U.S. FOOD & DRUG ADMINISTRATION

Regulating AI in Drug Manufacturing

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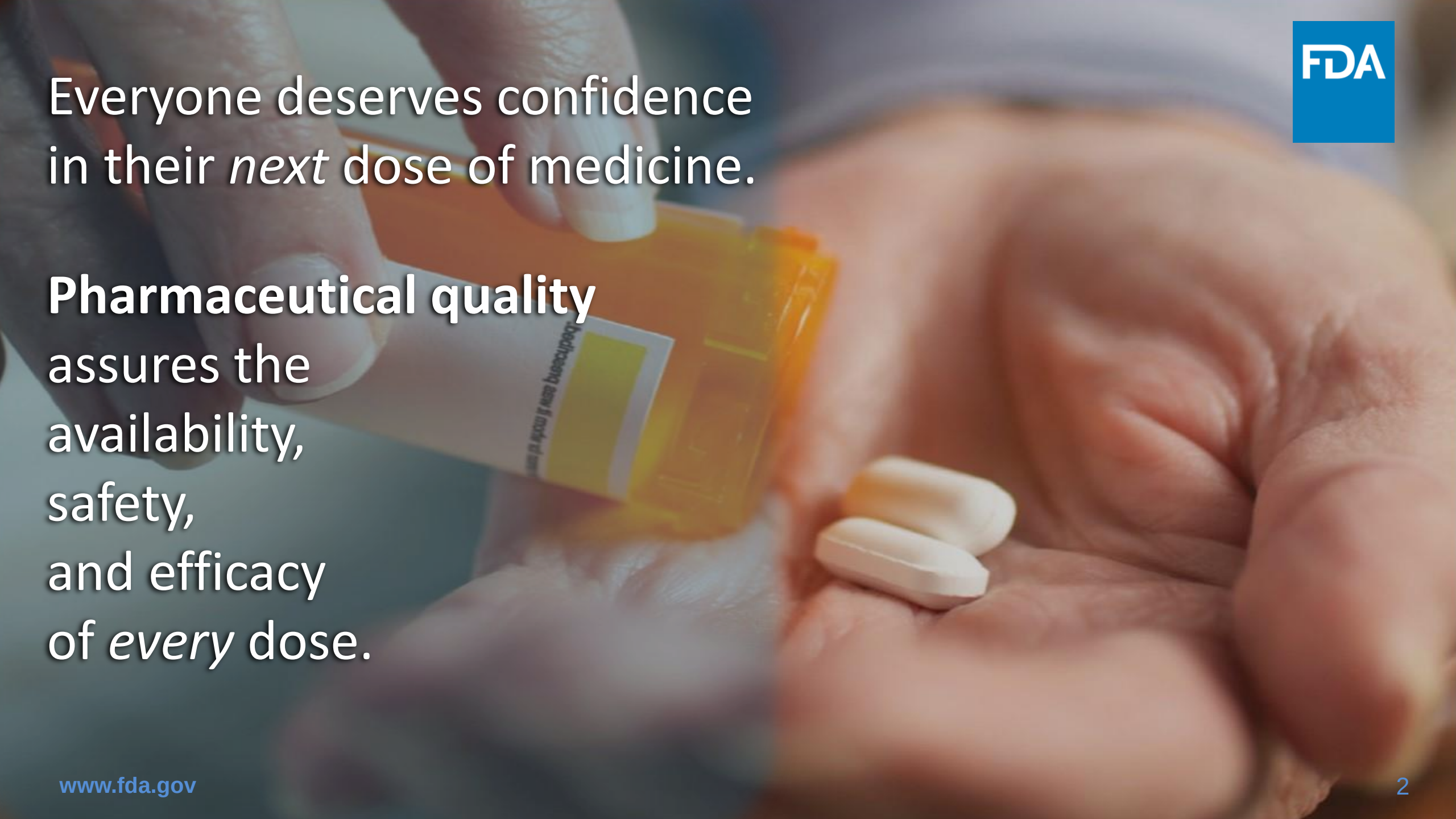
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

CASSS CMC Forum Europe
October 22, 2024



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

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

CDER Advanced Manufacturing Programs

ADVANCED MANUFACTURING

ASSESSMENT AND INSPECTION

Emerging Technology Program (ETP)

||

Advanced Manufacturing Technologies Designation Program (AMTD)

SCIENCE

Advanced Manufacturing Science & Research

POLICY

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

U.S. FOOD & DRUG ADMINISTRATION

Framework for Regulatory Advanced Manufacturing Evaluation (**FRAME**)

FRAME Priorities

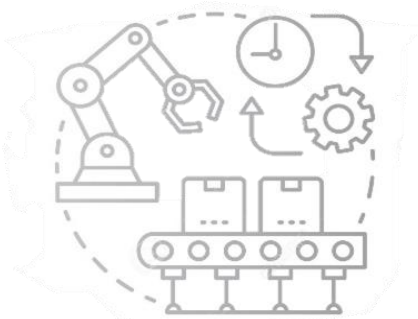
Seek and Analyze Input	Address Risks	Clarify Expectations	Harmonize Internationally
Ensure CDER's understanding of advanced manufacturing technologies is thorough and its analysis of the regulatory framework is science- and risk-based.	Ensure regulations and policy are compatible with future advanced manufacturing technologies.	Explain the current thinking on a regulatory issue via new or updated guidance as needed.	Ensure global regulatory practice is clear to interested parties implementing advanced manufacturing.

Cohesive regulatory framework for drugs

FRAME Priority Technologies

Distributed Manufacturing (DM)

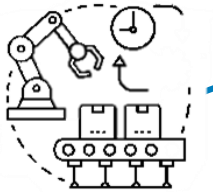
End-to-End Continuous Manufacturing (E2E CM)



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

Artificial Intelligence (AI)

What is AI?



Artificial Intelligence (AI)

"A machine-based system that can, for a given set of human-defined objectives, make **predictions, recommendations, or decisions** influencing real or virtual environments."

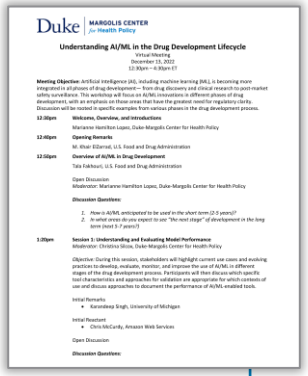
"**Perceive** real and virtual environments… abstract perceptions into **models** in an automated manner… use **model** inference for information or action."

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

Public Engagements Inform Regulatory Considerations

2022

Duke-Margolis Expert Workshop


Duke | MARGOLIS CENTER for Health Policy

Understanding AI/ML in the Drug Development Lifecycle

Virtual Meeting
December 15, 2022
12:30pm – 4:30pm ET

Meeting Objective: Artificial intelligence (AI), including machine learning (ML), is becoming more integrated in all phases of drug development — from drug discovery and clinical research to post-market safety surveillance. This workshop will focus on AI/ML innovations in different phases of drug development, with an emphasis on those areas that have the greatest need for regulatory clarity. Discussion will be rooted in specific examples from various phases in the drug development process.

12:30pm **Welcome, Overview, and Introductions**
Marianne Hamilton Lopez, Duke-Margolis Center for Health Policy

12:40pm **Opening Remarks**
M. Khair ElZarrad, U.S. Food and Drug Administration

12:50pm **Overview of AI/ML in Drug Development**
Tala Fakhouri, U.S. Food and Drug Administration

Open Discussion
Moderator: Marianne Hamilton Lopez, Duke-Margolis Center for Health Policy

Discussion Questions:

1. *How is AI/ML anticipated to be used in the short term (2-5 years)?*
2. *In what areas do you expect to see "the next stage" of development in the long term (next 5-7 years)?*

1:20pm **Session 1: Understanding and Evaluating Model Performance**
Moderator: Christina Silcox, Duke-Margolis Center for Health Policy

Objective: During this session, stakeholders will highlight current use cases and evolving practices to develop, evaluate, monitor, and improve the use of AI/ML in different stages of the drug development process. Participants will then discuss which specific tool characteristics and approaches for validation are appropriate for which contexts of use and discuss approaches to document the performance of AI/ML-enabled tools.

Initial Remarks
- Karandeep Singh, University of Michigan

Initial Reactant
- Chris McCurdy, Amazon Web Services

Open Discussion

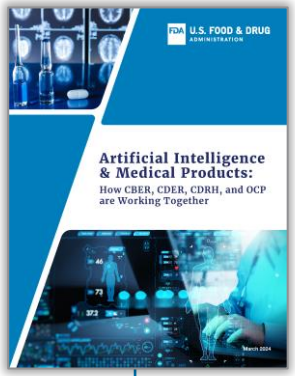
Discussion Questions:

2023

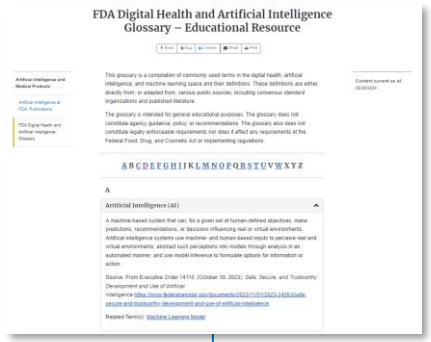
FDA Discussion Papers

2024

Areas of Focus



Digital Health & AI Glossary


FDA Digital Health and Artificial Intelligence Glossary – Educational Resource

This glossary is a compilation of commonly used terms in the digital health, artificial intelligence, and machine learning space and their definitions. These definitions are either directly from, or adapted from, various public sources, including consensus standard organizations and published literature.

The glossary is intended for general educational purposes. The glossary does not constitute agency guidance, policy, or recommendations. The glossary also does not constitute legally enforceable requirements; nor does it affect any requirements of the Federal Food, Drug, and Cosmetic Act or implementing regulations.

A B C D E E F G H I J K L M N O P Q R S T U V W X Y Z

A

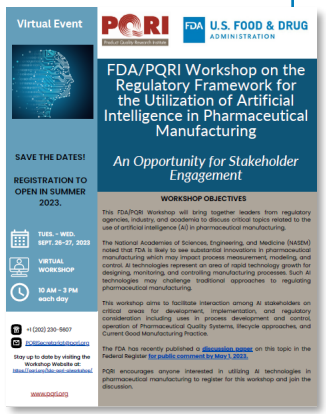
Artificial Intelligence (AI)

A machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments. Artificial intelligence systems use machine- and human-based inputs to perceive real and virtual environments; abstract such perceptions into models through analysis in an automated manner; and use model inference to formulate options for information or action.

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

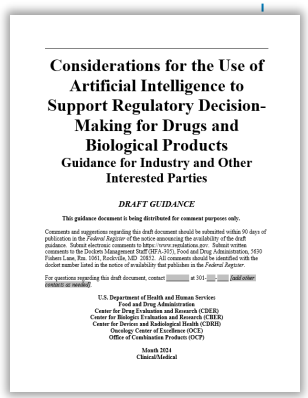
Related Term(s): Machine Learning Model

FDA/PQRI Public Workshop



EO 14110

AI Guidance


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 [redacted] at 301-[redacted] [redacted] (and other contact as needed)

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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

AI-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)

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**

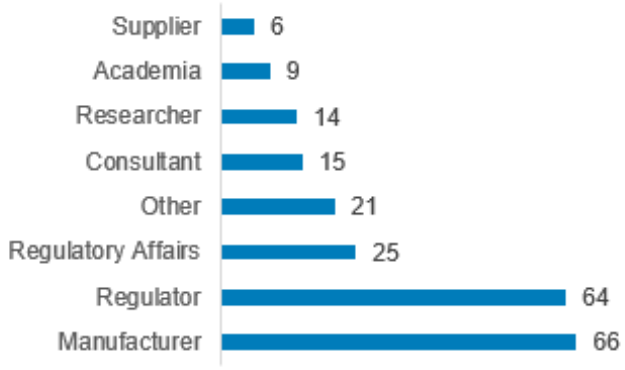
FRAME AI Discussion Paper Key Topics

- Cloud applications might affect oversight of pharmaceutical manufacturing data and records
- The amount of data could affect existing data management practices
- Regulatory oversight of AI'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

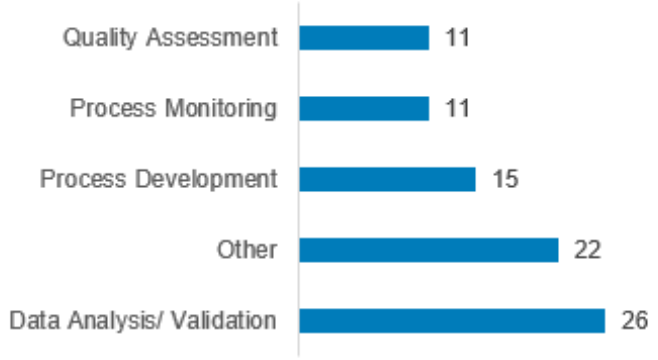
AI Workshop Registration Survey

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

Expected Role in AI



Actively Utilizing AI

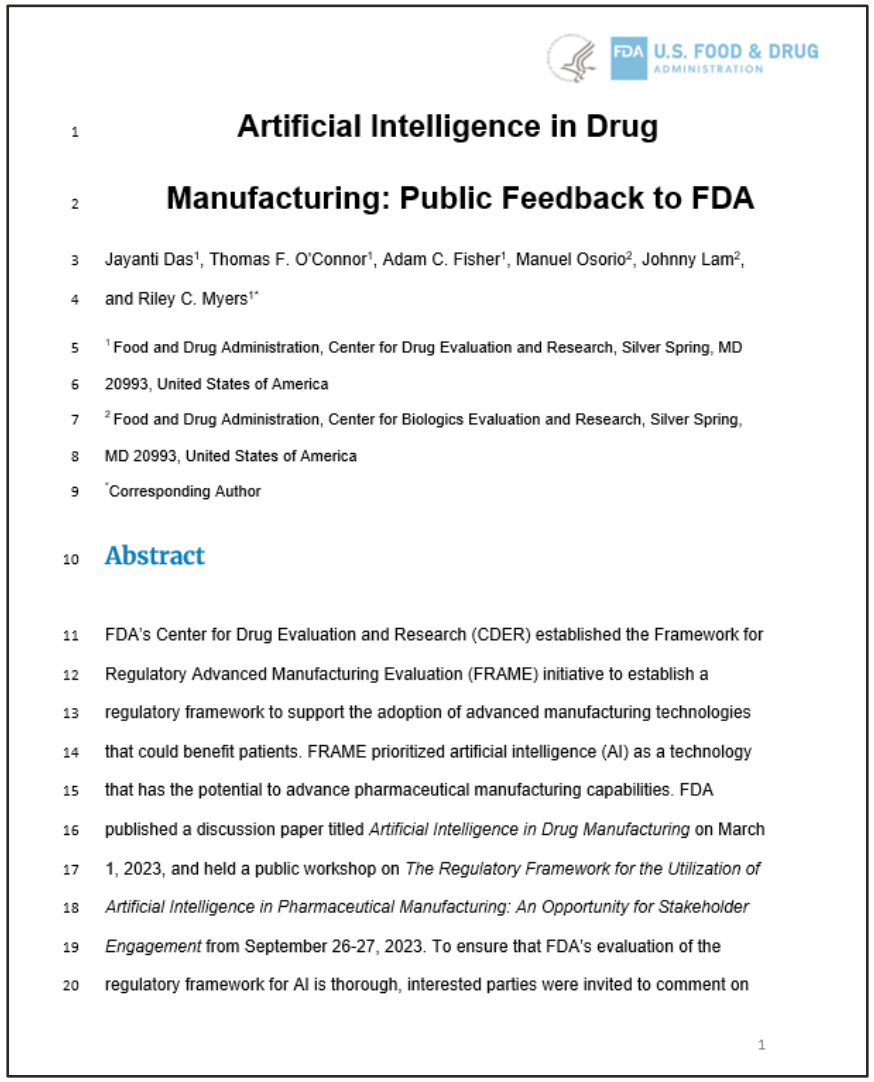


Do you plan to engage with FDA regarding manufactured product utilizing AI?

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



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Artificial Intelligence in Drug Manufacturing: Public Feedback to FDA

Jayanti Das[1], Thomas F. O'Connor[1], Adam C. Fisher[1], Manuel Osorio[2], Johnny Lam[2], and Riley C. Myers[1*]

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[2] Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, MD 20993, United States of America

*Corresponding Author

Abstract

FDA's Center for Drug Evaluation and Research (CDER) established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative to establish a regulatory framework to support the adoption of advanced manufacturing technologies that could benefit patients. FRAME prioritized artificial intelligence (AI) as a technology that has the potential to advance pharmaceutical manufacturing capabilities. FDA published a discussion paper titled *Artificial Intelligence in Drug Manufacturing* on March 1, 2023, and held a public workshop on *The Regulatory Framework for the Utilization of Artificial Intelligence in Pharmaceutical Manufacturing: An Opportunity for Stakeholder Engagement* from September 26-27, 2023. To ensure that FDA's evaluation of the regulatory framework for AI is thorough, interested parties were invited to comment on

1

Public feedback:

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

Application of AI in Drug Manufacturing: Reported Use Cases

AI in Drug Manufacturing: 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*.”

Source: *FDA Digital Health and Artificial Intelligence Glossary – Educational Resource*

AI in Drug Manufacturing: Use Cases

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

AI in Drug Manufacturing: Use Cases

Advanced Process Control

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

AI in Drug Manufacturing: Use Cases

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 AI 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

3rd Party Data and AI applications

- Breaches in 3rd party data security can undermine trust in data management.
- Establishing expectations for 3rd 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

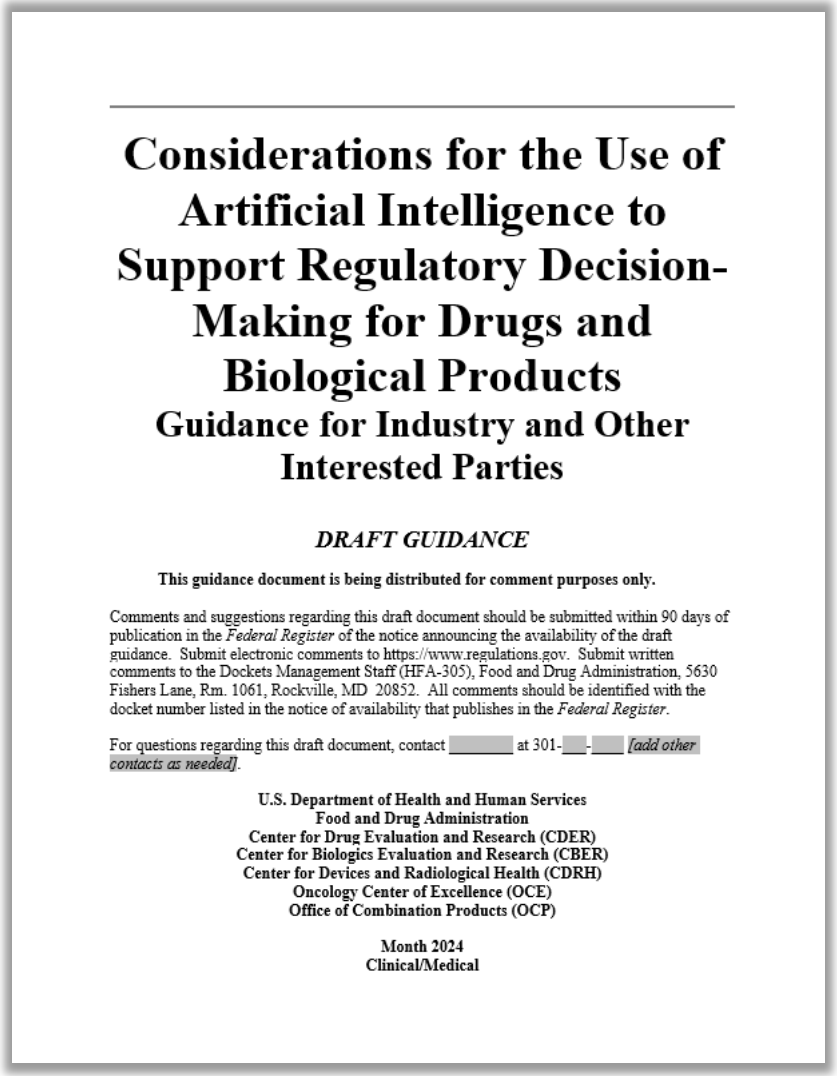
- Terminology, flexibility in multiple regulatory domains, international harmonization, cybersecurity

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

Upcoming

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



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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


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