GENERAL COMMENTS ON THE DOCUMENT

Harmonization

This document is welcome as a starting point for engagement between industry and regulators to give orientation and guidance where new technologies in connection with digital transformation are used. ISPE recommends a harmonized playing field, to the extent possible, through alignment and harmonization with developments in other countries and regions, such as the European Commission Proposal for a Regulation of the European Parliament and of the Council (Artificial Intelligence Act) and the European Union Aviation Safety Agency. Aligned regulatory expectations and vocabulary would enable regulatory convergence and support multinational companies to apply AI technology, thereby increasing operating efficiencies and reducing the cost of goods. Engagement with industry professional societies, like ISPE, could enable faster and more complete guideline development.

Q1. What types of AI applications do you envision being used in pharmaceutical manufacturing?

ISPE members have identified broad applications of AI, potentially in the following areas:

- CMC Development
- Process Control and Process Development
- Process Design and Scale Up
- Autonomous system for drug manufacturing.
- Production planning
- Asset management
- Quality control (e.g., AI for text, image, or video processing during quality deviation, investigation, and report generation)
- Quality Assurance (e.g., release testing)
- Stability/shelf-life modeling
- Documents management
- Training
- New technologies
- Potential use of AI to support molecular discovery efforts to predict the clinical performance of a drug in development based on the relationship between its molecular structure and function.

Q2. 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?

In general, the basic principles and regulatory framework for quality oversight should not be changed but may be fulfilled through industry-accepted risk-based approaches.

Q3. Would guidance in the area of AI in drug manufacturing be beneficial? If so, what aspects of AI technology should be considered?

AI guidance in drug manufacturing is considered beneficial, for the areas of application and the principles of application listed below.

<u>Areas of application</u>

- Data systems/architecture
- Data Collection and preparation
- Model development, maintenance, validation, documentation
- Selection of balanced and representative training, validation, and test data
- Algorithm verification and validation
- Technical transfer
- Computer System Validation/Assurance

Principles of application

- Defining the scope of what AI innovations would be considered cGMP; application of risk-based approaches.
- Expectations for “Explainability” and “Transparency”. Approaches for off-the-shelf “black box”-type solutions with no explainability possible (e.g. smart cameras)
- AI/ML component’s pre- and post-filters, for example, to assure that manufactured output does not drift away from established conditions as a machine learning component learns.
- Approaches for differing levels of human AI-interaction
- Risk-based approach to data storage requirements and cybersecurity
- Defining what AI/ML applications would be required in a regulatory dossier.
- Post approval change requirements for AI filed in dossiers.
- Application of ICH principles for AI (i.e., impact level from ICH Q8/9/10 Points to Consider; established conditions from ICH Q12)

Q4. What are the necessary elements for a manufacturer to implement AI-based models in a CGMP environment?

The Data Management framework should have:

- Equipment with suitable interfaces
- Quality management for AI applications
- Appropriately trained workforce
- Pharmaceutical quality system with adequate maturity and readiness
- Additionally, FDA should define Good Machine Learning Practices for drug manufacturing, such as the guiding principles adopted for medical device development.

Q5. What are common practices for validating and maintaining self-learning AI models and what steps need to be considered to establish best practices?

Considerations for self-learning AI models include:

- AI Quality Management System
- Transparency and security
- Avoiding the introduction of bias
- Testing and training
- Automated validation and testing, as appropriate
- Rules for unsupervised learning

Q6. What are the necessary mechanisms for managing the data used to generate AI models in pharmaceutical manufacturing?

Data Management

Data management should include existing data management practices including data recovery, transmission, standardization, contextualization, storage, security, testing, and training. The approach should be transparent and explainable at all stages. Cultural support for data excellence is essential.

Data management needs can be viewed similarly to classical data practices – data governance, validation, security, traceability, and life cycle management.

Data should be structured and standardized with appropriate data adequacy (i.e., quality, quantity, and significance for the intended use). Data may need to be contextualized for understanding. Data recovery and transmission need to follow established, standardized and transparent processes.

Siloed systems should be connected, contextualized, and structured to drive decisions. 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.

Data used to train, validate, and test AI models can be managed according to the applicable guidelines (for example ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition) or similar guidelines).

New raw data should be collected using automated systems where possible with minimal user interaction/transcription.

Data should be stored with metadata to give context. Any pre-processing operations should be documented, logged/audited and the output data tagged/linked back to the source raw data files.

Datasets used to train and validate models should be documented and linked to any raw or pre-processed datasets used.

It should be possible to test whether any data (raw, pre-processed) or models have been changed, and if so how and according to what processes/procedures.

Data processing prior to feeding it to the model could be a necessary step for the adoption of AI/ML models in certain cases.

The databases used should be able to handle both univariate and multivariate types of data.

Considering Edge and Internet of Things (IoT) applications, an important aspect is that the consistency and completeness of the data can be verified locally on the Edge node as well.

Data may be sourced or housed from systems on the premises of a manufacturing site or in a public or private cloud.

Mechanisms for ensuring the data interpreted and used by these models should be validated, available in real-time or nearly real-time, and stored in a system that meets 21 CFR part 11 standards.

The presentation of the data and the utilization of data within the AI algorithm should be in keeping with where the data was generated.

3rd parties should follow applicable regulations (e.g., for cloud services).

Culture and Organization

Companies should establish a culture of data-aligning incentives to contribute to data excellence, with dedicated roles and responsibilities.

Companies should have a corporate data strategy with the right incentives to ensure long-term benefits from high-quality data pools.

Roles, like data owners and data stewards, should be defined in the specific context of data.

Development practices should consider data from end to end, implementing service components within a data asset ecosystem; Data Dictionaries; Software Quality Excellence.

Concepts should be translated into operational procedures, supported by technology to master the operational burden (e.g., quality management, workflows).

Q7: Are there other aspects of implementing models (including AI-based models) for pharmaceutical manufacturing where further guidance would be helpful?

Additional guidance on the following operational aspects would be beneficial:

- Considerations for integration of human factors – collaboration between humans and machines.
- Risk-based approaches for raw data retention, particularly for raw data or metadata that is only used at a point in time for input to an AI/ML model.
- Expectations for AI in process monitoring, including validation and maintenance of post-approval changes. Description of how these models would fit into the ICH Q12 established conditions paradigm.
- Clarity on whether data that are used to train AI models for use in manufacturing must be procured, documented, labeled, and stored per cGMP standards.
- Acceptability of "black box" algorithm or models.
- Considerations for identification and elimination of bias, and evaluation and promotion of algorithm (model) robustness in learning algorithms.

Q8: Are there aspects of the application of AI in pharmaceutical manufacturing not covered in this document that FDA should consider?

Regulatory harmonization with other agencies and related regulations is essential to support the advancement of technology in pharmaceutical development and manufacturing.

For an approved product, the use of AI/ML tools that make use of operational data to improve process control within established conditions should be managed within a company's pharmaceutical quality system and subject to cGMP, provided there are no changes to the control strategy described in the approved New Drug Application/Biologic License Application. Alternatively, if the planned use of AI/ML will potentially go outside the approved control strategy then a post-approval change should be submitted.

Publication of clear use cases for developing and validating AI in specific pharmaceutical applications would help companies reduce regulatory uncertainty regarding the acceptance of the technology and speed the time to implementation. Use cases should include both product specific (e.g., process control) and non-product-specific examples (e.g., equipment monitoring). Potential topics for use cases of AI in pharmaceutical manufacturing include:

- Process Monitoring/Advanced Process Control
- Fault Detection, Equipment Monitoring, and Maintenance
- Documentation, Filings, and Reporting
- Model maintenance and post-approval changes

Any guideline should discuss how manufacturers or technology developers can interface with FDA, for example through the ETT.