01 August 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
via online submission to https://www.regulations.gov/

RE: Docket No. FDA-2023-N-0743 "*Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products.*"

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) appreciates the opportunity to comment on the above-referenced paper.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. The 21,000+ members of ISPE lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take a political position or engage in lobbying activities or legislative agendas.

We appreciate the opportunity to submit these comments for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

Thomas B. Hartman
ISPE President and CEO
thartman@ispe.org

cc: Michael L. Rutherford, ISPE Chair

Introduction

As a global industry leader in connecting pharmaceutical knowledge to deliver manufacturing and supply chain innovation and operational excellence, ISPE recognizes the importance of Artificial Intelligence (AI) and Machine Learning (ML) to pharmaceutical manufacturing and welcomes the opportunity to share views on this emerging topic with FDA. The ISPE comments below are focused on the pharmaceutical manufacturing process lifecycle, from development through commercialization. ISPE also refers FDA to our comments to the previous docket, FDA-2023-N-0487 "*Artificial Intelligence in Drug Manufacturing*."

ISPE agrees with the potential uses of AI/ML in pharmaceutical process design describe in Section II.E, including optimization, process control, monitoring and maintenance, and trending. More potential uses are likely to emerge with increased experience. Some models, such as digital twins, can be used across the product and process lifecycle, acting as knowledge storage, and increasing learning through all stages.

ISPE would like to emphasize the importance of the following factors for AI/ML models for pharmaceutical manufacturing:

- model selection
- data adequacy (quantity, quality, visibility, sensibility, significance for the model)
- data management activities, including associated validation and documentation.
- periodic review, including data acquisition and data management.
- understanding model uncertainty and prediction uncertainty along with the sources of uncertainty (e.g., structural uncertainty of model parameters, uncertainty about the residual error).

ISPE would also like to emphasize the importance of FDA's alignment with other regulatory agencies which will lower barriers to advancing AI/ML models in pharmaceutical manufacturing and contribute to increased assurance of the availability of quality medicines for patients.

The following is ISPE's response to the questions in Section III of the document.

(1) Human-led governance, accountability, and transparency

(1a) In what specific use cases or applications of AI/ML in drug development is there the greatest need for additional regulatory clarity?

- The regulatory expectations for models used in drug manufacturing are unclear, especially for AI/ML models. It would be helpful for FDA to describe how AI/ML models fit into the context of Low, Medium, and High Impact models, described in the *ICH Quality IWG: Points to Consider for ICH Q8/Q9/Q10 Implementation (2011)*

- Clarity and examples are needed on what information is needed in the dossier, and what information is needed at the manufacturing site, for example, the expectations for model training, continual verification, changes, and the degree of human oversight/control.
- A regulatory mechanism is needed to allow for AI/ML model updates with no or minimal regulatory reporting. A comparability protocol (CP) / Post Approval Change Management Protocol (PACMP) could be useful for infrequent post-approval changes, but frequent changes would need a more dynamic approach, such as performance-based established conditions, as described in ICH Q12. Alternatively, a new tool such as CDRH's predetermined change control plan could be effective in ensuring seamless continued model update and maintenance.
- Considerations are needed for transferring models (e.g., between sites, products, or software platforms) and expectations on representativeness.
- International alignment is needed to advance the use of AI/ML in advanced pharmaceutical manufacturing. Without a common regulatory approach, implementation of new technology will likely be limited, since most pharmaceutical manufacturing is international.

(1b) What does transparency mean in the use of AI/ML in drug development (for example, transparency could be considered as the degree to which appropriate information about the AI/ML model – including its use, development, performance, and, when available, logic – is clearly communicated to the regulators and/or other stakeholders)?

- Transparency includes a clear description of how the AI/ML system was taught, validated, and updated throughout its development lifecycle, and how it remains in a state of control, including performance and known failure modes.
- Transparency also includes communication of the results in a way explainable to the customer.
- Transparency also could include a rationale on why specific AI/ML technology is applied, including its expected benefits and risks in comparison to non-AI/ML approaches.
- Transparency also could mean the degree to which an AI/ML solution links the result or other information provided to the subject matter experts' (SMEs') mental model of processes, leveraging explainable AI techniques.

(1c) In your experience, what are the main barriers and facilitators of transparency with AI/ML used during the drug development process (and in what context)?

- A major barrier is how to explain to an audience how an AI/ML system is taught, validated, and updated throughout its development lifecycle, and how it remains in a state of control. In general, these models cannot be dissected into constituent equations, so the user must rely on understanding the relationship between inputs and outputs. Additionally, the model must be trained with sufficient diversity to reduce bias. Systems and procedures should be in place for appropriate validation and reporting of results.

(1d) What are some of the good practices utilized by stakeholders for providing risk-based, meaningful human involvement when AI/ML is being utilized in drug development?

- The level of human involvement should be proportional to the utilization and risk of the AI/ML model. Models that provide suggested or optional direction for human follow-up would have less need for human involvement than one that makes decisions, for example as related to process control. Models that make independent decisions related to product quality, safety, or efficacy (e.g., batch release) would have the highest level of risk, and thus merit the greatest human oversight.
- The level of human involvement should also be related to the uncertainty of the model.

(1e) What processes are in place to enhance and enable traceability and auditability?

- Versioning of models
- Links between the models and training data
- Structured account of development process and insights, with comparison to the original understanding prior to AI/ML
- Periodic review of the model under the pharmaceutical quality system

(1f) How are pre-specification activities managed, and changes captured and monitored to ensure safe and effective use of AI/ML in drug development?

- Development (i.e., pre-specification) of AI/ML model can follow the approach outlined in the ICH Q8/Q9/Q10 Points to consider, including:
    - Defining the purpose of the model
    - Deciding on modeling approach and experimental/sampling methodology
    - Selection of variables/inputs
    - Understanding model limitations and assumptions
    - Collecting data to support model development
    - Developing and validating the model (may be repeated)
    - Evaluating model uncertainty and mitigating, if needed
    - Documentation of model development and validation, and lifecycle verification plans
- Model maintenance and changes are managed in the pharmaceutical quality system.

(2) Quality, reliability, and representativeness of data

(2a) What additional data considerations exist for AI/ML in the drug development process?

- Time of data origination, to identify potential drifts due to the course of time, progress in process understanding, or changes in the data origination process.
- Source of data (internal, external), as relevant drivers of representativeness.
- Diversity and variability of source data to reduce the risk of bias.

(2b) What practices are developers, manufacturers, and other stakeholders currently utilizing to help assure the integrity of AI/ML or to address issues, such as bias, missing data, and other data quality considerations, for the use of AI/ML in drug development?

- De-identification of data, as needed.
- Legal considerations (e.g., check of contracts with stakeholders) regarding the use of data.
- Encryption of data during storage and transfer, as needed.
- Principles for appropriate access to data.
- Use of federated learning approaches (i.e., training of models on disjunct data sets, aggregating to a combined model, rather than combining the data), as relevant.

(2c) What are some of the key practices utilized by stakeholders to help address issues of reproducibility and replicability?

- Versioning of data with timestamps.
- Versioning of models.
- Linkage of versions of models with the exact data points entered training, including the order, if relevant, during training.
- Control of random elements (e.g., random seeds in the setting of random forests, including policies on how to choose appropriate seeds or changes of such seeds)
- Robust change control within the pharmaceutical quality system.

(2d) What processes are developers using for bias identification and management?

- Assessment of performance on stratifications of the data sets, along dimensions relevant from a subject matter experts' perspective.
- Statistical tests on the conformance to quality objectives across segmentation criteria
- Assessment of effects of isolated factors and features regarding plausibility as to the prediction, if feasible.

(3) Model development, performance, monitoring, and validation

(3a) What are some examples of current tools, processes, approaches, and best practices being used by stakeholders?

- Information provided in the ISPE's Good Automated Manufacturing Practice - GAMP 5 Second Edition.
- Explainability features such as the use of heat maps for image recognition techniques, or Shapley Additive Explanations (SHAP) for disaggregation of prediction effects on the level of individual features.
- Use of KPIs such as F1-Scores (and other metrics related to the confusion matrix) in classification setting, or metrics like mean absolute error for point estimation cases.

- Statistical tests assess bias in the data among various dimensions such as time or other groups of input data.
- Selecting Models - the process of determining the best model architecture/algorithm during the specification of the system should be documented and presented.
- Explainability should extend to the inference code surrounding the model execution, not just the model itself.
- Open source could apply to models in addition to other software (e.g., when deploying transfer learning.) All systems should be fully documented with the version of the code/model used and the whole system should be validated.

(3b) What practices and documentation are being used to inform and record data source selection and inclusion or exclusion criteria?

- Capture of metadata (e.g., point in time of data capture, source system).
- Linkage between business analysis on the use case from a subject matter perspective and how this reflects in inclusion or exclusion criteria for a dedicated use case, i.e., justification and comprehensible explanation.
- Diversity in the selection of subject matter experts, developers, and reviewers.

(3c) In what context of use are stakeholders addressing explainability, and how have you balanced considerations of performance and explainability?

- A risk-based approach, as aligned with ICH Q8 through Q11, should inform the decision-making on suitable models and system designs, also with respect to the complexity and explainability. This should involve a thorough understanding of the user group prior to a decision for or against more complex models that might exhibit challenges regarding explainability.
- Expectations on user acceptance should be understood to help select among various alternatives, ranging from simpler to more complex models, and to identify the optimal solution with respect to the human-AI-team, which may differ, optimal technical model, if measured by statistical KPIs alone.

(**3d) What approaches are being used to document the assessment of uncertainty in model predictions, and how is uncertainty being communicated? What methods and standards should be developed to help support the assessment of uncertainty?**

- Use of confidence intervals around point estimates or probabilities based on product understanding and process knowledge.
- Design of dedicated control measures including both, the estimate or probability and its technical uncertainty, and design of appropriate operational model (e.g., human-in-the-loop, human-on-the-loop, action by exception only.

- Regular monitoring regarding statistical KPIs as to the model performance, augmented by more qualitative means such as user acceptance/rejections and feedback.

Many methods for uncertainty assessment exist. (e.g., Psaros, Apostolos F., Meng, Xuhui, Zou, Zongren, Guo, Ling, & Karniadakis, George Em. *Uncertainty quantification in scientific machine learning: Methods, metrics, and comparisons*. United States. https://doi.org/10.1016/j.jcp.2022.111902).

It would be useful for FDA to provide scientific guidelines describing approaches for uncertainty approximation in pharmaceutical drug development and manufacturing.

End of Document