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April 7, 2025

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry; Availability; Comment Request (Docket No. FDA-2024-D-4689)

Dear Sir or Madam,

The Consumer Healthcare Products Association (CHPA)[1] submits these comments on the U.S. Food and Drug Administration's ("FDA's" or "the Agency's") draft guidance titled "Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry. The Draft Guidance was announced in the January 7, 2025 *Federal Register* (Vol. 90 No. 4 Fed. Reg. 1157-1159; Docket No. FDA-2024-D-4689). CHPA and its industry partners engaged in the development and marketing of over-the-counter (OTC) drug products and ingredients appreciate the opportunity to provide feedback on this important guidance, which addresses the use of artificial intelligence (AI) models – including machine learning – throughout the drug product lifecycle, particularly when used to generate data or information supporting regulatory decision-making related to safety, effectiveness, or quality.

Several recent publications highlight the promise that artificial intelligence and machine learning (AI/ML) hold in producing quality, reliable data that could support regulatory decision-making related to ingredient safety. For example, a recent publication[2] from the National Center for Toxicological Research (NCTR) emphasizes the urgent need for more efficient approaches to assessing carcinogenicity. Conventional experimental methods, including in vitro and in vivo assays, are both scientifically valid but require significant time and financial resources. Another NCTR study[3] describes the DeepCarc model, which

[1] Founded in 1881, the Consumer Healthcare Products Association (CHPA) is the national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. Every dollar spent by consumers on OTC medicines saves the U.S. healthcare system more than $7, contributing a total of $146 billion in savings each year. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products. www.chpa.org

[2] Fradkin P, et al. A graph neural network approach for molecule carcinogenicity prediction. Bioinformatics (2022) doi: 10.1093/bioinformatics/btac266. PMID: 35758812; PMCID: PMC9235510.

[3] Alonso, José M., and Alberto Bugarín. Explainable Artificial Intelligence (XAI) and Fuzzy Logic in Medical Applications: A Review. Frontiers in Artificial Intelligence 4 (2021): 757780.

demonstrates how AI-based predictive tools could enable earlier detection and prioritization in carcinogenicity assessment.

By implementing the predictive capabilities of AI/ML and omics technologies, researchers and regulators can strengthen public health protection, enhance the efficiency of regulatory decisions, and promote sustainable development[2]. Responsible development and application of interpretable, human-centered AI tools - supported by multidisciplinary collaboration - can accelerate evidence-based toxicology to better protect human health and the environment[2]. CHPA appreciates FDA's proactive efforts in issuing this guidance and providing a foundational framework for the use of AI in regulatory decision-making. We respectfully offer the following comments and suggestions for the Agency's consideration as it works to finalize the guidance. International perspectives reinforce these goals—for example, the Dutch National Institute for Public Health and the Environment (RIVM) has emphasized the value of embedding AI development in a regulatory context early in the process and promoting interdisciplinary approaches to ensure that model limitations are properly understood and addressed[4].

Risk-Based Credibility Assessment Framework (Section IV)

CHPA supports the overall structure of the risk-based credibility assessment framework presented in Section IV of the draft guidance. This structured approach is a helpful way to promote transparency and consistency. However, we recommend that FDA provide greater clarity on how "model risk" should be interpreted in contexts where AI models are used to inform, but not directly determine, regulatory outcomes. For example, models used for data visualization, internal quality monitoring, or post-marketing trend analysis may pose different levels of risk than those used to make direct clinical or safety decisions.

> Recommendation 1: We recommend that FDA include a tiered framework or decision-tree with illustrative examples of low-, medium-, and high-risk AI model applications. One potential resource could be the Decision Tree for the Responsible Application of Artificial Intelligence[5] published by the American Association for the Advancement of Science (AAAS), which provides a practical lens for interpreting model risks based on context of use and potential impact.

[4] National Institute for Public Health and the Environment (RIVM). "Artificial Intelligence/Machine Learning and Advanced Materials." RIVM, 7 Mar. 2023, https://www.rivm.nl/en/weblog/artificial-intelligencemachine-learning-and-advanced-materials.

[5] American Association for the Advancement of Science (AAAS). "Decision Tree for Practitioners." AAAS, https://www.aaas.org/ai2/projects/decision-tree-practitioners. Accessed 25 Mar. 2025.

Transparency and Explainability of Models

We agree with FDA that transparency is critical for regulatory trust and scientific reproducibility. We also recognize that in practice, explainability can vary significantly, particularly for small companies or those using third-party AI tools.

> Recommendation 2: We ask FDA to clarify expectations for documentation and methodological transparency when companies use commercially available or vendor-developed models, especially in low-risk applications. Additionally, due to the complex statistical foundations of many AI models, we suggest FDA provide examples of what constitutes sufficient methodological disclosure - such as summaries of development methods, training data characteristics, and validation processes - to assist sponsors in preparing appropriate documentation.

AI Model Lifecycle Management

We commend FDA's attention to lifecycle management of AI models and encourage the Agency to elaborate on expectations for post-deployment oversight and maintenance.

> Recommendation 3: FDA should provide clear guidance on what constitutes a significant model change requiring revalidation or reassessment of model credibility, especially for models used in cGMP systems or quality control. Expectations for version control, revalidation frequency, and performance drift thresholds would help ensure model reliability. Sponsors should be prepared to assess both intentional and system-driven changes. More detailed lifecycle guidance would support consistent oversight of AI models that may impact product quality, safety, or regulatory decisions.

Aligning with Industry Experience and Real-World Data Sources

CHPA supports FDA's emphasis on ensuring that training data used in AI applications is high-quality and representative. In consumer health contexts, data may often come from novel sources, including digital health platforms, mobile health tools, consumer-reported data, or other forms of real-world evidence.

> Recommendation 4: We encourage FDA to provide further guidance on acceptable practices for using real-world or consumer-derived data in AI models. This could include recommendations for ensuring data sufficiency, representativeness, and strategies to mitigate bias in non-traditional datasets. Examples from real-world use cases would help industry better understand how to apply these principles to consumer-facing products and applications.

> Recommendation 5: We suggest that FDA consider issuing a standalone guidance document that more fully addresses AI model utilization in post

market surveillance and pharmacovigilance. These applications may warrant distinct considerations beyond the performance-related focus of the current draft guidance.

CHPA appreciates the opportunity to comment on this important draft guidance. As AI tools continue to evolve and play a greater role in regulatory science, clear and practical guidance will be critical to ensure their responsible and effective use across the product lifecycle. We welcome continued engagement with FDA to support the advancement of transparent, science-based frameworks for AI in regulatory decision-making.

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