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Elizabeth Giaquinto Friedman
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 4162
Silver Spring, MD 20993

Docket Number: **FDA-2023-N-0487**

Dear Ms. Giaquinto Friedman,

I am submitting comments to **Discussion Paper: Artificial Intelligence in Drug Manufacturing, Notice; Request for Information and Comments (FDA-2023-N-0487)** on behalf of the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL). NIIMBL, a part of the ManufacturingUSA network, is a public private partnership of approximately 200 members in academia, government service, and across the biopharmaceutical supply chain. NIIMBL is sponsored by the Department of Commerce, administered through the National Institute of Standards and Technology (NIST), and supported by State, Federal, and private funding. NIIMBL has a Collaborative Research and Development Agreement (CRADA) with the United States FDA and the relationship between FDA and NIIMBL's Federal Sponsors is expanded upon in MOU 225-21-006 dated January 15, 2021.

NIIMBL's mission is to accelerate biopharmaceutical manufacturing innovation and we aim to reduce barriers to adoption of advanced manufacturing technologies, therefore our comments are specific to the manufacture of biologics that would be marketed under a Biologics License Application. We consulted with subject matter experts from within our membership and have endeavored to make our comments brief and specific. They do not represent the full scope of comment and concern raised by NIIMBL members but are fully consistent with the themes and arcs of member feedback.

We appreciate the FDA providing the public and technical communities of practice an opportunity to comment on this Discussion Paper and recognize that Artificial Intelligence is a rapidly evolving area of technology development with potentially profound implications on the industry. The feedback provided in this response focuses on considerations for advancing risk-based, patient-centered biopharmaceutical manufacturing through clarity of expectation, consistency with existing guidance and regulation, and technical excellence in manufacturing controls.

Sincerely,

Gene Schaefer, Ph.D.
Senior Fellow, NIIMBL

NIMBL

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1. What types of AI applications do you envision being used in pharmaceutical manufacturing?

- AI can aid decision making or be decisional in existing elements of a production quality management systems such as lot release, conduct of maintenance, and CAPA related activities.
- AI could become transformational in establishing new paradigms within a production quality management system such as parsing for relevance to common cause and special cause variation, enabling automation of visible inspection activities, or even identifying previously undetected biases such as between vendors of raw materials.
- The value of digital twins resides in their ability to predict the performance of commercial operations. AI holds great promise to confirm the validity of digital twin models and assuring an understanding of systems decay or analytical attribute drift.

It is key to distinguish between applications where AI is being used to define the operational space, for example, "This is what it looks like when the process runs correctly" and where AI is being used for control within the operational space, for example, "This lot was produced by a process that ran correctly." In addition to its role in pharmaceutical development and manufacturing, AI will likely play a role in other parts of the product lifecycle, such as supply and distribution networks to encourage end-to-end quality-by-design approaches.

2. Are there additional aspects of the current regulatory framework (e.g., aspects not listed above) that may affect the implementation of AI in drug manufacturing and should be considered by FDA?

- The regulatory framework is generally adequate for implementing AI in drug manufacturing.
- It would be helpful to clarify the role of 21 CFR Part 11 Electronic Records; Electronic Signatures as it applies to the use of AI in drug manufacturing.
- It is noted that ICH Q10 was omitted from the "Potentially Associated Requirements and Policies," and we feel that the principles of the quality management system are fully appropriate for the use of AI in drug manufacturing.
- Global regulatory divergence is a hurdle to implementing AI in drug manufacturing processes and adds unnecessary complexity. Using existing global harmonization approaches, such as ICH, where possible, is beneficial. Further, harmonization between the centers at FDA around the topic of AI for drug manufacturing would be helpful as well.

3. Would guidance in the area of AI in drug manufacturing be beneficial? If so, what aspects of AI technology should be considered?

- We strongly support the use of global harmonization and clarity through existing venues such as ICH. Additional guidance on the use of AI in drug manufacturing would be helpful, but USFDA guidance in isolation within a global marketplace might add unintended complexity for manufacturers.
- One aspect of AI technology that might be considered for additional clarity is the integration of AI into decisional quality management systems.

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- Another aspect of AI technology that might be considered for additional clarity is the mobility of AI technologies between organizations, for example if Company A acquires or merges with Company B.

4. What are the necessary elements for a manufacturer to implement AI-based models in a CGMP environment?

- The sector can build upon the current principles of technical advocacy, patient-centered risk management, and good documentation/data integrity practices as necessary elements for implementation of AI in a cGMP environment. As this is a rapidly changing area of emerging technology and application, it would not be helpful for the Agency to establish specific constraints or criteria for submission. We appreciate and encourage ETT and CATT engagement (perhaps in partnership with one another) and hope FDA will make experts available to participate in the development of consensus standards arising in the regulated industry.

5. What are common practices for validating and maintaining self-learning AI models and what steps need to be considered to establish best practices?

6. What are the necessary mechanisms for managing the data used to generate AI models in pharmaceutical manufacturing?

- In response to both questions 5 and 6, we would like to note that common practices for validating and maintaining self-learning AI models and for data management are being developed in a breadth of settings and it is premature to fully identify best practices in biopharmaceutical manufacturing. There may be an opportunity for FDA to partner with NIST to establish practices and standards per MOU 225-21-006 (see https://www.nist.gov/artificial-intelligence).

7. Are there other aspects of implementing models (including AI-based models) for pharmaceutical manufacturing where further guidance would be helpful?

- Please see responses to Questions 2 and 3.

8. Are there aspects of the application of AI in pharmaceutical manufacturing not covered in this document that FDA should consider?

- We'd like to take this additional opportunity to suggest that the FDA consider mechanisms to train reviewers and site assessors on the use of AI-based models and other AI applications in drug manufacturing. It might be helpful to establish an expert AI team in ORA to be available for AI CMC-related consults.