REAL-WORLD EVIDENCE ALLIANCE

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September 22, 2023

The Honorable Bill Cassidy
Ranking Member
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, DC 20510

Re: Comments on White Paper, "Exploring Congress' Framework for the Future of AI"

Dear Ranking Member Cassidy:

Thank you for your leadership to advance artificial intelligence (AI) policy. The Real-World Evidence (RWE) Alliance appreciates the opportunity to comment on your white paper: "Exploring Congress' Framework for the Future of AI: The Oversight and Legislative Role of Congress over the Integration of Artificial Intelligence in Health, Education, and Labor."[1]

The RWE Alliance is a coalition of real-world data (RWD) and analytics organizations with a common interest in harnessing the power of 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

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[1] Senator Bill Cassidy, M.D., *Exploring Congress' Framework for the Future of AI: The Oversight and Legislative Role of Congress over the Integration of Artificial Intelligence in Health, Education, and Labor* (Sep. 2023), available at https://www.help.senate.gov/imo/media/doc/help_committee_gop_final_ai_white_paper1.pdf (the "AI White Paper").

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

(5) recognize the unique aspects of and opportunities for RWD/E.[3]

The RWE Alliance commends you for your efforts to help inform and develop the regulatory framework for the use of AI in our health system, including the identification and development of new treatments and cures. We also appreciate your efforts to establish a dialogue with stakeholders on this topic. Your efforts will help foster innovation and ultimately benefit patients and public health.

The RWE Alliance provides the below comments for your consideration.

I. General Comments

The RWE Alliance applauds your acknowledgment of the enormous good that AI can accomplish in healthcare settings and the variety of applications of AI that can benefit all stages of medical product lifecycles, including pharmaceutical research and development, diagnostic and treatment applications, patient- and provider-facing support, and healthcare administration and coverage. We appreciate your commitment to ensuring legal frameworks maximize AI's benefits, foster innovation, and minimize risks. We agree with your statement that Congress should support continued growth in the use of health-related AI, and we encourage FDA to continue the Agency's efforts to do so as well. The RWE Alliance supports your goals and believes that policy efforts to regulate AI applications should be grounded in the overall objective of enhancing patient care and well-being.

We also appreciate your acknowledgement that effective frameworks must account for the specific context in which AI's capabilities are applied, as we agree that requirements for AI systems should be calibrated to the risk presented for a particular case and any associated guidelines should be fit-for-purpose. The RWE Alliance supports your stated goal of leveraging existing frameworks, as these frameworks can serve as a robust foundation for evaluating AI risks and controls for AI deployed in healthcare and life sciences contexts. As just one example, we agree that the current framework for preclinical and clinical investigation of new drugs is generally well suited to incorporate the use of AI in the research and development of new drugs, but these frameworks may require further clarification and flexibility, as acknowledged in FDA's recent discussion papers.[4] We support FDA's efforts and encourage the Agency to continue to engage with stakeholders to understand and address considerations to facilitate use of AI in early-stage drug development, consistent with the feedback we provided on the Agency's May 2023 discussion paper.[5]

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

[4] *See* FDA, *Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products* (May 2023), available at https://www.fda.gov/media/167973/download; FDA, *Artificial Intelligence in Drug Manufacturing* (Mar. 2023), available at https://www.fda.gov/media/165743/download.

[5] *See* Real-World Evidence Alliance (The RWE Alliance), Comment No. FDA-2023-N-0743-005 (Aug. 9, 2023), available at https://www.regulations.gov/comment/FDA-2023-N-0743-0054.

We also wish to highlight that RWD/E organizations can contribute to safe, effective, and responsible deployment of AI. For example, characterizing the population from which RWD/E datasets are obtained consistently with the relevant parameters for the AI product, determining the size of the RWD/E dataset based on the statistical questions posed and in consideration of the risks of the AI product, and predefining RWD/E quality characteristics according to the intended use of the AI product, all could help support the successful development and use of AI models that ultimately benefit patients. AI-generated synthetic data based on RWD datasets also present opportunities for benefitting public health. Synthetic data provides "digital twins" of RWD datasets that are generated from machine learning (ML) and deep learning models built from the source data to replicate the statistical characteristics and patterns of the underlying RWD. AI-generated synthetic data can help to address privacy considerations around data sharing by enabling privacy-protected analyses of synthetic copies of data that otherwise might not be available for research. AI-generated synthetic data also can amplify the creation of data by taking a relatively small underlying dataset and extrapolating until there is a sufficient quantity of data for meaningful analysis, which could help support the development of treatments for rare diseases and assist with research involving treatment effects in underrepresented populations.

Finally, the RWE Alliance supports efforts to adopt a consistent taxonomy of AI terms, which will be crucial for effective communication and understanding within the healthcare domain.[6] As part of implementing nomenclature that is consistent with emerging AI regulatory frameworks, the RWE Alliance encourages Congress to advance and endorse rules for AI that are role based and take into account the role that various AI actors play in the AI ecosystem.

II. Specific Comments

We appreciate the opportunity to provide feedback on select questions posed in the AI White Paper. The RWE Alliance offers the below comments for consideration.

A. Health Care Supporting Medical Innovation

1. How can FDA support the use of AI to design and develop new drugs and biologics?

To foster innovation and the appropriate use of AI in new drug and biologic development for the benefit of public health, it will be important for FDA to continue to consult stakeholders, including regulated industry, health technology experts, and academia. It also will be crucial for FDA to seek international harmonization in AI regulation with global health authorities, as different AI standards in different jurisdictions will stifle incentives to use AI in medical product development due to global

[6] *See, e.g.*, standardized terminology efforts such as ISO/IEC 23053:2022, *Framework for Artificial Intelligence (AI) Systems Using Machine Learning (ML)*(June 2022), available at https://www.iso.org/standard/74438.html; ISO/IEC 22989:2022, *Information Technology – Artificial Intelligence – Artificial Intelligence Concepts and Terminology* (July 2007), available at https://www.iso.org/standard/74296.html.

compliance issues. Ongoing collaboration—including through participation and leadership in international fora such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and International Coalition of Medicines Regulatory Authorities (ICMRA)—is important to advancing our collective understanding of the potential benefits and limitations of AI in healthcare and life sciences, and continued engagement by FDA is crucial for achieving the right approach for use of AI in drug development (e.g., enabling continued innovation while ensuring patient safety, product quality). Collaboration also will help FDA keep pace with the rapid development of technological innovation and, where appropriate, develop and update guidance on topics where regulatory clarity is needed to advance innovation or risk-based regulatory approaches. We encourage Congress to continue to enable FDA to collaborate with stakeholders and develop guidance or sponsor pilot projects, including in response to stakeholder feedback received during collaborations and on the discussion papers FDA released regarding the use of AI and digital health technologies in drug and biologic product development and commercialization.[7]

It will be equally important for FDA to have a transparent and consistent approach to the scope of FDA's regulatory oversight involving AI. To the extent the Agency opines on AI deployed in use cases not traditionally scrutinized by FDA, such as target identification in early drug discovery, it should do so with clear explanations regarding the Agency's jurisdiction and interest. Having predictability in FDA oversight would help guide model development and inform expectations for biopharmaceutical companies and their third-party partners when developing and using AI tools.

Congress should encourage FDA to further enhance cross-Agency understanding of AI tools—including how they work and how they are validated—to promote consistent application of regulatory review approaches. We applaud and support FDA's efforts to establish a Digital Health Technology Steering Committee that will facilitate consistent approaches to the review and evaluation of submissions that contain data derived from digital health technologies and appreciate other efforts across centers to develop frameworks, guidance documents, and discussion papers on the use of AI tools in medical product development and commercialization.[8] We also encourage Congress to work with FDA to ensure that the Agency's review centers and the Digital Health Center of Excellence are adequately resourced to support various applications of AI in regulatory reviews and internal FDA systems, where appropriate.

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[7] *See* 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; FDA, *Artificial Intelligence in Drug Manufacturing* (Mar. 2023), available at https://www.fda.gov/media/165743/download; FDA, *Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products* (May 2023), available at https://www.fda.gov/media/167973/download.

[8] *See* FDA, *Framework for the Use of Digital Health Technologies in Drug and Biological Product Development* (Mar. 2023), at 8-9, 11, available at https://www.fda.gov/media/166396/download.

2. What updates to the regulatory frameworks for drugs and biologics should Congress consider to facilitate innovation in AI applications?

The RWE Alliance encourages Congress to take into account FDA's existing authority to establish expectations and develop guidance on the use of AI applications in medical product development. For instance, to help enhance and enable traceability and auditability in AI applications in drug development, we believe Congress should encourage FDA to continue thinking through how to use its authorities to help create a transparent and accountable environment for AI applications in drug and biological product development. For example, FDA should provide clarity on appropriate data governance practices, documentation practices, evaluation criteria for model validation, and monitoring practices where appropriate for a particular use. This could include new guidance to address how FDA will apply its existing IND application requirements to applications for drugs or biologics for which the sponsor utilized AI in some manner in the development process, or revised guidance on Drug Master Files to address submission of proprietary information about AI algorithms when drug or biologic sponsors utilize AI services provided by a third party. As discussed above, clarity, consistency, and predictability in FDA oversight with respect to AI tools will be important to facilitate innovation and to realize the potential benefits of AI in the development of drugs and biologics.

We also encourage Congress to work with FDA to ensure the Agency is sufficiently familiar with AI products and research and data innovations. For example, the use of more diverse and granular data sources captured over longer periods of time has the potential to support patient-centered medical product development but could also create patient confusion and discourage participation. Improving familiarity with dynamic consent, novel data sources, and reliable data-capture mechanisms that support patient understanding and increase trust will help to advance participant interactions and enrollment in research. Supportive regulatory frameworks could enhance AI technologies and software to accomplish these aims in a way that affirms transparency, trust, and ultimately more efficient patient participation in research.

3. How can Congress help FDA ensure that it has access to the expertise required to review products that are developed using AI or that incorporate AI?

We support Congress taking steps to ensure FDA has the resources necessary to recruit, hire, and retain additional staff with appropriate expertise to enable FDA to review AI-based submissions, and we encourage Congress to seek FDA feedback on the Agency's current and future needs in this important area. The RWE Alliance also supports Congress exercising oversight and working with FDA on its implementation of last year's user fee agreements to advance these goals.

4. How can FDA harness external expertise to support review of products that are developed using AI or that incorporate AI?

The establishment of a Digital Health/AI Advisory Committee should be considered. Such an advisory committee could be composed of external experts with appropriate subject matter expertise, including the development of RWD/E. As with use of any FDA advisory committee, care should be taken to ensure the advisory committee does not itself introduce inconsistency into the Agency's review processes.

5. What are the potential consequences of regulating AI in the United States if it remains unregulated in other countries?

The RWE Alliance applauds the great strides the United States has made in terms of AI use and innovation to maintain global technological leadership. United States regulation of AI should be done in a manner that considers the developing legal standards in other key jurisdictions.[9] Creating excessive, duplicative, or conflicting frameworks in the United States would stunt AI development here and pave the way for other countries to move ahead. As such, we encourage Congress and FDA to be mindful of these potential consequences as we work toward the shared goal of ensuring AI tools enhance patient care and well-being. As noted above, we also encourage Congress to advise FDA to take advantage of opportunities to collaborate with other health authorities and demonstrate leadership at the international level through participation in fora such as the ICH and ICMRA. As noted above, international harmonization in AI regulation is important to supporting the use of AI to design and develop new drugs and biologics for patients.

B. Medical Ethics and Protecting Patients

1. What existing standards are in place to demonstrate clinical validity when leveraging AI? What gaps exist in those standards?

The RWE Alliance appreciates and applauds the standards-setting bodies that have published standards to demonstrate clinical validity when leveraging AI. For example:

- CONSORT-AI (Consolidated Standards of Reporting Trials – Artificial Intelligence) and SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials – Artificial Intelligence) are guidelines that provide recommendations for transparent and comprehensive reporting of AI studies in healthcare research, with CONSORT-AI focusing on the reporting of AI studies and SPIRIT-AI assisting stakeholders in documenting the protocol for AI model

[9] *See, e.g.*, Proposal for a Regulation of the European Parliament and of the Council Laying Down Harmonised Rules on Artificial Intelligence (EU AI Act) and Amending Certain Union Legislative Acts (Apr. 21, 2021), available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52021PC0206; Artificial Intelligence and Data Act, Digital Charter Implementation Act of 2022, Bill C-27, 44th Parliament (Nov. 22, 2021) (Can.), available at https://www.parl.ca/DocumentViewer/en/44-1/bill/C-27/first-reading.

development and evaluation in drug development.[10] Together, these standards aim to support transparency and reproducibility.

- ISO 13485 contains internationally agreed requirements for a quality management system specific to the medical devices industry that can help to ensure AI system quality and safety.[11]

- The DICOM Standard[12] and Health Level Seven Standards[13] aim to support data compatibility and interoperability.

- The National Institute of Standards and Technology's AI Risk Management Framework for AI risk management to promote trustworthiness and performance.[14]

The RWE Alliance also appreciates FDA's efforts to engage stakeholders on considerations for how emerging standards and existing FDA regulations will be applied to the use of AI in drug, biological product, and device development through recent discussion papers. We support continued application of FDA's existing regulations relating to good clinical practice and clinical trials, which help to enhance transparency and reduce bias.[15] The RWE Alliance also acknowledges FDA's existing suite of guidance documents specific to RWD/E and encourages Congress and FDA to further consider the intersection of RWD/E and use of AI. Appropriate use of RWD/E is essential to the training and validation of AI, and poolability of RWD/E across data sources can be an important consideration in AI validation. Effective use of RWD/E also is critical to building representative training datasets that help minimize biased outputs. For example, when using RWD/E for AI training and validation, sponsors should use independent training and validation datasets, clearly define ground truth, and consider the significance of missingness in assessing whether a RWD/E dataset is fit-for-purpose.

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[10] *See* The CONSORT-AI and SPIRIT-AI Steering Group, *Reporting Guidelines for Clinical Trials Evaluating Artificial Intelligence Interventions are Needed*, 25 NATURE MEDICINE 1467 (2019).

[11] *See* ISO 13485, *Medical Devices*, available at https://www.iso.org/iso-13485-medical-devices.html.

[12] Medical Imaging & Technology Alliance, National Electrical Manufacturers Association, *Digital Imaging and Communications in Medicine*, *Current Edition*, available at https://www.dicomstandard.org/current.

[13] HL7 International, *Introduction to HL7 Standards*, available at https://www.hl7.org/implement/standards/index.cfm?ref=nav.

[14] *See, e.g.*, NIST, *AI Risk Management Framework*, available at https://www.nist.gov/itl/ai-risk-management-framework.

[15] *See, e.g.*, FDA, *Regulations: Good Clinical Practice and Clinical Trials*, available at https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials.

2. What practices are in place to mitigate bias in AI decision-making?

The RWE Alliance supports efforts to mitigate bias in AI decision making. It is essential for industry to leverage and establish transparency standards that enable stakeholders and regulators to assess a model's validity, reliability, and potential biases. Transparency will encourage trust in AI by stakeholders, which is essential to support greater AI adoption and deployment and to deliver safe and effective patient care.

Important and promising practices used to mitigate bias in AI decision making include:

- Pre-specification activities in AI-based drug development;
- Reviewing training datasets to ensure that they are fit-for-purpose and representative of the population in which the AI system will be deployed;
- Implementing robust validation processes and conducting bias and impact assessments to identify and mitigate risks of bias and unfair outcomes, including research on fairness in AI and common biases in ML;
- Red-teaming to test models for potential biases in real-world simulations;
- Documenting the intended use, capabilities, and limitations of an AI system, as well as data sources, validation, and version control, to enhance reproducibility;
- Specifying and documenting criteria used to include or exclude data from analyses based on clinical relevance, data quality, completeness, and model requirements;
- Tracking and monitoring algorithm performance, identifying potential issues, implementing adjustments, and ensuring AI systems maintain accuracy and quality performance over time;
- Collaborating with academic institutions and researchers to stay current on the latest findings and techniques for addressing bias and fairness in AI models; and
- Describing bias identification and management in regulatory submissions and labeling.

The RWE Alliance also notes that sources of potential bias should be addressed in the RWD/E used for the training and validation of AI models and that transparency and communication regarding the use of RWD/E and limitations of validation testing should be described in AI labeling. Although choices made during data selection, curation, preparation, and model development are crucial in reducing bias, it may not be possible to identify all potential biases, and thus ongoing assessment of algorithms and model output in real-world settings is vital. Further, any practices used to mitigate bias in decision making—and any expectations on this front—should generally be consistent with how FDA would evaluate non-AI based tools for the same purpose.

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The RWE Alliance appreciates your leadership and initiative to provide oversight of and further develop the policy landscape for this emerging technology. We look forward to continued engagement with you and your staff. Thank you for considering our comments, and please let us know if you have any questions.

Sincerely,

The RWE Alliance