May 1, 2023

RESPONSE TO FOOD AND DRUG ADMINISTRATION REQUEST FOR INFORMATION AND COMMENTS ON "DISCUSSION PAPER: ARTIFICIAL INTELLIGENCE IN DRUG MANUFACTURING"[1]

ACM, the Association for Computing Machinery, is the world's largest and longest established association of computing professionals, representing approximately 50,000 individuals in the United States and more than 100,000 worldwide. ACM is a non-profit, non-lobbying and non-political organization whose U.S. Technology Policy Committee ("USTPC") is charged with providing policy and law makers throughout government with timely, substantive, and apolitical input on computing technology, and the legal and social issues to which it gives rise. Consistent with that charge, USTPC is pleased to submit these comments in response to the recent Request for Information and Comments by the Food and Drug Administration ("FDA")[2] on the Center for Drug Evaluation and Research ("CDER") *Discussion Paper: Artificial Intelligence in Drug Manufacturing*:[3]

General Observations

- USTPC concurs with CDER that a risk-based approach to regulating AI in the present context is appropriate and necessary;
- We urge the FDA in devising that regime to be guided by how AI is (or may be) governed when a component of hybrid software systems, in other industries,[4] and by other nations and international bodies;[5] and
- USTPC also suggests that the FDA explicitly consider whether AI-based applications should be held to a specialized, more rigorous standard than conventional automated systems.

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[1] The principal author of these comments for USTPC was committee member Harish Arunachalam with significant input from fellow member Arnon Rosenthal. Also contributing were: USTPC Security Subcommittee Co-Chair Carl Landwehr, AI & Algorithms Subcommittee Co-Chair Jeanna Matthews, and past USTPC Chair Stuart Shapiro.

[2] 88 FR 12943 (March 1, 2023), Document Number 2023-04206 in Docket FDA-2023-N-0487.

[3] https://www.federalregister.gov/documents/2023/03/01/2023-04206/discussion-paper-artificial-intelligence-in-drug-manufacturing-notice-request-for-information-and

[4] See, *e.g.*, *Supervisory Guidance on Model Risk Management*, published by the Board of Governors of the Federal Reserve System, Office of the Comptroller of the Currency (OCC 2011-12, April 1, 2011).

[5] See, *e.g.*, the UNESCO Ethics of AI Agreement; Council of Europe Convention of AI; European Union AI Act; White House's Blueprint for an AI Bill of Rights; and multiple national AI strategies (including China's AI rulebook and upcoming transatlantic "Trustworthy AI" Guidelines).

Comments on Select "Areas of Consideration Associated with AI"

2. The IOT may increase the amount of data generated during pharmaceutical manufacturing, affecting existing data management practices.

The digital automation of processes in drug manufacture is bound to increase the volume of data generated independent of the growth of the Internet of Things ("IoT"). Regulatory attention thus should focus on the trustworthiness (*i.e.*, accuracy and integrity) of data from the IoT or any source, leaving volume management as an issue for implementers. This consideration thus might be more appropriately and generically headed "Adapting existing data management practices to increased data volume" with an emphasis in this section on data quality and trustworthiness.

3. Continuously learning AI systems that adapt to real-time data may challenge regulatory assessment and oversight.

Continuous learning systems, including most AI-enabled ones, can create or increase operational risks in drug manufacture depending upon the nature and scope of system changes adaptively made. Governance and oversight of such systems, particularly their periodic review, is thus critical to assuring system compliance with developed standards.

Responses to Select "AI Questions and Feedback"

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 the FDA?

USTPC recommends that the final report provide primary pharmaceutical manufacturers and their AI vendors/developers with development guidance specific to AI systems.

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

All systems that generate decision mechanisms (whether by using AI or statistically derived models) require particularly strong oversight and auditability. To that end, USTPC recommends that standard current pharmaceutical industry data governance and management practices be augmented by regulation requiring AI system developers to preserve data and methods used to train AI systems, as well as inferences and outcomes of such systems' operation while in development and subsequent use.

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

Good governance of AI models requires that they be documented and understood. At minimum, effective governance models would afford regulators access to: information related to use cases, the specific purposes for which a model was developed, model development lifecycle stages, artifacts generated during each step, expert reviews, data lineage, development/deployment platforms, and risk assessments.

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

The FDA, in addition to proposing a risk-based model validation/regulatory framework, should encourage AI developers and pharmaceutical manufacturers to follow principles of Responsible AI when developing and using AI, including those initially developed by USTPC in 2017[6] as updated in late 2022.[7]

Additional Observations and Recommendations

USTPC urges the FDA in the context of this proceeding to consider a number of its 2019 comments on AI-augmented software:[8]

> *All the usual quality checks and regulatory requirements for development and testing should still have the desired effects of guaranteeing quality.*
>
> *[N]ew regulatory models will be essential if a manufacturer proposes to use AI to dynamically change a device's behavior in the field without being subject to a regulated development and testing process.*
>
> *Removing the human from the "loop," coupled with bypassing testing, would increase the risk that the AI employed will have unintended effects on data accuracy and device safety.*
>
> *There are many possible regulatory responses to these important statistical and physical issues. These include:*
>
> - *Banning . . . dynamic, significant AI-dictated updates to device behavior because the results cannot be guaranteed accurate and safe;*
> - *Requiring a manufacturer to install "governor" software in its device which will reliably assure that the device's behavior cannot degrade beyond articulable and enforceable limits;*
> - *Mandating or encouraging data sharing among health care providers and device manufacturers to maximize the amount, and assure the validity, of large quantities of training data.*
>
> *[USTPC] also urges the FDA, in devising its new Artificial Intelligence/Machine Learning testing and certification protocols, to:*

[6] Statement on Algorithmic Transparency and Accountability, ACM U.S. Public Policy Council, ACM Europe Council Policy Committee (2017)

[7] Joint Statement on Principles for Responsible Algorithmic Systems, ACM TPC, Europe/US Technology Policy Committees (October 26, 2022)

[8] Comments to Food and Drug Administration on AI-Augmented Software as a Medical Device Discussion Paper, ACM US Technology Policy Committee (June 3, 2019)

- *Employ and require verified and validated systems as well as outcomes-driven, automated, and (where possible) deterministically reproducible testing of the vendors' own development laboratories;*
- *Require manufacturers to create a common pool of data for input to AI analyses, including both real-world deidentified data and synthetic data; and*
- *Foster the development of a common pool of varied simulation and other test environments using the deidentified and synthetic data endorsed above.*

USTPC also further suggests that the FDA:

- Expand its existing software regulations to expressly include AI systems and to address them at a detailed technical level;
- We also propose that sufficient attention be provided to AI security and privacy preservation to develop systems that are safe against adversarial attacks;
- Prioritize transparency of model development lifecycle information, data used for: training, testing, and associated risks in models whenever vendor AI is used in drug manufacturing; and
- Encourage the responsible development, governance, and use of AI systems regardless of their field of use consistent with USTPC's ACM's October 2022 joint Statement on Principles for Responsible Algorithmic Systems to foster the development of more robust, explainable, harmless, auditable, and transparent AI solutions.