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April 7, 2025

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry

To Whom It May Concern:

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is pleased to submit these comments in response to the Food and Drug Administration ("FDA" or "the Agency") request for comments on the Draft Guidance entitled "Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products" ("Draft Guidance").[1] PhRMA represents the country's leading innovative biopharmaceutical research companies, which are laser focused on developing innovative medicines that transform lives and create a healthier world. Together, we are fighting for solutions to ensure patients can access and afford medicines that prevent, treat, and cure disease. Over the last decade, PhRMA member companies have invested more than $800 billion in the search for new treatments and cures, and they support nearly five million jobs in the United States. PhRMA appreciates FDA publishing this Draft Guidance and the opportunity to provide feedback.

I. AI will play an increasingly important role in developing innovative medicines for patients, and the Draft Guidance is an important step toward providing clear FDA expectations on how AI can be used to support regulatory decision-making.

PhRMA strongly agrees with FDA that "advancements in [artificial intelligence ("AI")] hold the potential to accelerate the development of safe and effective drugs and enhance patient care."[2] PhRMA believes the increasing use of AI in drug development and throughout the drug life cycle holds enormous promise for patients by speeding the pace of innovation while also providing new tools for evaluating safety and effectiveness and ensuring quality. While we offer comments below on areas for FDA to clarify or develop further, FDA's risk-based credibility assessment framework ("Credibility Framework") is a welcomed step toward enabling greater use of AI technologies in regulatory decision-making for drugs and biologics.[3] Given the rapid

[1] *See* FDA, Draft Guidance for Industry and Other Interested Parties: *Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products* (Jan. 2025), available at https://www.fda.gov/media/184830/download [hereinafter *Draft Guidance*].

[2] Draft Guidance at Lines 70–72.

[3] For the purposes of these comments, all references to "drug" or "drugs" include both drugs and biological products unless stated otherwise.

evolution in AI capabilities, it is critical for FDA to adopt a regulatory framework that accommodates a wide variety of AI uses, calibrates AI assessments to the level of risk associated with the specific context of AI use, and sets clear expectations for sponsors to document and provide relevant information about AI models to FDA, when appropriate and feasible.

We believe the Draft Guidance provides a strong foundation for developing and evaluating uses of AI models to inform regulatory decision-making and will play an important role in encouraging the further development and adoption of AI in drug development. A risk-based approach is essential to fostering innovation in this space given the use of AI covers a wide range of use scenarios with varying risk levels. We recognize that the Draft Guidance reflects FDA's experience reviewing AI uses in drug submissions over the past several years. Similarly, PhRMA's comments below on the Draft Guidance are informed by the substantial efforts to date of PhRMA members to enhance drug development, manufacturing, pharmacovigilance, and other processes through adoption of AI technologies. While PhRMA agrees that the Credibility Framework should remain flexible to accommodate this rapidly evolving field of technology, we have identified several areas where additional clarity or examples in the Draft Guidance would increase certainty about FDA's regulatory expectations.

II. PhRMA supports FDA's efforts to provide guidance that applies to a broad range of AI use cases but urges the Agency to clarify the scope of its regulatory authority.

PhRMA agrees with FDA that the potential uses of AI are "broad and rapidly evolving"[4] and supports the Agency's efforts to provide guidance that addresses the wide range of potential uses of AI that "produce information or data to support regulatory decision-making regarding safety, effectiveness, or quality for drugs."[5] PhRMA strongly agrees with and supports FDA's decision to exclude from the scope of the Draft Guidance uses of AI models in drug discovery and for "operational efficiencies . . . that do *not* impact patient safety, drug quality, or the reliability of results from a nonclinical or clinical study;"[6] FDA should also clarify that such AI uses are outside the Agency's purview and focus its efforts on areas where it has regulatory authority.

PhRMA urges FDA to clarify how sponsors should identify the regulatory decision to be informed by the output of an AI model as part of the Credibility Framework. For example, FDA could recommend that, as part of defining the question of interest (in Step 1 of the Credibility Framework), sponsors should consider the regulatory decision(s) that may be informed by an AI use. Identifying a regulatory basis for a question of interest and the regulatory decision-making associated with the use of an AI model will help to ground the Credibility Framework in the applicable regulatory framework and reduce ambiguity about the regulatory purpose and goals of the application of the Credibility Framework.

PhRMA also acknowledges that use of AI models for regulatory decision-making may fall in

[4] Draft Guidance at Lines 287–288.
[5] Draft Guidance at Lines 13–15.
[6] Draft Guidance at Lines 47–50.

scope of other relevant guidances.[7] As such, PhRMA recommends that FDA revise existing guidance(s), as needed, to help ensure consistency in approaches to AI in regulatory decision-making and confirm that such guidances can be referenced to inform credibility assessment plans.

III. Clearer definitions for key terms could reduce ambiguity and ensure broader understanding among stakeholders.

PhRMA appreciates FDA's efforts to harmonize the definition of AI with the Agency's Digital Health and Artificial Intelligence Glossary and the federal definition used in 15 U.S.C. § 9401(3). Harmonization is crucial for fostering innovation in this space, as it minimizes inconsistent approaches to regulation. FDA should acknowledge, however, that there are different types of AI models with varying levels of autonomy. The recommendations in the Draft Guidance should take these nuances into account, rather than applying recommendations broadly to all "models." This approach would align with the stated goals of ensuring credibility evidence is commensurate with risk and tailored to the context of use.

Additionally, the Draft Guidance does not define "model," despite the term's use throughout the Draft Guidance. To foster harmonization across FDA's medical product centers, FDA should consider defining "model" and aligning with the approach taken in FDA's draft guidance entitled, "Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations,"[8] including as to whether "AI model" and "model" are interchangeable in the Draft Guidance. PhRMA requests more clarity on how FDA expects sponsors to evaluate the credibility of an AI system that consists of multiple AI models, or that interfaces with other software, hardware, or users.

Finally, PhRMA encourages FDA to include the definitions of other key terms in the Draft Guidance, including validation,[9] federated learning,[10] locked data,[11] and machine-based systems,[12] drawing upon definitions in other FDA guidance documents and FDA's Digital Health and Artificial Intelligence Glossary as appropriate to ensure consistency. FDA should consider adding a glossary to the Draft Guidance to define important terms and updating the Digital Health and Artificial Intelligence Glossary as needed with any modifications.

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[7] FDA, Guidance for Industry, Investigators, and Other Stakeholders: *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (Dec. 2023), available at https://www.fda.gov/media/155022/download; FDA, *M15 General Principles for Model-Informed Drug Development* (Dec. 2024), available at https://www.fda.gov/media/184747/download.

[8] FDA, Draft Guidance for Industry and FDA Staff: *Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations* (Jan. 2025), available at https://www.fda.gov/media/184856/download.

[9] Draft Guidance at Line 326, n. 29.

[10] Draft Guidance at Line 367.

[11] Draft Guidance at Line 522.

[12] Draft Guidance at Line 24.

IV. PhRMA considerations for the seven-step Credibility Framework.

PhRMA believes the Credibility Framework helps to provide a clear understanding of the critical steps involved in developing and evaluating AI models. We support the Agency's risk-based approach that balances flexibility with appropriate evaluation of higher-risk uses of AI to inform regulatory decision-making. The Credibility Framework also enhances transparency in the implementation of AI models to support regulatory decision-making, which is crucial for mitigating concerns about bias and reliability. Given the rapid pace of AI developments and emerging technologies, there is a critical need for flexibility. To that end, PhRMA encourages FDA to continue engaging with stakeholders to keep pace with advancements, including through hosting stakeholder workshops. FDA also should consider supplementing the Draft Guidance and providing examples within more easily updated resources—such as Q&As, FDA websites, and white papers—as the Agency gains real-world learnings and the ecosystem continues to evolve.

Below, we highlight additional considerations for the Credibility Framework.

A. Assessing AI Model Risk.

PhRMA would welcome additional guidance on how sponsors can consistently evaluate risk across different use cases. For example, it would be helpful for FDA to outline factors or criteria sponsors can examine when determining both the "decision consequence" and "model influence" and to provide additional examples of AI models with varying levels of risk, such as by outlining hypothetical risk assessments for the use cases described in the Draft Guidance.[13] For decision consequence specifically, PhRMA encourages FDA to provide additional recommendations regarding how a sponsor should assess the potential severity and probability of any adverse outcomes.[14] PhRMA also notes FDA's statement that "[i]n some risk management tools, the ability to detect harm (detectability) also factors into the estimation of risk."[15] FDA should clarify which aspects of the referenced device-related guidance document FDA considers to be relevant to the assessment of model risk as described in Step 3 of the Credibility Framework. PhRMA also encourages FDA to explicitly address how to account for the context of use ("COU") in the estimation of "model influence," particularly given the Draft Guidance's assertion that the estimation of "decision consequence . . . should not consider the COU of the model."[16]

In addition, FDA should provide more detailed guidance on how risk mitigating measures—including employing a human in the loop—may impact the assessment of AI model risk in Step 3 of the Credibility Framework. The Draft Guidance states that if the COU involves a human in the loop, sponsors should "ensure that the evaluation methods consider the

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[13] Draft Guidance at Lines 75–84.

[14] Draft Guidance at Line 220, n.22.

[15] Draft Guidance at Line 220, n.22 (referencing FDA, Guidance for Industry and FDA Staff: *Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions* (Nov. 2023), available at https://www.fda.gov/media/154985/download).

[16] Draft Guidance at Line 220, n.22.

performance of the human-AI team, rather than just the performance of the model in isolation."[17] PhRMA agrees that sponsors should evaluate the performance of the human-AI team rather than the model in isolation where possible. Understanding that specific assessment strategies may vary depending on the use case, FDA should provide additional clarity on how to effectively assess the performance of the integrated human-AI system compared to the AI model operating independently.

B. Developing the Credibility Assessment Plan.

PhRMA appreciates FDA's detailed guidance on how sponsors should develop a plan to establish AI model credibility within the COU and offers the following comments:

- **Level of Information Recommended.** The Draft Guidance states that a "high-level" credibility assessment plan might be appropriate for early discussions with the Agency.[18] PhRMA encourages FDA to provide more specificity on the information that sponsors should include in a "high-level" credibility assessment plan provided in early stages. Such clarity would support more effective early engagement with the Agency and foster meaningful, efficient risk management. Additionally, the Draft Guidance acknowledges that FDA may request "minimal information" for credibility assessment plans for low-risk models uses as compared to those for high-risk model uses.[19] It would be helpful for FDA to clarify the actions and information the Agency recommends for high-risk versus low-risk model uses, while observing the principle described in the Draft Guidance that credibility assessment activities "should be commensurate with the AI model risk and tailored to the specific COU."[20] Importantly, FDA should ensure that the submission of credibility assessment plans and subsequent engagement with FDA does not unnecessarily delay or discourage the deployment of AI models.

- **Fit for Use Assessments.** PhRMA recommends that FDA provide additional clarification on evaluating whether data are "fit for use" in a particular COU. Specifically, examples would be particularly helpful to illustrate FDA's recommendations on the assessment of the fitness of model development data in contexts where the available volume of data is limited by the size of the relevant patient population, such as in the context of orphan drugs and rare diseases or in contexts where high volume data (e.g., real world data ("RWD") or synthetic data) have been used as training data instead of data from randomized controlled trials. Furthermore, it would be helpful to have additional information for: (1) how to assess data diversity, quality, representativeness, relevance, reliability, sufficiency, and algorithmic bias; and (2) how to assess data from different sources, such as from clinical studies or RWD.

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[17] Draft Guidance at Lines 446–449.

[18] Draft Guidance at Lines 282–285, 297–298.

[19] Draft Guidance at Lines 298–301.

[20] Draft Guidance at Lines 56–61.

- **Independent Datasets.** The Draft Guidance states that test data "should be independent of the development data and should not be shown to the algorithm during training."[21] It would be helpful if the Agency could define what is considered "independent." PhRMA recommends that FDA confirm that data from the same clinical trial but from different sites are considered independent under the appropriate circumstances. Additionally, in other instances, data independence may not be feasible, such as time-series data due to sequential dependencies. PhRMA urges FDA to allow flexibility on the Agency's recommendations where strict data independence will be difficult to accommodate.

- **Performance Metrics.** The performance metrics provided in the Draft Guidance are associated with classification and diagnostic quality.[22] FDA should address examples of other types of metrics as well, such as regression metrics (e.g., Mean Squared Error, Root Mean Squared Error) and metrics for image processing. PhRMA also encourages FDA to address performance evaluation of models with data other than the test data, such as with retrospective real-world tests to examine model performance in realistic conditions. FDA should also clarify how sponsors should describe performance metrics where incidence rates may vary. Finally, FDA should consider and address how performance metrics may differ for emerging technologies, such as generative AI.

- **Confidence Intervals.** For both the model training and model evaluation descriptions, FDA recommends that performance estimates should be provided with confidence intervals.[23] FDA should address how a sponsor should report performance metrics for categorical estimates (for which confidence intervals may be infeasible). FDA should include that there may be scenarios where confidence intervals for performance metrics may not be meaningful or where the model risk is low enough that confidence intervals are not necessary for the credibility assessment.

- **Modifications.** FDA should address how sponsors should allow for adjustments to a credibility assessment plan based on new data, changes to the AI model, or feedback from FDA during early engagement. FDA also should explicitly acknowledge that the seven steps of the Credibility Framework are interrelated and may be iteratively revised as the sponsor documents new information or otherwise makes changes throughout development.

- **Industry Experience.** In the Federal Register Notice ("FRN") for the Draft Guidance, FDA asked commenters to address "[h]ow well the [Credibility

[21] Draft Guidance at Lines 410–411.
[22] Draft Guidance at Lines 381–386.
[23] Draft Guidance at Lines 385–386, 456–457.

Framework] aligns with industry's experience."[24] At a high level, the Credibility Framework generally is aligned with PhRMA members' experiences with developing and assessing AI models. The specific comments in this letter are informed by this experience.

C. Executing and Documenting the Results of the Credibility Assessment Plan.

PhRMA agrees with FDA that "the activities . . . that may be used to establish credibility of AI model outputs should be commensurate with the AI model risk and tailored to the specific COU."[25] It would be helpful for FDA to provide additional information on how the Agency intends to ensure the creation and submission of a credibility assessment plan and "credibility assessment report"—which documents the results of a credibility assessment plan[26]—is appropriate for the level of risk and is streamlined to avoid unnecessary delay or discourage the deployment of AI models thus slowing drug development. For example, PhRMA strongly believes that credibility assessment plans and reports for lower-risk model uses (e.g., model uses with low influence and low decision consequence) do not need to be submitted or otherwise made available to the Agency (e.g., upon inspection) and recommends such a reflection in the Draft Guidance. Although PhRMA appreciates that sponsors may "discuss with FDA whether, when, and where to submit the credibility assessment report to the Agency,"[27] additional clarity in guidance would inform planning by sponsors, particularly for contexts without established options for meeting with FDA. This clarity would help to encourage the deployment and use of innovative and credible AI models.

The Draft Guidance also indicates that a credibility assessment report "may be held and made available to FDA on request (e.g., during an inspection)."[28] FDA should ensure that such procedures are commensurate with the AI model risk, take into consideration the specific regulatory requirements that may be implicated by an AI use, and incorporate appropriate flexibility to account for the diversity of AI use cases.

Finally, PhRMA would welcome additional information on how sponsors should incorporate documentation generated under the Credibility Framework into existing submission pathways, which will create efficiencies for sponsors and FDA. Additional clarity would help mitigate ambiguities around the appropriate timing and context for these submissions and help to ensure sponsors understand how to best incorporate the Credibility Framework into their regulatory strategy.

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[24] 90 Fed. Reg. 1157, 1159 (Jan. 7, 2025) ("Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry; Availability; Comment Request"), available at https://www.govinfo.gov/content/pkg/FR-2025-01-07/pdf/2024-31542.pdf.

[25] Draft Guidance at Lines 56–61.

[26] Draft Guidance at Lines 486–487.

[27] Draft Guidance at Lines 490–492.

[28] Draft Guidance at Lines 492–495.

D. Determining the Adequacy of the AI Model.

PhRMA encourages FDA to disseminate—with appropriate protections for trade secret or confidential commercial information—examples of successfully evaluated AI model uses and the associated credibility assessment plans and reports, including the model development and evaluation processes that were deployed, performance results, and how the model risk assessment impacted the evaluation. It will be beneficial for sponsors to see how the various steps of the Credibility Framework are used by FDA to reach a final decision on an acceptable demonstration of credibility for a given COU. This would not only foster greater transparency on FDA's expectations and consistency in assessments, but it would also guide sponsors in implementing the Credibility Framework.

E. Additional Comments on the Credibility Framework.

It would be helpful to have additional information on the circumstances in which sponsors should apply the Credibility Framework. For example:

- **Application of the Credibility Framework.** It would be helpful to have additional guidance on whether or how the Agency envisions sponsors applying the Credibility Framework in various cases, including: the use cases described in the Draft Guidance;[29] when the AI component is part of a combination product; when AI-derived outputs are employed to generate novel endpoints or biomarkers; when an AI model is used to evaluate an exploratory or secondary endpoint; and in contexts such as postmarketing surveillance, adverse event detection, real-world evidence, pharmacovigilance, clinical trial site selection and patient screening, and biologics manufacturing. It would be helpful for FDA to include examples where the safety risk is minimal to better illustrate how sponsors should apply the Credibility Framework for varying levels of risk.

- **AI-Enabled Devices.** FDA acknowledges that the recommendations in the Draft Guidance "may be relevant across all medical products, including to support regulatory decision-making for medical devices intended to be used with drugs," and that an AI model "may meet the definition of a device."[30] In instances where AI models meet the definition of a device, they may have already been evaluated by FDA as part of the FDA clearance or approval process. Additionally, investigational AI-enabled devices may have already been evaluated for risk under Investigational Device Exemption ("IDE") requirements. Applying the Credibility Framework to such models may result in duplicative and overly burdensome regulatory requirements on sponsors. PhRMA recommends that for an approved or cleared AI-enabled device (or an AI-enabled device with an approved IDE) used to support regulatory decision-making, sponsors could reference the approval or clearance status of the AI-enabled device instead of performing a credibility assessment, as appropriate.

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[29] Draft Guidance at Lines 75–84.

[30] Draft Guidance at Line 15, n.6; Line 17, n.7.

- **Types of Models.** The Draft Guidance states that FDA intends for the recommendations in the Draft Guidance to apply to uses of AI models beyond machine learning models.[31] Given the emphasis on machine learning models in the Draft Guidance, PhRMA recommends that FDA provide additional clarity on any specific recommendations for models outside of machine learning models. Considering the prevalence of large language model ("LLM")-based tools and generative AI and the potential impact on drug development, PhRMA also encourages FDA to explicitly address the application of the Credibility Framework to such emerging technologies. For example, many of the recommendations pertaining to training and tuning data and those related to confidence intervals would be challenging to fully meet or not meaningful for LLM-based AI models.

- **Alternative Approaches.** FDA should clarify that sponsors may use alternatives to the Credibility Framework to assess AI models.

- **Existing Models.** Sponsors currently use, and FDA has reviewed, many AI models that produce information or data to support regulatory decision-making regarding safety and effectiveness.[32] PhRMA encourages FDA to clarify that the Draft Guidance does not apply to previously reviewed uses of AI models. To the extent FDA seeks to have the credibility model apply to new uses of accepted models, we seek more clarity on how sponsors should assess such models to meet current recommendations.

- **Ensemble Methods.** The Draft Guidance states that the credibility assessment plan should "[d]escribe the use of ensemble methods."[33] It would be helpful for FDA to clarify the specific information the Agency is looking for with respect to ensemble methods, such as guidance on how FDA envisions this description differing from the model description itself.

- **Synthetic Data.** The use of simulated or synthetic data can be a valuable tool in drug development and crucial in the adoption of innovative technologies. PhRMA recommends that FDA address the various ways in which simulated or synthetic data can be used for development and testing of AI models used to support regulatory decision-making and continue discussions with sponsors on these issues.

V. PhRMA encourages the Agency to provide additional specificity on expectations for the life cycle maintenance of AI models.

PhRMA appreciates FDA's recommendations for life cycle maintenance of the credibility

[31] Draft Guidance at Lines 31–32.

[32] Draft Guidance at Line 73, n.14 (citing Liu, Q, R Huang, J Hsieh, et al., 2023, Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021, Clin Pharmacol Ther, 113(4):771–774, doi:10.1002/cpt.2668).

[33] Draft Guidance at Line 398.

of AI model outputs to help ensure the model remains fit for use. To help ensure alignment on the Agency's expectations, PhRMA encourages FDA to provide additional clarity on when model changes should be reported to the Agency "in accordance with regulatory requirements."[34] It would also be beneficial for FDA to provide examples or additional recommendations to clarify how a sponsor should determine whether a credibility assessment plan should be re-executed when there are changes to a model.

Recognizing that many of the requirements applicable to AI-enabled devices might necessarily be more stringent than those standards applicable to AI models used to support regulatory decision making for drugs and biologics, PhRMA encourages FDA to consider whether there are aspects of the Predetermined Change Control Plan ("PCCP") approach in place for AI-enabled medical devices that might be relevant for uses of AI in the context of regulatory decision-making for drugs.[35] PhRMA generally encourages sharing learnings across FDA's medical product centers to further appropriate consistency in approaches.

VI. PhRMA encourages FDA to establish clear engagement options that increase certainty for sponsors.

In the FRN for the Draft Guidance, FDA requested that commenters address whether "the options available for sponsors and other interested parties to engage with FDA on AI are sufficient."[36] PhRMA appreciates the Draft Guidance's list[37] of existing options that can be used to engage with the Agency, depending on the intended use of an AI model, and recommends that the Quantitative Medicine Center of Excellence be included on the list. We encourage the Agency to continue discussions with stakeholders as the Agency gains experience in making regulatory decisions that involve AI models. Engagement opportunities are particularly useful in the context of AI, where there may be novel regulatory questions associated with emerging technologies.

To enhance these discussions, FDA should focus on complex, high-risk AI models and share learnings across engagement options to foster consistent regulatory decision-making. Additionally, FDA should provide clearer guidance on the stage(s) of the Credibility Framework at which sponsors should engage with the Agency, the appropriate engagement option(s) for each stage, and how to engage in more targeted or limited conversations with the Agency on certain aspects of credibility assessment plans.

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[34] Draft Guidance at Lines 548–550.

[35] *See* FDA, Guidance for Industry and FDA Staff: *Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence-Enabled Device Software Functions* (Dec. 2024), available at https://www.fda.gov/media/166704/download.

[36] 90 Fed. Reg. 1157, 1159 (Jan. 7, 2025).

[37] Draft Guidance at Table 1, Lines 587-589.

VII. PhRMA urges FDA to address the challenges associated with use of third-party technologies and foundation models.

A. Third-Party AI Models.

PhRMA encourages FDA to clarify its expectations regarding the use of third-party AI models that may be within the scope of the Draft Guidance, including the information about such models that should be included in a credibility assessment plan. Third-party AI models may present unique challenges for sponsors due to limited access to proprietary information and intellectual property concerns. In these circumstances, it may be difficult for sponsors to provide or document certain information that is recommended in the Draft Guidance, such as information on pre-trained models.[38] Options for sponsors to navigate these challenges are needed. For example, Drug Master Files or a similar mechanism that would enable submission of detailed, confidential information about models, model uses, or model assessments, which the file holder may authorize a sponsor to incorporate by reference. PhRMA also encourages FDA to consider a range of options for assessing third-party AI models, including assessment approaches that allow performance testing to establish the credibility of AI models for which limited data about model development are available.

B. Generative AI and Foundation Models.

Foundation models often are not developed or trained by their developers for a specific or predefined COU. Rather, foundation models typically are designed to serve a wide range of applications. This can complicate a credibility assessment, as discussed further below.

Applying the Credibility Framework to foundation models could impose a significant burden on sponsors, as it is often challenging to obtain and sufficiently describe the information outlined in the Draft Guidance (e.g., training and tuning data). Some AI models, particularly those trained on broad, general-purpose datasets and later fine-tuned, may not have initially been developed or trained for a specific COU. Limited information may be available about the development of large commercial or open-source foundation models, which could make the documentation and performance assessment described in Draft Guidance infeasible for these models. Additionally, sponsors often apply additional steps to fine tune a foundation model for specific uses (e.g., through use of an adapter), and it would be useful for FDA to address the applicability of the recommendations of the Draft Guidance to such fine tuning, particularly as methods in this area continue to evolve.

Given the increasing prevalence of these technologies and potential benefits associated with the use of foundation models in AI that may support regulatory decision-making for drugs, specific recommendations regarding the development, assessment, and regulatory submission to ensure the credibility of foundation models for regulatory decision-making would be helpful. FDA should also clarify how risk mitigation strategies, such as human oversight, could be effectively applied when using AI models trained on general datasets, particularly in higher-risk contexts.

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[38] Draft Guidance at Lines 393–396.

VIII. Harmonization amongst global health authorities is key to fostering innovation.

Given the global nature of drug development, driving alignment across global regulators and achieving harmonization, where feasible, would help foster innovation by minimizing duplicative, overlapping, or inconsistent approaches to regulation. Venues such as the International Council for Harmonisation ("ICH"), the International Coalition of Medicines Regulatory Authorities ("ICMRA"), the International Medical Device Regulators Forum ("IMDRF"), and Pharmaceutical Inspection Co-operation Scheme ("PIC/S") are useful forums to engage other regulators to work towards global alignment on regulatory expectations. Additional examples of collaborative engagements amongst regulators include FDA's previous work with Health Canada and the UK Medicines & Healthcare products Regulatory Agency ("MHRA") on guiding principles for transparency in machine learning-enabled medical devices, good machine learning practices, and PCCPs.

IX. Conclusion

PhRMA strongly supports FDA's efforts to facilitate innovation in the use of AI models to support regulatory decision-making regarding safety, effectiveness, or quality of drugs through the issuance of this Draft Guidance. We look forward to engaging with the Agency as it continues to evaluate and consider the application of the risk-based Credibility Framework.

Sincerely,

/s/
Rebecca Nebel, PhD
Senior Director,
Science and Regulatory Advocacy

/s/
Kristina DiPano
Senior Director, Law