REAL-WORLD EVIDENCE ALLIANCE

info@rwealliance.org
rwealliance.org

August 9, 2023

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

Re: Discussion Paper: Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products (Docket No. FDA-2023-N-0743)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on FDA's May 2023 Discussion Paper entitled "Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products."[1] We are a coalition of real-world data (RWD) and analytics organizations with a common interest in harnessing the power of real-world evidence (RWE) to inform regulatory decision making to improve patients' lives. Our members have deep knowledge and experience working with healthcare data across disease areas and patient populations, and we aim to bring these collective insights to bear in support of RWE policies.[2]

The RWE Alliance envisions a future in which data from electronic health records, administrative claims and billing data, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence to support regulatory decision making related to medical product safety and effectiveness. To achieve this goal, the RWE Alliance advocates for policies that will (1) advance FDA's RWE Framework, (2) encourage the use of RWE to better understand treatment effects in underrepresented populations, (3) enhance opportunities for RWE organizations to consult with FDA, (4) increase communication on the generation and use of RWE, and (5) recognize the unique aspects of and opportunities for RWD/E.[3]

We commend FDA for its efforts to help inform and develop the regulatory landscape for the use of artificial intelligence (AI), machine learning (ML), and natural language processing (NLP) in drug development, including through the publication of the

---

[1] 88 Fed. Reg. 30313 (May 11, 2023); FDA, *Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products* (May 2023), available at https://www.fda.gov/media/167973/download (the "Discussion Paper").

[2] For information about our members, please see our website, https://rwealliance.org/who-we-are/.

[3] Additional information about what we believe is available on our website, https://rwealliance.org/what-we-believe/.

Agency's March 2023 Framework for the Use of Digital Health Technologies in Drug and Biological Product Development[4] and Discussion Paper on Artificial Intelligence in Drug Manufacturing.[5] The RWE Alliance appreciates FDA's commitment to enhance mutual learning and establish a dialogue with FDA stakeholders on this topic. These efforts will ultimately foster innovation and benefit patients.

The RWE Alliance provides the below comments for consideration.

I. FDA should consider providing more specific examples of use cases that would fall in and out of scope of direct FDA oversight.

The Discussion Paper highlights that AI, ML, and NLP may be applied in various use cases—including those involving RWD—throughout all stages of the biopharmaceutical development and commercialization process. The Discussion Paper acknowledges that FDA oversight "may or may not be applicable" to the outlined examples, but does not provide further specificity about which use cases FDA believes are subject to FDA oversight and which are not.[6] Because certain use cases described in the Discussion Paper generally would not typically be subject to FDA regulation in the absence of AI, ML, or NLP, it would be helpful for FDA to provide more clarity about whether and to what extent FDA expects to oversee these or other use cases in some manner when AI, ML, or NLP tools are deployed. For example:

- The Discussion Paper describes a number of different uses for AI/ML in drug discovery, such as early target identification, selection, and prioritization, as well as the use of RWD to identify previously unknown effects of drugs on disease pathways. As FDA typically does not scrutinize how companies identify potential new targets in drug discovery, it would be helpful for FDA to be more specific about whether and to what extent the deployment of AI/ML for such activities changes FDA's typical approach. Specifically, we recommend that FDA provide more clarity about whether and to what extent sponsors should explain to FDA how AI/ML was used in activities not typically scrutinized by FDA and, in those instances, how the output of the AI/ML was verified, including what information (if any) sponsors utilizing AI/ML in drug discovery should document to justify that the use of AI/ML was appropriate.

- Building on the prior example, the Discussion Paper raises questions about whether and to what extent ML or NLP algorithms used to curate RWD to support clinical trial design would be subject to FDA oversight. ML models may be used for automated abstraction purposes, and AI (including AI-based analyses of RWD) could be used to predict clinical outcomes, identify potential biomarkers, select appropriate inclusion or exclusion criteria, or assess and predict

[4] FDA, *Framework for the Use of Digital Health Technologies in Drug and Biological Product Development* (Mar. 2023), available at https://www.fda.gov/media/166396/download.

[5] 88 Fed. Reg. 12943 (Mar. 01, 2023); FDA, *Artificial Intelligence in Drug Manufacturing* (Mar. 2023), available at https://www.fda.gov/media/165743/download.

[6] Discussion Paper, Lines 91-93.

pharmacokinetic profiles. Currently, FDA does not have specific regulations or guidance regarding the data or tools biopharmaceutical companies may use to *design* a clinical trial or generate RWD/E. However, in some instances, sponsors may need to demonstrate that the information and decisions obtained through the use of AI, ML, or NLP tools are scientifically appropriate and valid. As above, the Discussion Paper leaves open the questions of how FDA may expect sponsors to justify their use of AI, ML, or NLP—including AI-based analyses of RWD—for these purposes and what data third parties should collect and provide to sponsors to help with such a justification. As above, we encourage FDA to provide more clarity on these issues left open in the Discussion Paper.

- The Discussion Paper describes how sponsors of clinical trials may seek to utilize AI, ML, and RWD to assist in the conduct of a clinical trial, such as data mining for recruitment by applications of inclusion and exclusion criteria on NLP-derived data points, participant stratification, site identification, and clinical trial data management. FDA has general Investigational New Drug regulations that govern the conduct of a clinical study, but currently these regulations do not specifically address the use of AI, ML, or RWD. The RWE Alliance acknowledges and applauds FDA's existing suite of guidance documents specific to RWD/E but notes that Agency guidance thus far has not focused on the intersection of RWD/E and use of AI or ML. For example, FDA has issued draft guidance addressing considerations for externally controlled clinical studies, including when data from RWD sources are used as external controls,[7] but the guidance does not address how AI or ML might be used in this context and whether additional considerations apply. For any future draft or final guidance relating to use of RWD/E, the RWE Alliance encourages FDA to address AI/ML-specific considerations, as appropriate.

In sum, it would be helpful to have more clarity on whether and to what extent the Agency will seek to oversee the operation and performance of AI, ML, and NLP in use cases not traditionally scrutinized by FDA, particularly where data are ultimately used to support regulatory decision making. Having additional clarity on scope and applicability of FDA's expectations would guide model development and inform expectations for biopharmaceutical companies working with third-party organizations that make use of AI, ML, and NLP tools. We encourage FDA to continue to seek stakeholder feedback about these topics as the Agency further develops its thinking.

II. Sponsor testing and Agency evaluation of AI, ML, and NLP tools should be tailored to each use case.

We appreciate the opportunity to provide feedback to the Agency on considerations for the use of AI, ML, and NLP in drug development and look forward to continued engagement with FDA in helping to understand how AI, ML, and NLP tools may be

[7] FDA, Draft Guidance for Industry, *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (Feb. 2023), available at https://www.fda.gov/media/164960/download.

deployed in the RWE space, including around risk frameworks and model validation approaches. If FDA intends to evaluate the performance or nature of such tools as part of its regulatory oversight, it is crucial that stakeholders have clarity on the specific standards and considerations that FDA would seek to apply to these tools in different use cases. For example, the Discussion Paper highlighted general principles for the use of emerging technologies (such as reliability, representativeness of data, accountability, and transparency), but did not clarify whether the principles apply broadly to all potential use cases for AI, ML, and NLP in biopharmaceutical development, or whether different considerations would apply in different contexts or at different stages of development and commercialization. We strongly encourage FDA to tailor any performance evaluations of these tools to each specific use case and develop guidelines that are fit-for-purpose. In addition, we encourage FDA to seek contributions from subject matter experts before outlining any specific approaches, to continue engaging stakeholders and leveraging existing performance characteristics frameworks[8] toward this end, and to consider ways to involve relevant experts in developing any framework meant to evaluate AI, ML, and NLP models for purposes of regulation.

III. FDA should consider implementing more specific definitions of AI, ML, and NLP.

The definitions for AI, ML, and NLP in the Discussion Paper do not clearly differentiate between these concepts, although their approaches and potential utility in the drug development and commercialization processes differ widely. Adopting a consistent taxonomy of terms is crucial for effective communication and understanding within the health care domain.[9] We request that the Agency provide additional granularity in these definitions to shed light on how the Agency plans to differentiate between these concepts for the purposes of regulation and guidance.

IV. FDA should consider that many AI, ML, and NLP models are proprietary in nature.

We appreciate FDA's recognition that an AI/ML systems may exhibit limits as to explainability or transparency;[10] moreover, many AI, ML, and NLP models are proprietary in nature. We encourage FDA to consider and provide clarity on where full disclosure of specific algorithms is not necessary or where other means could be deployed to achieve FDA's regulatory objectives (e.g., appropriate performance frameworks). We also ask the Agency to clarify that, during the course of a regulatory

---

[8] *See, e.g.*, Estevez, et al., *Considerations for the Use of Machine Learning Extracted Real-World Data to Support Evidence Generation: A Research-Centric Evaluation Framework*, *Cancers* 2022, *14*(13), 3063, available at https://doi.org/10.3390/cancers14133063.

[9] *See, e.g.*, standardized terminology efforts such as ISO/IEC 23053:2022, *Framework for Artificial Intelligence (AI) Systems Using Machine Learning (ML)*, available at https://www.iso.org/standard/74438.html; ISO/IEC 22989:2022, *Information technology – Artificial intelligence – Artificial intelligence concepts and terminology*, available at https://www.iso.org/standard/74296.html.

[10] Discussion Paper, Lines 598-599.

inspection and in submissions to the Agency, AI, ML, and NLP models will be treated as confidential commercial or trade secret information, as appropriate, and be protected from disclosure under information disclosure laws.

V. FDA should advance cross-agency understanding of these tools.

Implementation of regulatory review approaches for AI, ML, and NLP will inherently be complex due to rapid technological innovations in this evolving field. We recognize and applaud the Agency's efforts across Centers to develop frameworks, guidance documents, and discussion papers on the use of AI, ML, and NLP tools in medical product development and commercialization. We encourage FDA to consider how it will facilitate cross-agency understanding of these tools—including how they operate and the validity of the results produced—to promote consistent application of regulatory review approaches.

VI. Conclusion

The RWE Alliance appreciates the Agency's commitment to informing the regulatory landscape in this evolving area and looks forward to continued engagement. Thank you for considering these comments, and please let us know if you have any questions. We would welcome the opportunity to discuss further.

Best regards,

The RWE Alliance