimize confusion and avoid unnecessary administrative burden for sponsors.

As noted previously, we encourage the FDA to monitor implementation of the guidance to assess whether it achieves the intended reductions in administrative burden and drug development costs. If the FDA finds that unnecessary administrative requirements remain after implementation of the guidance, the agency should consider additional refinements to further streamline the drug development process while maintaining appropriate standards for safety and scientific rigor.

Additional Commentary and Summary

ASH believes the guidance has the potential to encourage investment in innovative oncology drug development, including therapies for rare cancers, by reducing unnecessary nonclinical testing and associated development costs. Clarifying when animal testing is and is not needed may also facilitate development of antibody and cellular therapies.

Even though the draft guidance specifically addresses PD-1/PD-L1 inhibitors and bispecific antibodies, it contains limited discussion of cell therapy products. While the guidance may facilitate development of the antibody-based therapies it does address, in vivo animal testing may continue to play an important role for certain cell therapies, including chimeric antigen receptor (CAR) T-cell products, because in vivo testing for CAR T-cell products may not be as readily replaced by alternative clinical trial approaches.

We support the FDA's objective of accelerating product development while maintaining patient safety. The guidance has the potential to improve patient access to novel therapies by reducing unnecessary nonclinical testing, while FDA's case-by-case review of proposed nonclinical approaches helps ensure that appropriate safety data support first-in-human studies.

We also encourage the FDA to consider how the guidance may be applied to pre-malignant hematologic conditions, including inherited bone marrow failure syndromes, where novel NAMs may help accelerate development of therapies for ultra-rare diseases. Ex vivo hematopoietic models, including organ-on-chip platforms, may provide disease- and mutation-specific evidence that can support a WoE approach when conventional clinical trials and extensive animal testing are particularly challenging.

Thank you for the opportunity to comment on this valuable and timely draft guidance. We look forward to working with the agency on these issues. Should you have any questions please contact ASH Director, Government Relations and Public Health, Stephanie Kaplan, at *skaplan@hematology.org* or 202-776-0544.

Sincerely,

Robert Negrin, MD
ASH President