PERSONALIZED MEDICINE COALITION

April 7, 2025

Dockets Management Staff
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations [FDA-2024-D-4488]

To Whom It May Concern:

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising more than 200 institutions from across the health care spectrum, thanks the U.S. Food and Drug Administration (FDA) for the opportunity to submit comments related to the draft guidance titled *Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations*.[i] PMC believes that emerging and potential uses of AI may begin to improve patient experiences with health care and help address challenges to the clinical adoption of personalized medicine.[ii] PMC applauds the FDA for recognizing opportunities AI presents for medical product development, and we appreciate the Agency's efforts to establish a regulatory framework for AI-enabled medical products that can ensure high standards for effectiveness, accountability, and continuous oversight.

Personalized medicine is a rapidly evolving field in which physicians use diagnostic tests and individual details about a person and their health to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms that impact health. By combining data from diagnostic tests with an individual's medical history, circumstances, and values, health care providers can develop targeted treatment and prevention plans with their patients.

Personalized medicine is helping to shift the patient and provider experiences away from trial-and-error toward a more streamlined process for making clinical decisions, which leads to improved patient outcomes, a reduction in unnecessary treatment costs, and better patient and provider satisfaction. PMC and its members are leading the way in personalized medicine and in developing evidence showing how patients and the health care system can benefit from appropriate testing and tailored treatment as soon as possible during their clinical experiences.

Statement of Neutrality

PMC's members may present their own responses to the FDA's draft guidance titled *Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations* and actively advocate for those positions.

PMC's response is designed to provide feedback so that the general concept of personalized medicine can advance, and is not intended to impact adversely the ability of individual PMC members, alone or in combination, to submit separate responses to FDA on this draft guidance.

PMC advocates for public policies that can help AI realize its full potential for improving patient access to personalized medicine and for making the health care system more efficient across disease areas. The following comments share our observations on challenges in AI development and use. They also highlight relevant recommendations from PMC's *Policy Principles on AI*, developed in collaboration with PMC's AI Working Group. We encourage the FDA to incorporate these recommendations in finalizing this guidance and when developing any future guidance documents relevant to AI-enabled medical products that support personalized medicine.

I. Challenges in the Development and Use of AI

AI has applications in pre-clinical and clinical settings. PMC's focus is on ensuring the right framework for AI is used from the point of evidence generation and commercialization, to use by patients and doctors to make health care decisions. In developing frameworks for regulatory oversight, certain cross-cutting policy challenges will need to be considered.

Regulatory Oversight Challenges

AI tools rely on large amounts of data from various sources. These data sources can vary in their quality and representativeness. When AI algorithms are neither created nor validated using the same dataset, this creates challenges for regulatory bodies like the FDA to compare and consistently evaluate tools. The sensitivity of an AI tool may not be comparable across applications, and AI models can have differing levels of explainability, or transparency into the reasoning behind the model's output. This lack of standardization can complicate and lead to inconsistencies in regulatory oversight, since it is difficult to establish clear benchmarks for AI performance across different applications. To facilitate predictable regulatory oversight and build trust in the quality of AI technologies when used in real-world clinical settings, collaborative efforts are needed to create comprehensive and standardized datasets – representative of all patient populations – for training and validating AI algorithms, including tests for biases that could impact real-world implementation across different health care settings.

For some AI tools, the technology's training data and decision-making process can be opaque. Training data must be reflective of the intended population and product developers must take steps to address bias and account for limitations in health data throughout the product's lifecycle. Clear regulatory processes and frameworks that establish or clarify technical standards for the quality and representativeness of training data, result reporting, data governance, data sharing, data privacy, data security, transparency, bias mitigation, and informed consent where required will be essential to set consistent expectations for developers and build trust among providers and patients in the real-world use of AI. Real-world monitoring can also help track biases and other issues that may emerge with implementation of AI, as well as document benefits that could support broader implementation.

Real-World Implementation Challenges

Human-related biases and biased data can seep into AI algorithms during deployment that lead to treatment recommendations that are inaccurate. AI models should be designed to mitigate algorithmic

bias throughout their product lifecycle. Since AI can come to false conclusions, AI tools should be used to support, and not supplant, human decision-making. Human oversight, transparency in how and when AI algorithms are used, and other bias mitigation strategies can help ensure health care decisions appropriately reflect individual patients' needs and preferences.

AI applications are also more likely to be implemented in large, well-resourced academic medical centers. Considering how the implementation of AI technologies can be made more accessible regardless of geography and facility type would help avoid exacerbating existing health care access barriers. Studies generating best practices or evidence on the value of integrating AI can collectively help realize its full potential for improving patient access to personalized medicine. Public-private collaborations can also aid in developing solutions for integrating and maximizing the use of AI across disease states, patient populations, and health care settings.

II. Recommendations for Regulatory Oversight of AI-enabled Medical Products and Support for a Risk-based Total Product Lifecycle Approach

There are many use cases for AI in health care relevant to personalized medicine and, depending on the use case, developers may be subject to different regulatory requirements. PMC's focus is on ensuring the right framework for AI is used throughout the total product lifecycle. The right framework for regulatory oversight of AI will ensure confidence in the performance and use of AI and mitigate risks to patients while continuing to foster innovation.

Regulatory oversight **should adopt an appropriate risk-based and flexible approach that ensures predictability**. Regulatory frameworks should ensure AI models are trained on appropriately validated data by specifying technical standards for the quality and comprehensiveness of training data, standards to improve the comparability of reported results, and be comprehensive enough to apply to various use cases. In developing a risk-based framework for oversight, regulators should consider differing levels of explainability in how AI models arrive at their outputs. Regulators should also allow adaptive regulatory approaches that allow for iterative development and continuous improvement of AI-based tools and technologies.

Furthermore, to assess potential benefits and risks to patients comprehensively, regulatory oversight should consider a product's **total product lifecycle**, from evidence generation and commercialization, to use by patients and doctors to make health care decisions. This approach could include the use of real-world monitoring to identify and address issues or challenges that may emerge with implementation of AI, as well as identify realized benefits that could expand a product's utility and permissible uses. **The FDA's total product lifecycle approach, as envisioned in the draft guidance on AI-enabled devices, is a critical starting point for managing software-driven modifications, real-world performance monitoring, and continuous risk assessments. Within this framework, Predetermined Change Control Plans can enable the controlled evolution of AI models in the post-market setting.**

AI-enabled medical products often rely on cloud-based infrastructure, networked environments, and integration with electronic health record systems—introducing potential vulnerabilities to data breaches, unauthorized access, and manipulation of algorithmic functions. Because AI-enabled devices may interact with live clinical systems and continuously learn or update over time, ensuring secure and trustworthy system operation is essential to protecting patient safety. **To facilitate trust and accountability over how AI is developed and deployed for personalized medicine purposes,**

prescribed processes regarding the use, disclosure, confidentiality, integrity, and availability of patient data should be transparent and robust. This can include, for example, considerations for how to obtain informed consent when it is required; clarification of when it is not required; how to securely transfer individuals' personal health information with encryption; and how to mitigate threats to cybersecurity and data integrity. **The draft guidance and the Agency's previous cybersecurity guidance[iii] provide some detailed elements for developers to include in their submissions. Clarity in data governance and interoperability for AI tools and technologies is also needed to help scale and facilitate their use in stratifying patients for personalized medicine.**

Ensuring that AI-enabled medial products perform consistently in different clinical contexts and across a broad array of patient populations is vital to maintaining patient safety and reliable health outcomes. Although AI holds promise in accelerating clinical decision-making, inconsistencies in real-world performance have been observed. **To help mitigate biases in AI, developers and regulators should prioritize efforts to ensure training data is reflective of the intended population and account for shortcomings in health data** throughout the product development lifecycle. AI algorithms should be transparent in the data they are trained on, and regulators should test for biases that could impact their real-world implementation. **The draft guidance includes how these data should be described in labeling submissions for AI-enabled devices.**

Finally, in order to avoid the adoption of disjointed frameworks for regulatory oversight that will make it difficult for AI developers to manage compliance with quality and privacy controls, **PMC recommends that oversight should be appropriate to the technology and harmonized with other regulatory frameworks AI may be subject to, including both domestic and global regulatory frameworks. Through participation in venues such as the International Medical Device Regulators Forum, FDA can ensure that harmonization benefits innovation and broader adoption of AI by avoiding duplicative, overlapping, and conflicting jurisdiction of regulatory authorities.**

Conclusion

PMC appreciates FDA's interest in advancing in the use of AI-enabled medical products. We look forward to working with you and your colleagues to finalize this guidance so that it considers the current and future role of AI in advancing personalized medicine. If you have any questions about the content of this letter, please contact me at cbens@personalizedmedicinecoalition.org, or David Davenport, PMC's Director of Public and Science Policy, at ddavenport@personalizedmedicinecoalition.org.

Sincerely,

Cynthia A. Bens
Senior Vice President, Public Policy

[i] U.S. Food and Drug Administration. *Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations: Draft Guidance for Industry and Food and Drug Administration Staff.* January 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/artificial-intelligence-enabled-device-software-functions-lifecycle-management-and-marketing (Accessed April 1, 2025).

[ii] C.S. Ajmal, S. Yerram, V. Abishek, et al. "Innovative Approaches in Regulatory Affairs: Leveraging Artificial Intelligence and Machine Learning for Efficient Compliance and Decision-Making." *AAPS Journal* 27 (2025): 22. https://doi.org/10.1208/s12248-024-01006-5 (Accessed April 1, 2025).

[iii] U.S. Food and Drug Administration. *Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions Guidance for Industry and Food and Drug Administration Staff.* September 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cybersecurity-medical-devices-quality-system-considerations-and-content-premarket-submissions (Accessed April 1, 2025).