Biocom California

May 1, 2023

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Artificial Intelligence in Drug Manufacturing (FDA-2023-N-0487)

Submitted electronically

Dear Sir/Madam:

Biocom California appreciates the opportunity to offer comments on the Food & Drug Administration's (FDA) discussion paper on Artificial Intelligence in Drug Manufacturing[1].

Biocom California is the largest, most experienced leader and advocate for California's life science sector, which includes biotechnology, pharmaceutical, medical device, genomics and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,700 members dedicated to improving health and quality of life, Biocom California drives public policy initiatives to positively influence the state's life science community in the research, development, and delivery of innovative products. California's life sciences industry generates over $375 billion in annual economic activity, supports 435,000 jobs, and increases labor income by $115 billion per year[2].

Artificial intelligence (AI) is a constantly evolving technology that has been leveraged by multiple industries, including biopharma, to improve the quality of processes and increase the overall efficiency of systems. Biocom California is pleased that FDA recognizes the role that AI can play in monitoring and controlling advanced manufacturing for pharmaceuticals. As AI continues to advance, there is a need for regulatory policies and programs to evolve at a pace that matches its development and enables the adoption of this technology for drug manufacturing. Industry and academia stakeholders can collaborate with regulators and share their knowledge on how to best harness and leverage AI in a safe and effective way that supports pharmaceutical manufacturing. Biocom California offers responses to the discussion paper questions below:

[1] Federal Register, 88 FR 12943, pp. 12943-12944, March 1, 2023.
[2] Biocom California 2022 Economic Impact Report Databook. https://www.biocom.org/eir/

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

For general pharmaceutical manufacturing, we envision AI to be used for process simulation, technology transfers, modeling for raw material optimization and selection, and advanced process controls including in-process data collection, analysis, closed-loop feedback, and model predictive controls. This technology could also be used for data-sharing models for point-of-care manufacturing at hospitals or clinics. Additionally, AI could predict critical quality attributes and necessary equipment maintenance, recognize process and equipment issues via pattern identification, categorize issues, and forecast system performance.

When manufacturing new modalities with small drug volumes such as pre-filled syringes, complex and high-value products can challenge the learning curves of current Automated Visual Inspection (AVI) systems. This limitation can significantly raise the rate of false rejects, and, in turn, cost manufacturers time and materials. AI could be coupled with serialization at the unit level to enhance AVI performance, while also aligning with United States Pharmacopeia (USP) <1790> guidelines for fill-and-finish applications[3]. This would especially benefit and improve AVI performance related to identifying false rejects, performing trend analysis, and supporting root cause investigations for complex processes such as prefilled syringe container closure systems.

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?*

When developing a regulatory framework for AI in drug manufacturing, we recommend that FDA consider the challenges associated with model lifecycle management and biases. General challenges that may affect the implementation of AI for system design and process understanding include system complexity, limited workforce expertise, and the availability of robust data for model training. Additional challenges may arise in building models for existing manufacturing processes and equipment versus for new installations. Furthermore, a significant resource investment is required to manage a model throughout its lifecycle, and this can limit the availability of contract development and manufacturing organizations, which are responsible for a large portion of drug manufacturing in the United States. Lastly, the lack of interpretability of some models and their continuously evolving nature should also be considered as the agency develops an AI regulatory framework.

Biocom California suggests that the agency publish clear guidance for drug manufacturers explaining best practices for handling and documenting model development, changes, and integration in a manner that is least burdensome for both the manufacturer and FDA. We recommend that FDA's Center for Drug Evaluation and Research (CDER) reference the work being done by the Center for Devices and Radiological Health (CDRH) and industry groups to create guidelines for using AI in medical device manufacturing. For example, CDRH has developed qualification rules for off-the-shelf software (OTS) or software of unknown provenance (SOUP) and has issued guidance documents on how to manage these elements within the device and its quality management system (QMS). Furthermore, many AI and machine learning (ML) development systems are created from external libraries outside of the end user's control. In these situations, it is currently unclear what the role and responsibility of manufacturers and suppliers are to control the AI system and whether AI systems should be used if manufacturers cannot control upgrades or changes to them. **We recommend that FDA consider the level of control which should exist for manufacturers and suppliers and, if control cannot be enforced, the actions a manufacturer can take to ensure that the AI system is being used and maintained correctly. FDA should also consider how manufacturers can implement controls or mitigators to continue maintaining a state-of-the-art AI system with the least burdensome approach.**

[3] United States Pharmacopeia (2023). General Chapter, ⟨1790⟩ Visual Inspection of Injections. USP-NF. Rockville, MD: United States Pharmacopeia.

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

Biocom California believes that additional guidance for the industry would be beneficial and necessary to continue the development, implementation, and support of AI in drug manufacturing. We suggest that FDA publish a series of guidance documents outlining their current thinking and regulatory expectations on the following topics as they relate to drug manufacturing:

a) **Control, management, and minimum requirements for the AI model development life cycle** including managing bias, the use of open-source libraries, and data management with examples for both low and high-complexity models.

b) **AI model validation requirements** including recommendations for validating and documenting iterations.

c) **Recommendations on the level of control that should exist for manufacturers and suppliers when managing models**, the actions a manufacturer can take to ensure that the AI system is being used and maintained correctly, and how controls or mitigators can be implemented to continue maintaining a state-of-the-art AI system with the least burdensome approach.

d) The relationship between **Chemistry, Manufacturing, and Controls (CMC) and AI**, and the level of information that should be provided by manufacturers at each phase of clinical development.

e) **Existing applicable global standards**, or certain aspects of these standards, which manufacturers can reference for implementing and managing AI technologies in drug manufacturing.

f) The relationship between **AI and the Internet of Things (IoT) infrastructure** and FDA should highlight the different types of technologies and their methodology (i.e., unit-level identification).

g) **Inspections and audits** of AI technology in drug manufacturing.

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

In order to implement AI-based models in a current good manufacturing practice (CGMP) environment, a manufacturer would require process knowledge and management, including adequate sensing and measurement abilities (i.e., process observability). Additionally, a manufacturer would need an established QMS, data systems, architectures, and a strong, talented workforce to implement the model. Manufacturers should also be mindful of and develop fail safes for architecture, computing speed, and connectivity, as these are key factors required for the successful operation of AI-based models. The risk of these processes failing, as well as the general risk of using an AI model, should be assessed in relation to the product, patient population, end-user requirements, and safety profiles. Furthermore, data and model governance should be considered as an AI model would need to be powered and validated by robust data. Therefore, data granularity at the unit level would be necessary to address these needs.

Lastly, many deep learning models utilize a complicated neural network architecture which can be challenging to audit. Manufacturers should be able to build confidence in the model, understand the level of transparency needed for regulatory agencies and end users, and develop audit trails for the data and the continuous learning system. **We encourage FDA to keep these challenges in mind when developing a regulatory framework and suggest that the agency maintain a degree of flexibility in its regulatory requirements.** For example, in lieu of a full understanding of an ML-based model in certain situations, we recommend that FDA consider using a result-based comparison to standard practices such as a comparison of model performance versus human-based results.

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

Common practices for validating and maintaining self-learning AI models will depend on the model type, the algorithm's degree of openness or "human-in-the-loop" capabilities, and its use case. Self-learning models, especially those with ML algorithms, should be validated using standard metrics such as specificity. For example, if specificity is not demonstrated in a model with a ML algorithm, the algorithm may be unstable if it is modeling secondary correlations that may break due to a change in the process conditions (i.e., a change in raw materials) and this is especially true for biological processes. **Biocom California recommends that general principles such as risk management, good ML practices, and data quality and integrity should be consistently followed as best practices. Lastly, we also suggest that FDA leverage industry working groups to develop best practices for validating and maintaining self-learning AI models.**

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

A risk-based approach to data and model governance is necessary for managing data used to generate AI models. While this mechanism will vary for models based on their level of complexity and use case, a strong, foundational data management structure can facilitate a risk-based approach in most use cases. Additionally, manufacturers should consider the accuracy and frequency of data, as well as its storage in validated databases. Manufacturers should establish additional data governance requirements and expectations such as identifying the data used as part of the training and validation sets, rules for manual and auto-labeling of data, how data from different sites will be used for the same process, and the use of data from external organizations outside of the manufacturer's control.

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

Biocom California suggests that FDA consider issuing further 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, yet some of these aspects are not included in the current FDA guidance[4]. The addition of unit-level traceability coupled with AI would bring higher granularity to the process and would facilitate a unit-level learning and decision-making approach instead of at the batch level. As part of this approach, manufacturers could use a unique identifier as part of the data collection system for an AI application. This practice can facilitate the collection of manufacturing-specific data and, when combined with market outcomes data, can help manufacturers accelerate complaints analysis and improve the scope of an investigation. Furthermore, unit-level learning would allow primary container supplier metadata to be linked to pharmaceutical manufacturing process data. For example, in the case of prefilled syringes, this data could link the prefilled syringe length, flange dimensions, and concentricity together, thus increasing traceability throughout the drug manufacturing process.

We further recommend that FDA consider publishing guidance on cybersecurity considerations for pharmaceutical manufacturing, precision versus accuracy considerations, the use of real-world data or incomplete datasets to inform and validate an AI model, and how to leverage the post-approval process to adopt more advanced controls for these systems. Additionally, guidance on AI model validation requirements, beyond standard computer system validation, would be helpful for the industry. We also suggest that the agency consider recommendations for how manufacturers can validate model changes as they occur with new datasets, without independently assessing or reviewing each modification. Furthermore, the industry would welcome insights into the agency's current thinking on the future of healthcare planning and precision medicine manufacturing approaches such as at the point of care.

Lastly, we encourage inter-agency collaboration and communication between CDER, the Center for Biologics Evaluation and R esearch (CBER), and CDRH's Digital Health Center of Excellence (DHCoE). CDRH has made many regulatory advancements related to AI and medical devices and has published several white papers including the *Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan* and *Good Machine Learning Practice for Medical Device Development: Guiding Principles*[5,6]. These white papers outline regulatory frameworks and guiding principles with collaborative insights from industry and academic working groups, as well as foreign regulators. The regulatory foundation that is being developed by the DHCoE and its partners will likely mirror the needs of CDER and CBER stakeholders.

[4] https://ispe.org/initiatives/pharma-4.0
[5] https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices
[6] https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles

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

The production of biopharmaceutical products should adapt to the trends and drivers of manufacturing modernization to improve process capability and increase supply chain reliability. A key component of manufacturing modernization is the use of models to better predict and control processes. Data packages and knowledge used to identify and generate models are constantly evolving, and models can have multiple intended uses depending on the process control needed, available data package, knowledge level, modeling strategy, and process complexity. The model type and its intended use will define the types of actions which can be taken by the controller as well as the needed level of causes-to-relationship-to-symptoms understanding. In order to define the model's intended use and supporting business case, manufacturers must understand the difference between complex and simple systems, and the AI model's design should align with the level of system complexity.

Additionally, the industry should look to expand its current AI practices in drug manufacturing to also mitigate supply chain risk. Manufacturers and regulators should consider plans for AI model evolution and evolutionary intended use as this is important to achieving control and process intelligence while deriving value from modeling activities. We suggest that FDA look to international standards such as the International Council for Harmonisation (ICH) Q12 as these guidelines provide an opportunity to evolve process intelligence and control in a transparent, logical, and attainable manner[7].

Furthermore, due to the high frequency of change associated with AI models, predetermined change control plans (PCCPs) should be considered to ensure that change management processes are clearly and efficiently communicated to drug developers and technology providers. **Manufacturers may also benefit from guidance outlining recommendations on phase-appropriate AI implementation and qualification, in addition to the type of regulatory documentation FDA would require as part of a submission**.

Lastly, the growing usage of cloud computing technology continues to expand across many industries, and we suggest FDA consider the use of cloud platforms and services as they relate to the application of AI in pharmaceutical manufacturing.

We appreciate the opportunity to provide feedback on behalf of our members and thank you for your time and diligence in examining our comments. Please contact Biocom California's Associate Manager of Regulatory Policy, Zoe Bilis, at zbilis@biocom.org for additional information or questions. We look forward to continuing to work with you on this matter.

Sincerely,

Joe Panetta
President and CEO
Biocom California

[7] https://www.ema.europa.eu/en/ich-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management-scientific