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28 April 2023

Dockets Management Staff (HFA-305),
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

Reference: Docket No. FDA-2023-N-0487 for “Artificial Intelligence in Drug Manufacturing, Notice; Request for Information and Comments.

Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the FDA as the agency considers the development of a regulatory framework for the use of Artificial Intelligence in Drug Manufacturing. In general, the discussion paper identifies areas of consideration for AI that we agree are relevant and additional regulatory guidance will be of help to the industry. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important discussion.

PDA is a non-profit international professional association of more than 10,000 individual members scientists having an interest in fields of pharmaceutical, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA’s Science Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,



Glenn E. Wright
President and CEO

cc. Josh Eaton,PDA; Carrie Horton,PDA; Jessie Lindner, PDA

PDA responses to the AI Questions and Feedback Section are outlined below.

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

PDA agrees with the FDA’s points made in this discussion paper referencing that Artificial Intelligence (e.g. NLP) can be applied to:

Quality records (e.g., deviations, CAPAs, OOS, OOT, change controls, and complaints) to enable:

- a) Monitoring and trending of QMS records not only to identify problem areas but enable predictive analytics.
- b) Analysis and selection of QMS data to support activities such as conducting manufacturing or complaint investigations, classically done by 5 Whys, Brainstorming, Ishikawa, Rule in Rule Out etc. Historically these processes are very time consuming and may only capture a small portion of relevant data or ultimately capture data that is irrelevant.

PDA proposes the following for consideration:

- a) Manufacturing Execution Systems and their interfaces to LIMS, ERP, Batch Release, Finished Product Inventory Management, etc.
- b) Packaging operations applications could be used to predict potential failures, support/trigger adaptive actions, and avoid unexpected downtime and stoppages.
- c) Natural language processing (NLP) offers a wide range of opportunity with the ability to parse unstructured data/documents to extract structured data, including but not limited to:
 - i. Parsing adverse events or complaints to identify patterns/similarities etc.
 - ii. Extracting relevant information on trends
 - iii. Enabling predictive analytics
- d) Visual Inspection
 - i. AI coupled with serialization at the unit-level (i.e., primary container) creates opportunities to enhance Automated Visual Inspection performance (e.g., false rejects, trend analysis, root cause investigations) aligned with USP <1790> expectations. They may also be used for sterilization and authentication of products.
 - ii. Machine learning-based approaches for inspection of glass, dosage forms, packaging, and other products whose input is an image or video, and outputs are product attributes used to confirm that the product is acceptable (e.g. morphological particle grouping of microfluidic flow imaging). Outputs could include categorical values such as good versus defective, dimensional measurements of products, or bounding boxes or segmentation maps indicating the location(s) and type of defect.
- e) Digital Twins: using batch prediction in particular for, but not limited to, biopharmaceutical manufacturing. This includes digital twins of three levels:
 - i. Level 1 – Digital Model: Pure simulation and prediction for gathering process understanding
 - ii. Level 2 – Digital Shadow: Prediction for process control; the human performs manual adjustment of the process in response to the simulation result

- iii. Level 3 – Digital Twin: Information feeds back into the process without human interaction; measure → simulate → predict → adjust → measure

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?

PDA suggests the FDA take into consideration the following aspects:

- a) Implementation of a robust training program to ensure impacted personnel are well-versed in this new technology, particularly with continuously learning AI systems. This is also true for auditors (internal to a company or external / certifying bodies).
- b) Clarity on Limits on Process Control – It would be helpful to define a framework that addresses established conditions (control strategy and limits) where process decisions are made by an algorithm. Restricting the manipulated variables would be counterproductive to the ability of a controller to compensate for disturbances (e.g., driving a car but not being allowed to turn the wheel more than a few degrees). This framework could also address how the established process control limits will be supported and evidence, i.e development data, manufacturing data.
- c) Reproducibility of Cloud Based AI Services - Cloud-based providers of off-the-shelf AI services that enable access to models that can be utilized for a variety of services including image recognition, natural language processing, and anomaly detection are continuously improved by the vendor and customers may not have access to all versions of the models. A concern would be if the model previously used would still be usable in production environments at some later date (e.g., 2 years later). With the same input data, would the output be exactly reproduced?
- d) ALCOA+ principles as related to AI (and digital technologies in general), for example:
 - i. Handling of intermediate data, e.g., data which is cleaned to fulfill the ALCOA+ requirements?
 - ii. Data governance concepts and requirements, and principles such as FAIR data?
- e) Data extracted from a paper document(s) into a digital record. How will “true copy” apply for digitally transformed data that represents the original paper record but is not a “copy”?
- f) PDA believes it would be helpful to understand how feedback provided for this discussion paper will be shared with CBER and the Office of Advanced Therapies specifically to understand if the intent is to align across divisions.
- g) Harmonization of any new regulatory and/or industry guidance with current guidelines. This could include establishing standards for AI, and also considering areas outside of manufacturing such as clinical trials, medical devices, drug development, etc. For example:
 - i. The existing framework published by FDA around Software as a Medical Device (SaMD)
 - ii. Artificial Intelligence and Machine Learning in Software as a Medical Device (FDA website)
 - iii. “Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)” (April 2019)

- iv. ICH Q12 and ICH 13 (including whether lifecycle concepts as described in this guidance apply to AI models or not)

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

PDA recommends the following areas be considered:

- a) A deliberate assessment of which aspects should be specified in guidance versus aspects that could be presented in documents which are more easily updated, such as Q&As, reflection papers, and points-to-consider documents, in order to keep pace with the rapidly evolving field of AI.
- b) Key aspects of new guidance should include recommendations for ensuring that processes are under control when AI is applied continuously.
- c) The industry will benefit from a clear definition and example of artificial intelligence. This term is often used broadly to describe digital technology advancements, many of which are not algorithm or model based.
- d) Application of validation and qualification approaches for conventional process automation (e.g., process control system) to AI innovations for cGMP processes.
- e) A regulatory framework is needed to ensure access to AI models and control of data sets to prevent misuse. For example, identifying which aspects of an AI model should be validated, how sponsors should demonstrate evidence of the validation, use of third-party 'black box' models (e.g., smart camera), and any requirements for (re)validation and/or use of third-party certification.
- f) Clear guidance on the expectation of explainability of AI models (as defined by NIST) and requirements for validation of the outputs.
- g) For models where the explainability is difficult (as noted on page 10 of the FDA document), additional guidance from the agency on requirements for validation of the outputs would be important (e.g., validation against reference standards). Within such complex models, the agency could consider validation requirements that are scaled based on an assessment of risk. Where models are similar, the agency could also consider the applicability of one model's validation to additional use cases to reduce burden. In this case, additional guidance on the minimal information required (e.g., a comparator table between models demonstrating similarity) and how this information should be reported would be beneficial.
- h) Guidance on the applicable criteria for:
 - i. Data cleaning and preparation
 - ii. Identification of relevant variables, metadata, and calculated variables
 - iii. Algorithm selection and tuning the AI model's accuracy and performance
 - iv. Life cycle monitoring and continuous supervision of drift within the model
 - v. Traceability and auditability of all the involved steps

- i) Guidance on establishing binary classification. In most cases, these classifications feature class imbalance: the “positive” class that one is worried about is small in proportion to the “negative” class that one is not worried about. Incorrect predictions on the positive class can lead to missed opportunities for intervention. Incorrect predictions about the negative class can lead to the waste of resources through unnecessary interventions. Class imbalance usually adversely impacts the training of binary classifiers. It is common practice in machine learning (ML) to employ various methods of data augmentation to address class imbalance.
- j) Guidance regarding data management for models using IOT devices, as these devices will increase manufacturing data exponentially.
- k) Clarification of change control expectations with respect to learning models which addresses how learning models could be validated.

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

PDA recommends the following items for consideration:

- a) Machine Learning Operations (MLOps): Processes and people for automating training, evaluation, and real-time monitoring of machine learning models in production. For models in production, it is necessary to maintain a registry which indicates the data used for training/test, validation information, and appropriate usage.
- b) Expert audit and assessment of third-party management including IT suppliers.
- c) Understanding of the cost of implementation and maintenance for small/emerging companies, including CMOs
- d) Data Curation, Labeling, and Metadata: A manufacturer needs processes to gather and label/annotate data (e.g., images with good/defect labels). Data sets also need metadata associated to capture the settings under which they were gathered, their appropriate usage, and models that were trained or tested utilizing these data. These data may need to be gathered over time, ensuring that they are representative of varying production conditions and are robust to sources of variability. Versioning of the data is also required to ensure reproducibility of training and testing of AI models.
- e) Quality Management System considerations:
 - i. Additional guidance on regulatory expectations for computer system assurance artifacts associated with AI development and models. These are artifacts specific to ML models such as test evidence/model verification.
 - ii. Ensure data integrity, security, and robust testing with the flexibility to allow for a range of AI models, even those that utilize unsupervised learning and self-learning, as well those that are black box.
 - iii. Principles, standards and methodologies established through data governance and data culture initiatives as foundational for the implementation of AI technologies.

- iv. Risk assessment procedures that would assess the intended use of the model, the training data sets and their robustness, limits for drift in the model, the procedure for retraining the model (including fully autonomous computational procedures), and any redundancy that could be included.
 - a. Real-time monitoring to detect model failures/deviations/errors and associated mitigation strategies, as well as model maintenance processes that outline how such maintenance will be performed and what model changes need to be submitted to regulatory authorities (and specify the reporting mechanism for such filings)

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

PDA suggests the following for consideration:

- a) Data quality: High-quality data is essential for training AI models to produce meaningful outcomes from the learning process (particularly for self-learning AI models). To ensure data quality, data should be cleaned, normalized, and validated before being used to train the model.
- b) Intended Use: Clear goals and objectives for a self-learning AI model should be defined.
- c) Algorithm selection: The rationale for the selection should be described. The algorithm should be appropriate for the problem being solved and be able to handle data of different types and sizes as required by the problem. The selected algorithm should be described in sufficient detail to enable a reproduction of the selected solution.

Model Training: Self Learning Models

- a) Raw data, final data, and data transformation operations should be recorded as part of the AI model.
- b) For “self-learning” or continuous learning AI models, it is necessary to provide assurance that the model learns in a stable manner and continually improves in its accuracy and robustness. This can be accomplished in part by utilizing comprehensive and realistic simulations of the learning process to demonstrate the long-term performance and stability of the approach. Real-time monitoring would need to extend from tracking of input/output of the model to include metrics of model training and stability.
- c) The self-learning AI model should be trained on representative datasets to ensure that it can assimilate and adjust to new data. Training should be iterative, and the model should be evaluated at each stage to ensure that it is improving.
- d) Self-learning AI models should be evaluated on a regular basis to ensure that they are still performing as required. Evaluation should be done on new data that was not used for training the model.
- e) Assurance that unsupervised learning models have the flexibility to adapt within a validated range but are constrained from adapting outside of that range. This ensures the model’s consistency,

reliability, and robustness within the expected conditions. Guidance from the Agency would be appreciated as to how to determine this capacity and how to allow modification of the model without it being a reportable change.

- f) A procedure for real-time determination within an adaptive model to assess the trends/features of the data to which the model should adapt versus those which should raise an alarm (since these trends/features may represent an unexpected and undesirable behavior within the process).
- g) Application of Reinforcement Learning wherein the approach requires the model to be able to directly interact with the environment of interest. This experimentation process is generally done in a simulated environment since experimentation in the real world is often expensive or would require significant downtime. This requires development and validation of simulation environments to enable training and testing. This form of data is generative and requires versioning to ensure reproducibility of the results.

Considerations for the operational phase

- a) A clearly defined framework which details the rules regarding which changes can be made by the model and that fundamental algorithm details cannot be modified without initiating a formal Change Control process.
- b) A monitoring framework to continually evaluate a model’s fitness for use in the field and detect potential model degradation, including when and how to conduct periodic or real-time monitoring of the model performance and in response to changes in data patterns.
 - i. Continuous improvement including retraining the model with new data, updating the algorithm, or fine-tuning the model's parameters.

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

PDA recommends the following for consideration:

Data governance and data management processes:

- a) Data integration is essential to ensure that data from different sources can be combined to provide a comprehensive view of the manufacturing process (e.g., integrating data from various manufacturing systems, laboratory systems, and quality management systems). The integration should be clearly defined and planned in a strategic manner.
- b) Establish a data repository. One approach to doing so is pooling data into a centralized electronic data lake (EDL) that serves as an essential data engineering infrastructure for all data visualization and integration of AI data inputs.
- c) An adequately designed data collection process is of paramount importance to enable AI models to generate meaningful results which can then be understood and followed by the human. For example,

unit-level traceability represents a key digital enabler for a range of Pharma 4.0™ applications in the AI/ML space (see also question 7).

- d) Data quality is important to ensure that the data used to train AI models is accurate, complete, and consistent. This can involve data cleaning, normalization, and validation.
- e) Data security ensures that data is protected from unauthorized access, modification, or destruction. This includes adequate access controls, data encryption, and backup and recovery processes. Furthermore, it should be ensured that the data used for training and testing is kept separate and properly governed (e.g., no unauthorized changes as determined by defined access rights). Implementing a cybersecurity vulnerability assessment for the organization is advisable.
- f) Data and actions associated with the data must be traceable to the selected algorithm and model and hence enable explainability of the model and actions taken. Traceability must also be available for data used for Design of Experiments (DoE).

Technical Considerations:

- a) Cloud Computing Infrastructure: Implementation of AI solutions may have a huge impact on storage capabilities. Additional infrastructure is required. Scalable cloud-based computing solutions permit the handling of the vast amount of data needed. This could also trigger concerns regarding multinational data privacy laws.
 - i. Industrial edge computing devices can enable models to be pushed to the shop floor to support application and testing. This hardware and software must be secure, highly available, and requires the ability to push models to the lower levels of the network.

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

PDA recommends the following for consideration:

It would be helpful to clearly state the different natures of AI in fully automated systems vs human-aided AI systems. Human variability introduces an element of subjectivity in comparison to machine automated results. It is acknowledged that human subjectivity can introduce bias while human thinking may be beneficial (critical thinking). Guidance that addresses subjectivity in human-aided AI would be helpful. Guidance could be expanded to include the role of the human (e.g. operators, analysts) that interface with AI and are expected to provide oversight and/or make decisions based on AI generated information.

- b) Guidance which addresses the phenomenon that model inference can provide slightly different results based on the physical device on which it is implemented. Tracing all information in terms of model compilation and on which hardware it is deployed would make results more reliable.
- c) Guidance on data collection and management approaches. For example, unit-level traceability represents a key digital enabler for a range of Pharma 4.0™ applications in the AI/ML space. Some of these aspects are not covered in the current guidance. The addition of unit-level traceability coupled with AI would bring higher granularity and permit unit-level learning and decision-making instead of a batch level approach. In practice, a unique identifier could couple manufacturing data with market outcomes (i.e., complaints, investigations) or allow linking primary container supplier

metadata (like prefilled syringe length, flange dimensions, concentricity) to pharma manufacturing process data.

- d) More guidance on the agency’s cybersecurity expectations.
- e) Further details on the requirements for AI model monitoring and maintenance. For continuously learning AI, more clarity on expectations to demonstrate robustness over time would increase the adoption and consideration of these approaches. The maintenance approach should consider both data and model drifting.
- f) Guidance on process monitoring in relation to submission/amendment. As the agency has noted in its discussion paper on AI, it is challenging to determine how to regulate continuously learning algorithms that could drive changes without prior review by the agency. Thus, guidance would be helpful on employing AI models in process monitoring, particularly with respect to addressing variation management (i.e., post-market or lifecycle changes that typically require a regulatory submission/amendment).
- g) Guidance on how to justify and document changes driven by the algorithm based on the data inputs with little or no human intervention for audits and documentation purposes. Current approaches to manufacturing changes are well-established regarding human-driven processes.
- h) Guidance on how to assess which changes made by an AI-algorithm would require regulatory submissions and prior review by the agency, as well as what reporting category would be appropriate and when such filings should be submitted (particularly for unsupervised continuous learning algorithms that could make changes over time). It would be helpful to understand how the agency views the risk of certain changes and what approaches may be taken to align FDA on changes that can be made by the model without a prior submission (e.g., predetermined change control plans).
- i) Clarification of expectations as to whether data used to train AI models for use in manufacturing must themselves be procured, documented, labeled, and stored per GMP standards. Deep learning algorithms available for use in manufacturing may be trained on many data sources that are not controlled by, or even accessible to, the end user.

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

PDA suggests the FDA consider the following aspects:

- a) It would be useful to define and describe a process and mechanisms for interacting with FDA regarding AI methods in development, including through conferences, forums, reviews, or meetings where direct access to test and evaluate the models could be provided to expert teams within the agency.
- b) It would benefit the industry to describe systems and provide guidance around managing AI models in production (i.e., ML Ops). This could include the interconnection between the cloud and edge devices used to run the models, expectations around real time monitoring of performance, and how the agency may be provided access to evaluate the models used.

- c) It would be helpful to clarify the term data quality vs. data integrity and provide guidance as to roles, responsibilities, and expectations for assuring data quality across the lifecycle of data relevant to AI.
- d) It would be helpful to understand acceptable regulatory pathways for incorporating AI. For example: Is it required to incorporate AI pathways into Prior Approval Supplements (PASs)?
- e) It would be helpful to understand what the impact may be of organizations adopting AI, and the potential advanced capability and benefits associated, on organizations that do not (or cannot feasibly) adopt AI.
- f) Harmonization with other FDA guidance and with standards from other regulatory bodies on AI/ML application areas outside of manufacturing, e.g., clinical trials, medical devices, and software as a medical device.
- g) Guidance for Quality Assurance Agreements (QAAs) and other contracts for IaaS, PaaS, SaaS and AI/ML service providers would be of high value, similarly, to the existing QAA guideline on CDMOs.
- h) It would provide clarity to elaborate whether the agency expects incorporation of methods using AI models for US Pharmacopeia similar to the chemometric methods accepted in the European Pharmacopeia which use AI models.
- i) Guidance developed for AI applications should consider the risk to “overthink” decisions by trending more data than what the situation or process actually requires (“Analysis Paralysis”). This might be counterproductive to the desired process improvement as it could be better handled by a well-trained and experienced human operator.