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April 9, 2025

Sara Brenner, MD, MPH
Acting Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted electronically via Regulations.gov

Re: Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products; Guidance for Industry and Other Interested Parties. Docket No. FDA-2024-D-4689

Dear Acting Commissioner Brenner,

The American Society of Hematology (ASH) appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA) draft guidance outlining recommendations to sponsors and other interested parties on the use of artificial intelligence (AI) to produce information or data intended to support regulatory decision-making regarding safety, effectiveness, or quality for drugs.

ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematologic conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in developing innovative approaches to advance medicine specifically in the fields of stem cell biology, regenerative medicine, transfusion medicine, and cell and gene therapy. Our mission is to foster high-quality care, transformative research, and innovative education to improve the lives of all patients with blood and bone marrow disorders.

The Society generally supports the use of AI in the health care system and to improve the safety and efficacy of drugs and biologics approved by the FDA. With the appropriate foundation, and the additional guardrails around AI models, we believe AI has the potential to improve and transform clinical research, particularly in the field of hematology. We offer the following comments for consideration as the FDA crafts the final guidance on the use of AI to support its decision-making processes.

Comments on the Draft Guidance:

Transparency will be critical to ensuring the appropriate use of AI in the FDA's review processes. This will require comprehensive documentation as to how an AI model was developed. Accurate and complete documentation of any AI model is essential in order for it to be evaluated by other entities. ASH supports the use of rigorous risk-based assessments to ensure models are well-validated before regulatory use and believes that comprehensive documentation enhances transparency and reproducibility. Additionally, proactively addressing algorithmic fairness in an AI model is crucial, particularly for those living with rare diseases, and comprehensive documentation of addressing the algorithmic fairness is equally important.

Pre-planning for risk mitigation, especially data drift, is necessary, as well as clear guidance for the model risk assessment process. Data drift can occur when the inherent structure of the data changes over time. To prevent this, the data must be curated in an analogous fashion, or the algorithm must be updated to reflect the changes in data. In hematology research, this issue could arise depending on how genomics data is collected. Many institutions rapidly change how they receive genomics data, such as changing their third-party vendor or developing internal tests. Differences in the formatting of results would disrupt algorithms dependent on specific data structures. If AI algorithms are developed on previously accurate but currently outdated data, then that can potentially cause many unintentional issues.

ASH supports the final guidance language that would require greater transparency as to the data used to develop and evaluate AI models incorporated into drug and biologics development. Just as clinical trials report subject demographics, AI models should disclose dataset composition, so investigators have a clear understanding of the information used to generate the AI results. Standardizing databases and ensuring the use of high-quality, labeled datasets are crucial for training reliable healthcare AI models. Additionally, transparency should extend to disease-specific subgroups, such as molecular stratifications in conditions like acute myeloid leukemia, to improve model reliability and applicability.

While we support the guidance in general, we do believe that certain aspects of the guidance require additional thought and development. Hematologic diseases are very dynamic, and therefore AI models for these conditions must adapt to changes in disease markers (e.g., clonal evolution in myeloid malignancies). Additionally, hematologic disease classification often evolves with emerging biomarkers in a specific disease state. AI models for hematologic diseases will require continuous validation to ensure the model maintains its clinical relevance over time. Therefore, we believe that the final guidance should address AI adaptability in these conditions.

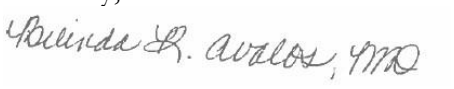
The Society also notes that rare blood disorders need special consideration because AI models trained on limited datasets, due to the rarity of a disease, may require the use or development of alternative credibility validation strategies. For example, in hematology, AI could be used to create a diagnostic tool for acute promyelocytic leukemia (APL) among newly diagnosed undifferentiated leukemia patients, which comprise < 10% of cases. Without proper data curation, one could accidentally create an AI tool with > 90% accuracy that simply states that every patient does NOT have APL, but this tool would have no clinical utility. Similarly, if cytogenetics were missing in a significant subset of APL patients, an AI algorithm could emphasize clinically irrelevant data for its prediction over known highly relevant cytogenetics. In the case of rare diseases, synthetic data may be used but these data come with their own set of limitations and advantages. We also believe the guidance should include more robust recommendations on how the AI model addresses algorithmic fairness. The FDA may wish to consider a requirement that AI models are tested across populations of people with rare diseases and if issues with fairness are evident, more robust algorithmic measures should be recommended.

To improve the guidance's relevance and usability, the Society recommends inclusion of both specific guidance for rare diseases and the acknowledgement of alternative methods. The inclusion of specific AI model guidance for rare diseases, which are prevalent in hematology is important because of inherent challenges due to the limited data available for rare disease states and the potential elevated risk of unfairness perpetuated in the AI model. A dedicated section on AI development for rare diseases would help address issues of generalizability and validation. Additionally, the guidance should acknowledge that simpler models, such as logistic regression or decision trees, may be preferable to complex "black box" AI systems in certain cases, particularly for their transparency.

We believe that Section 3, "Assess the AI Model Risk," is underdeveloped, lacks clarity, and is not actionable in its current form. Figure 1, the Model risk matrix on page 8, uses the terms Decision Consequence and Model Influence, but the terms are ill defined. Additionally, the draft guidance does not specify which entity (e.g., the drug manufacturer, the FDA, or a third party) would be responsible for determining the risk level of an AI model. The risk determination process is subjective under this guidance, making it susceptible to manipulation based on the priorities of different stakeholders. Therefore, we recommend that the FDA provide clear guidance as to who or what entity determines the model risk, to provide documentation of the risk assessment, and we suggest that the guidance provide enhanced definitions of Decision Consequence and Model Influence.

We thank the FDA for drafting such important guidance at a time when the use of AI and machine learning is rapidly evolving in drug and biologic development. If the Agency requires additional information or has questions about our comments, please contact ASH Director of Government Relations and Public Health, Stephanie Kaplan at skaplan@hematology.org or 202-538-3018.

Sincerely,



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