

# **Regulating AI in Drug Manufacturing**

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#### **CASSS CMC Forum Europe**

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www.fda.gov



Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

# **CDER Advanced Manufacturing Programs**



#### ASSESSMENT AND INSPECTION

Emerging Technology Program (ETP) || Advanced Manufacturing Technologies Designation Program (AMTD)





#### SCIENCE

Advanced Manufacturing Science & Research



Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)





## Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

# **FRAME Priorities**



#### Seek and Analyze Input

Ensure CDER's understanding of advanced manufacturing technologies is thorough and its analysis of the regulatory framework is science- and risk-based.

### **Address Risks**

Ensure regulations and policy are compatible with future advanced manufacturing technologies.

#### Clarify Expectations

Explain the current thinking on a regulatory issue via new or updated guidance as needed.

#### Harmonize Internationally

Ensure global regulatory practice is clear to interested parties implementing advanced manufacturing.

#### **Cohesive regulatory framework for drugs**

# **FRAME Priority Technologies**



#### Distributed Manufacturing (DM)



#### End-to-End Continuous Manufacturing (E2E CM)



# Self-Contained DM (e.g., at point of care)



#### Artificial Intelligence (AI)



# What is Al?



Source: Executive Order 14110. (October 30, 2023). Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence

## Public Engagements Inform Regulatory Considerations



# **Al-related Publications**

An examination of process models and model risk frameworks for pharmaceutical manufacturing, International Journal of Pharmaceutics (Aug '24)

- CDER, CBER, and EMA coauthors

**Considerations for Big Data** management in pharmaceutical manufacturing, Current Opinion in Chemical Engineering (Sept '24)

#### International Journal of Pharmaceutics: X 8 (2024) 10027-Contents lists available at ScienceDirect International Journal of Pharmaceutics: X An examination of process models and model risk frameworks for pharmaceutical manufacturing Thomas F. O'Connor ", Sharmista Chatteriee Dolores Hemán Pérez de la Ossa<sup>®</sup>, Leticia Martir Adam C. Fisher Available online at www.scienc Chemical Food and Drug Administration, Center for Drug Dreikeston and Research, Dilver (g ScienceDirect Food and Drug Administration, Center for Biologics Designation and Research, 5the ELSEVIER European Medicines Agency, Human Diriston, Dominico Scariaminan 6, 2083 Hit, European neuronal Agency, romana boston, convento currantana n. 2003 Ju., Prench National Agency for Medicines and Boalth Products Enfoy, P-93255, Sain Quality Imvestion Orcupa (2013), European Medicines Agency (2014), Ansarránn, CBD-MSE (Medicines Enduation Board), Utrecht, the Netherlande Considerations for Big Data management in pharmaceutical manufacturing Jayanti Das<sup>1</sup>, Adam C Fisher<sup>1</sup>, Lisa Hughey<sup>1</sup> ARTICLE INFO ABSTRACT Thomas F O'Connor<sup>1</sup>, Vidya Pai<sup>1</sup>, Cinque Soto<sup>2</sup> and John Wan Keywards Process models are Pharmaceuticals 4.0 paradigm promi Process models Model risk assessment such as Artificial late knowledge, however, is a complex endeavor, and digi Big Data technologies are advancing the manufacturing of drug trajectories. Several been shown in lyn and biological products. Such technologies include innovative talization poses an array of challenges. Building a robust Model validation Model lifecycle maints software and computational methods for data storage, mining, and flexible data infrastructure that supports the profi compression, and w cient gathering and analysis of data can overcome these and analytics. Increasingly vast, complex data sets are being the impact of the me produced by advanced manufacturing processes and sensor challenges and offer opportunities for innovation and product lifecycle. Se customization. The NIST Big Data Interoperability for statistical analysis and decision-making. Implementing Big discusses existing ri ramework defines Big Data as "consisting of extensive Data technologies, however, can introduce new challenges for adoption of proce organizations in areas of data generation, architecture, and datasets, primarily characterized by volume, variety tions of applying a manufacture of phar security. Big Data management includes implementing robus elocity, and/or variability that requires a scalable storage, complex data integration, and state-of-the-art analysis software. Upholding data integrity and security might require architecture for efficient storage, manipulation, and analysis" [1]. In fact, the entire realm of available data, designing a modernized risk-based framework plan for the known as the dataspheres, is growing at an exponentia organization. Once these challenges are successfully rate, with estimates indicating that by 2025, it could 1. Introduction addressed, the incorporation of Big Data technologies into produce upwards of 180 zettabytes of data [2]. In the pharmaceutical manufacturing is expected to enable more advanced manufacturing industry, the integration of vast In 2002, FDA laid the foundation for implementation of a me fficient production, lower costs, and greater quality control amounts of information from various sources, such as risk-based pharmaceutical quality assessment (U.S. Food as resulting in a stronger global pharmaceutical supply chain sensors, production lines, and monitoring and main-tenance equipment, enables supply chain manufacturers on, 2004). Part of FDA's initiative encouraged ma turers to use the latest scientific advances in pharmace predict maintenance needs, optimize production manufacturing technology throughout the lifecycle of a prod Addresses <sup>1</sup> Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20989, United States of America <sup>2</sup> Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, MD 20989, United States of America processes, and enhance product quality. To achieve mprove the efficiency of developing and manufacturing drugs. Th these modernization benefits, the augmented data voalso been encouraged by EU as part of the EU directive 2001/8 lume and complexity require robust data management various CHMP (Committee for Medicinal Products for Huma ecurity, and analysis tools. Any skills gap in the work guidelines e.g., CHMP guideline on manufacture of the finished d force for handling sophisticated data analytics technolo-Corresponding author: O'Connor, Thomas F (thomas.cconnor@tda.hhs.gov) form (EU CHMP, 2015). As scientific and engineering knowledge gies poses a considerable challenge that manufacturen pharmaceutical manufacturing has grown, the use of models must overcome to fully leverage the benefits of Big Data process development, enhance process control and forecast future in advanced manufacturing. Current Opinion In Chemical Engineering 2024, 46:101051 cess and product quality outcomes has increased. The types of n This review comes from a themed issue on Pharmaceutical With Big Data impacting manufacturing decisions, up Aanufacturing idited by Kimberley B. McAuley, Salvador Garcia Muñoz and · Corresponding author. E-mail address thomas.oconnor@iths.hbs.gov (T.F. O'Connor) https://doi.org/10.1016/j.ijps.2024.10027-Received 31 May 2024; Received in revised form 5 August 2024; Accent Available online xxx wailable online 8 August 2024 2590-1567/Published by Elsevier B.V. This is an open access article und identifying the most efficient data collection techni 211-3396/ID 2024 Published by Elsevier Ltd. Introduction The landscape of manufacturing is becoming increa

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ingly data-rich with the progression of analytical tech-nology tools, Industrial Internet of Things (HoT) devices, sensors, and integrated processes. Transforming this constant stream of Big Data into practical

holding the integrity of this data is critical for operational success. Data integrity refers to the accuracy, completeness, and quality of the data sets [1]. Regulators scholars, and industry professionals are now tackling a wide spectrum of challenges in the data lifecycle including discerning the data critical for a thorough understanding of operations, procuring available data, and organizing data strategically. The issue of data se curity demands attention due to the extensive array of processes, techniques, and personnel interacting with he data, which heightens the risk of breach. For endusers to leverage data for a competitive advantage, a robust, secure, and flexible data infrastructure might upport proficient data collection and analysis [3] Manufacturing pharmaceuticals brings unique require ments that need to be fulfilled with Big Data platforms such as adhering to processing parameters and using data quality standards to comply with applicable regulations

# FRAME AI Public Engagement

March 2023: CDER released Artificial Intelligence in Drug Manufacturing discussion paper.

September 2023: FDA/PQRI **public workshop** on AI in drug manufacturing

An opportunity for **interested parties** to share and discuss key topics **with regulators** 



# **FRAME AI Discussion Paper Key Topics**

Cloud applications might affect oversight of pharmaceutical manufacturing data and records

The amount of data could affect existing data management practices

**Regulatory oversight of Al's application in pharmaceutical manufacturing** 

Standards for developing and validating AI models for process control and release

Continuously learning AI systems might challenge regulatory assessment and oversight



# **AI Workshop Registration Survey**

Virtual Event U.S. FOOD & DRUG ADMINISTRATION FDA/PQRI Workshop on the **Regulatory Framework for** the Utilization of Artificial Intelligence in Pharmaceutical Manufacturing SAVE THE DATES! An Opportunity for Stakeholder Engagement REGISTRATION TO **OPEN IN SUMMER** WORKSHOP OBJECTIVES 2023. This FDA/PQRI Workshop will bring together leaders from regulatory agencies, industry, and academia to discuss critical topics related to the use of artificial intelligence (AI) in pharmaceutical manufacturing. TUES. - WED. SEPT. 26-27, 2023 The National Academies of Sciences, Engineering, and Medicine (NASEM) noted that FDA is likely to see substantial innovations in pharmaceutical manufacturing which may impact process measurement, modeling, and VIRTUAL control. Al technologies represent an area of rapid technology growth for designing, monitoring, and controlling manufacturing processes. Such Al technologies may challenge traditional approaches to regulating pharmaceutical manufacturina. 10 AM - 3 PM each day This workshop aims to facilitate interaction among AI stakeholders on critical areas for development, implementation, and regulatory onsideration including uses in process development and control operation of Pharmaceutical Quality Systems, lifecycle approaches, and +1 (202) 230-5607 Current Good Manufacturing Practice. ً PORISecretariat@parl.org The FDA has recently published a discussion paper on this topic in the Federal Register for public comment by May 1, 2023. Stay up to date by visiting the Workshop Website at https://pg

>50 parties reported plans to engage with the FDA in the next 5 years for regarding product manufactured using AI



Do you plan to engage with FDA regarding manufactured product utilizing Al?



#### Actively Utilizing Al



#### Do you plan to submit an application regarding a product utilizing AI?

	CDER	CBER	Both
Within 1-year	1	2	2
Within 3-years	5	3	7
Within 5-years	5	0	6

### **Artificial Intelligence in Drug Manufacturing: Public Feedback to FDA**

FDA U.S. FOOD & DRUG

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	ADMINISTRATION
1	Artificial Intelligence in Drug
2	Manufacturing: Public Feedback to FDA
3	Jayanti Das <sup>1</sup> , Thomas F. O'Connor <sup>1</sup> , Adam C. Fisher <sup>1</sup> , Manuel Osorio <sup>2</sup> , Johnny Lam <sup>2</sup> ,
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10	Abstract
11	FDA's Center for Drug Evaluation and Research (CDER) established the Framework for
12	Regulatory Advanced Manufacturing Evaluation (FRAME) initiative to establish a
13	regulatory framework to support the adoption of advanced manufacturing technologies

- 14 that could benefit patients. FRAME prioritized artificial intelligence (AI) as a technology
- 15 that has the potential to advance pharmaceutical manufacturing capabilities. FD
- 16 published a discussion paper titled Artificial Intelligence in Drug Manufacturing on March
- 17 1, 2023, and held a public workshop on The Regulatory Framework for the Utilization
- 18 Artificial Intelligence in Pharmaceutical Manufacturing: An Opportunity for Stakeholde
- 19 Engagement from September 26-27, 2023. To ensure that FDA's evaluation of the
- 20 regulatory framework for AI is thorough, interested parties were invited to comment on

#### Public feedback:

- 1. Industry expressed a desire to broadly implement AI.
- Industry seeks assurance that regulations and policies are compatible with AI strategies.
- 3. Industry feels that international harmonization will facilitate AI adoption.



# Application of Al in Drug Manufacturing: Reported Use Cases



#### **Process Design**

- Inform and expedite process design
  - Reduce time and cost
- Simulations to optimize manufacturing process conditions or planned modifications (e.g., "Digital Twin")
  - "A set of information constructs that mimics... a physical asset... dynamically updated with data from its physical twin... informs decisions. **Bidirectional interaction** between the virtual and physical is central to the digital twin."

### FDA

### **Process and Product Monitoring**

- Support troubleshooting
- Perform root cause analysis following unplanned events
- Predict future deviations and failures
- Identify corrective actions and preventive actions
- Reduce time to introduce new equipment and down time



- Implement model predictive sensors to control specific unit operations
- Enable autonomous manufacturing processes capable of self-optimization



### FDA

### **Strengthen Supply Chain**

- Predict demand
- Detect potential bottlenecks or interruptions
- Early fault detection/prediction for raw materials
- Automate scheduling to avoid stockouts and optimize replenishment





# Public Feedback on Regulatory Considerations for Al Applications

# **Feedback: Regulatory Considerations**

#### **Data Management**

- Data generated from various sources can result in data variability
- Data management standards (and lifecycle for data storage) can ensure high data quality and data integrity

#### Governance of data used to build AI/ML models

- Systemic framework for development, monitoring, and management of models can build trust
- Best ML practices can cover data management and regulatory oversight.

# **Feedback: Regulatory Considerations**

#### 3<sup>rd</sup> Party Data and AI applications

- Breaches in 3<sup>rd</sup> party data security can undermine trust in data management.
- Establishing expectations for 3<sup>rd</sup> party data and applications can build trust.

#### Model development and validation requirements

- Using a framework to evaluate AI systems is important.
- Risk-based validation standards can be used to assess performance of complex models.

# **Feedback: Regulatory Considerations**



### AI in Pharmaceutical Quality System (PQS)

- Personnel needed to implement and integrate with existing systems.
- Human-in-the-loop can help for verification and managing complex tasks

#### Lifecycle considerations of AI models

 Risk-based methodologies can help to manage/document modifications to AI/ML models and regulatory reporting/notification within a CGMP framework.

#### Other aspects to consider

 Terminology, flexibility in multiple regulatory domains, international harmonization, cybersecurity

# AI - Summary of Public Feedback



Industry values good data management practices



Industry seeks best practices for models, including development, validation and maintenance of AI models



Industry may face uncertainty when managing AI models provided by third parties



Industry is challenged by the implementation of AI in the PQS framework

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# Upcoming

- A risk-based framework for establishing and evaluating the credibility of AI in regulatory decision-making
- Al models used to answer regulatory questions are:
  - Sufficiently credible for a particular context of use
  - Supported with the appropriate level of evidence

Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drugs and Biological Products Guidance for Industry and Other Interested Parties

#### DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact \_\_\_\_\_\_ at 301-\_\_\_\_ [add other contacts as needed].

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Center for Devices and Radiological Health (CDRH) Oncology Center of Excellence (OCE) Office of Combination Products (OCP)

> Month 2024 Clinical/Medical



# What's Next?

- Receive critical feedback on draft guidance, update guidance
- Inform future guidance development (e.g., AI related pharmaceutical quality/manufacturing)
- Continue risk-based regulation approach that keeps pace with technology
- Continue advancing regulatory science in this area
- Continue our collaborative engagement approach





# **Responsibility Lies Beyond Machines**



