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August 29, 2025

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RE: *Myelodysplastic Syndromes: Developing Drug and Biological Products for Treatment; Draft Guidance for Industry; Availability (FDA-2025-D-0649)*

Dear Dr. Makary,

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance for industry on Myelodysplastic Syndromes: Developing Drug and Biological Products for Treatment (FDA-2025-D-0649).

ASH represents more than 18,000 clinicians and is 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 (SCD). In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be 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.

Comments on Draft Guidance:

The Society commends the FDA for releasing draft guidance outlining the Agency's expectations for the development of disease-modifying therapies for myelodysplastic syndromes (MDS). The Society is generally supportive of this draft guidance and appreciates the Agency's thoughtful approach. ASH supports patient-centered clinical research that improves outcomes for individuals with MDS and believes the guidance reflects much of the current state of MDS clinical practice and therapeutic drug development.

The Society believes that trial populations should be inclusive of all populations impacted by the disease and that includes older adults, racial and ethnic minorities, and patients with renal/hepatic impairment. Inclusive trial populations are essential for the resultant therapeutic to be generally applicable to patients in the real-world. ASH recommends the Agency encourage industry partners to include individuals with well-controlled human immunodeficiency virus (HIV) in MDS clinical trials. People living with HIV have increased cancer incidence and cardiovascular diseases compared to the general population; as such this epidemiology needs to be better studied in the context of MDS trials. By excluding patients with well controlled HIV, MDS clinical trials are selecting out these important populations that are reflective of the US real world population.

The guidance also suggests, and the Society agrees that pediatric populations should be considered in the early clinical development plan stage. However, it is important to keep in mind that MDS in pediatric and adolescent populations is rare, and in many cases is often hypocellular. As only a few individuals within this population have comparable MDS features

such as those in adult or older adult individuals, this could create challenges for industry partners seeking to include pediatric or adolescent patients in their trials. Trial developers should also keep in mind that MDS in children and adolescents may also be considered a different disorder, especially when occurring in predisposition syndromes. The Society recommends inclusion of pediatric MDS populations in cases of pediatric MDS that mimic adult disease with comparable genetic mutations and phenotypes. In such situations, it is critical that these pediatric patients be included in early phase trials to benefit from targeted therapies.

ASH recognizes that MDS can present in distinct types and degrees of severity according to the characteristics of the patients and progression risk of the disease creating differing life expectancies and therapeutic endpoints depending on the individual. Industry partners should therefore be cognizant of low-risk MDS subtype endpoints and goals which may differ from higher-risk MDS individuals.

Overall survival (OS), the standard endpoint for full approval of clinical trials studying therapies for MDS, may be the appropriate endpoint for most individuals. However, consideration should be given to other clinically meaningful endpoints such as partial response (PR) or complete response (CR), or transfusion independence endpoints where survival for children and adolescents can be achieved by hematopoietic stem cell transplantation (HSCT). In addition, given the fact that the field is unclear about secondary and surrogate endpoints, ASH recommends that the FDA consider convening stakeholders in the field to reach consensus on relevant and appropriate endpoints for MDS trials. This is important because overall survival as a core primary endpoint may require large sample sizes and follow ups over several years which may limit the development of novel therapies and could be further confounded by cross over designs or sequential therapies being studied, especially for low risk MDS.

The Society is also supportive of the draft guidance's recommendation that dose selection should prioritize the biological activity and tolerability of the drug rather than maximum tolerated dose, although it should be recognized that lowest minimum biological activity does not always correspond with therapeutic response. ASH acknowledges that this may be dependent on pharmacodynamic effects if the trial seeks to target a specific antigen or pathway. ASH suggests that the FDA should encourage industry partners to further refine dose selection strategies after the evidence of a drug's therapeutic promise is made evident.

ASH approves of the draft guidance's recommendations for safety reporting that advises trial sponsors to account for the high rates of cytopenias and other common MDS-related events when determining what constitutes a reportable adverse event. While data on the highest degree of cytopenia observed in MDS clinical trials should be collected, it should be performed to a degree that is manageable for all sites in the United States running these trials.

Additionally, the Society supports the recommendation that in cases where an in vitro companion diagnostic device may be needed, trial sponsors should consider this crucial component early in trial development and ensure that the companion diagnostic has appropriate approval from the FDA.

We also recommend that the Agency include guidance on the use of Bayesian statistics in early phase trials to minimize the number of patients needed to evaluate investigational therapies.

We also believe there would be benefits to the Agency encouraging industry partners and trialists to collect cardiovascular data during MDS trials to further understand drug and biological side effects. Some data have also suggested that clonal cytopenias of unknown significance patients behave like low-risk MDS[i] [ii] [iii] and should be included in low-risk MDS clinical trials. We ask that the Agency encourage trial designers to make such adjustments as further information regarding low-risk MDS patients is developed. Finally, we also suggest that feasibility guidance on extremely rare subtypes such as Isocitrate Dehydrogenase 1 (IDH1) be included or provided by the Agency.

ASH appreciates the opportunity to provide these comments and looks forward to any response you might have. Please consider ASH a resource; we would be pleased to provide additional information or support. If you have any questions, please use ASH Director of Government Relations and Public Health Stephanie Kaplan (*skaplan@hematology.org* or 202-776-0544) as your point of contact.

Sincerely,

Belinda A. Avalos, MD

Belinda Avalos, MD
ASH President

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[i] https://www.sciencedirect.com/science/article/pii/S000649712403101X
[ii] https://ashpublications.org/bloodadvances/article/5/8/2272/475824/Clinical-molecular-and-prognostic-comparisons
[iii] https://pmc.ncbi.nlm.nih.gov/articles/PMC11216976/