U.S. FOOD & DRUG ADMINISTRATION

Overview on FDA's risk-based approach to using artificial intelligence (AI) to support regulatory decision-making for drugs and biological products

Johnny Lam, PhD
Associate Director for Policy
Office of Therapeutic Products (OTP)
Center for Biologics Evaluation and Research (CBER) | FDA

SESSION II: AI in the Pre-Clinical Development of Regenerative Medicine Therapies
Developing Regenerative Medicine Therapies with Artificial Intelligence: A Workshop

November 18, 2025

Informal Communication Disclaimer

My comments are an informal communication and represent my own best judgement. These comments do not bind or obligate FDA.

Outline

- Background and Highlights of Cross Center Efforts in Artificial Intelligence
- Risk-Based Approach – Artificial Intelligence in Drug Development
  - Guidance Overview
    - Scope & Approach
    - A Risk-Based Credibility Assessment Framework
    - Special Consideration: Life Cycle Maintenance of the Credibility of AI Model Outputs in Certain Contexts of Use
- Artificial Intelligence Efforts and Engagement Opportunities in CBER

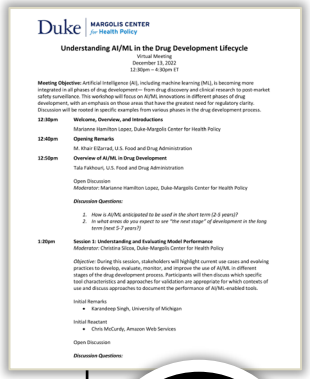
Recent History of FDA Activities Leading to AI Guidance

2019

CDER/CBER/CDRH AI Coordination

2022

Duke Margolis Expert Workshop


Duke | MARGOLIS CENTER for Health Policy

Understanding AI/ML in the Drug Development Lifecycle

Virtual Meeting
December 13, 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 (2-3 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

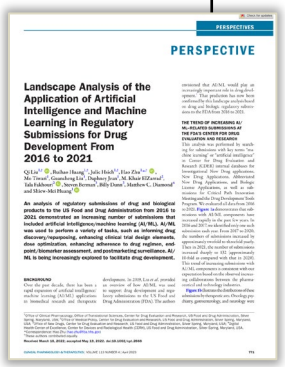
Initial Reactant
- Chris McCurdy, Amazon Web Services

Open Discussion

Discussion Questions:

2022

Qi et al CDER Landscape Analysis

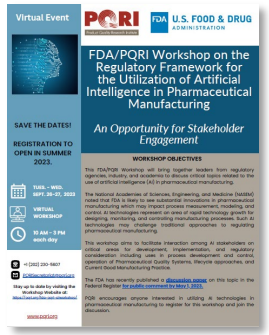

PERSPECTIVE

Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021

2023

Discussion Papers

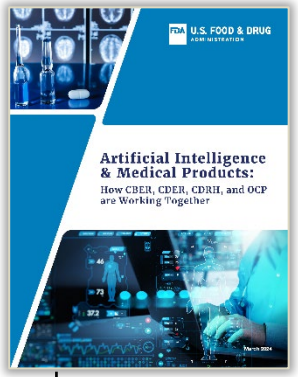
FDA/PQRI Public Workshop



2024

CBER AI Coordinating Committee

Areas of Focus

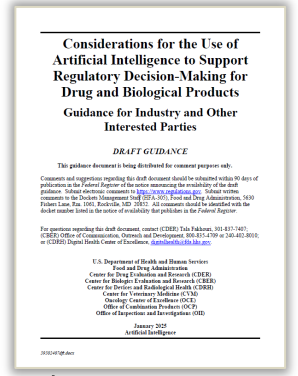


2025

CDER AI Council

CTTI Workshop August 2024

AI Guidance


Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry and Other Interested Parties

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Digital Health Center of Excellence, digitalhealth@cdrh.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Center for Veterinary Medicine (CVM)
Oncology Center of Excellence (OCE)
Office of Combination Products (OCP)
Office of Inspections and Investigations (OII)

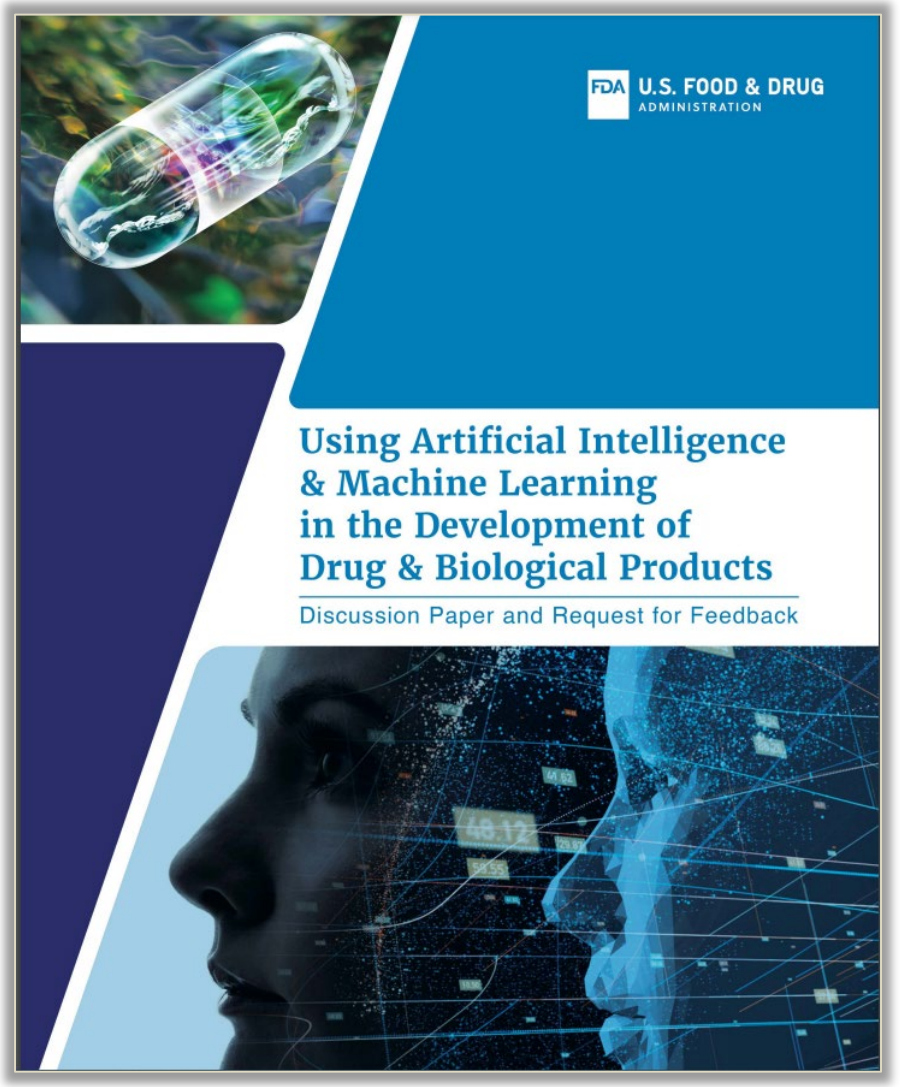
January 2025
Artificial Intelligence

Guidance Informed by May 2023 Discussion Paper Feedback

- Discussion Paper Published May 11th, 2023
- Collaboration between CDER, CBER, CDRH/DHCoE
- Comments closed August 9th, 2023
- 65 entities responded with over 800 comments

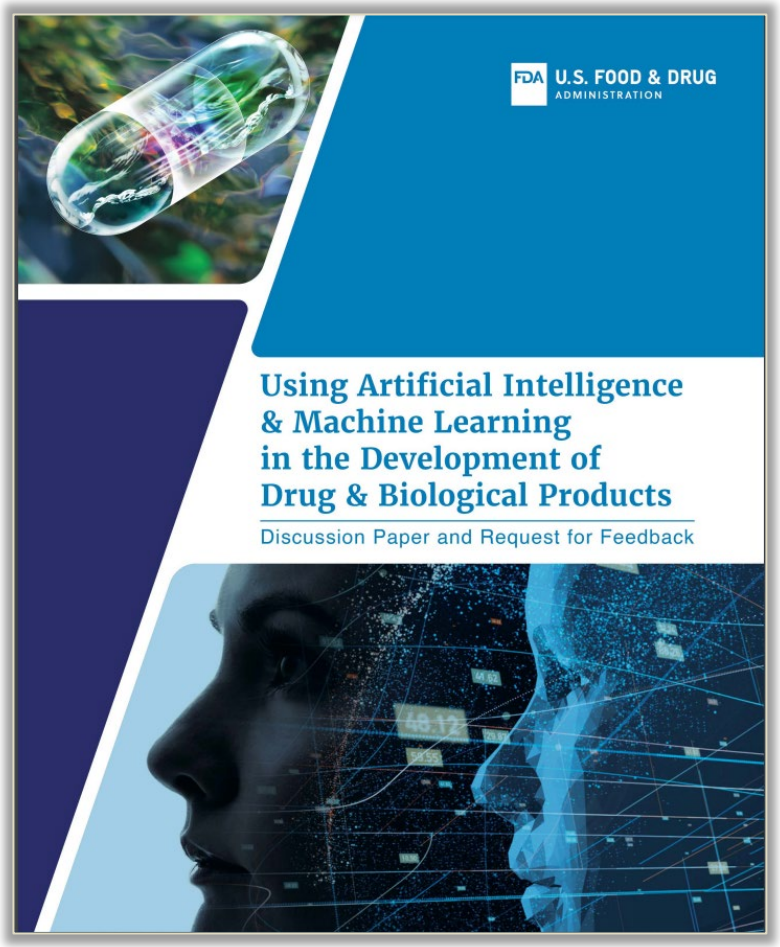
<u>Policy informed by discussion papers feedback</u>

- Goal to promote mutual learning around three main core issues:
  - Human-led governance, accountability, and transparency
  - Quality, reliability, and representativeness of data
  - Model development, performance, monitoring, and validation



Responses to the May 2023 Discussion Paper

- Clarity on what falls within/outside the scope of FDA's oversight
- Clarity on how to operationalize a risk-based approach
- Clarity on "transparency" and the level of detail and documentation required
- Calls for harmonization globally, and alignment with medical devices
- Calls for the establishment of partnerships to advance the creation/sharing of machine-readable data sets



FRAME AI Public Engagement

Public engagement under the CDER-led Framework for Regulatory Advanced Manufacturing Evaluation Initiative (**FRAME**)[1] – focus on manufacturing

- March 2023: CDER, with CBER collaboration, released *Artificial Intelligence in Drug Manufacturing* **discussion paper**

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

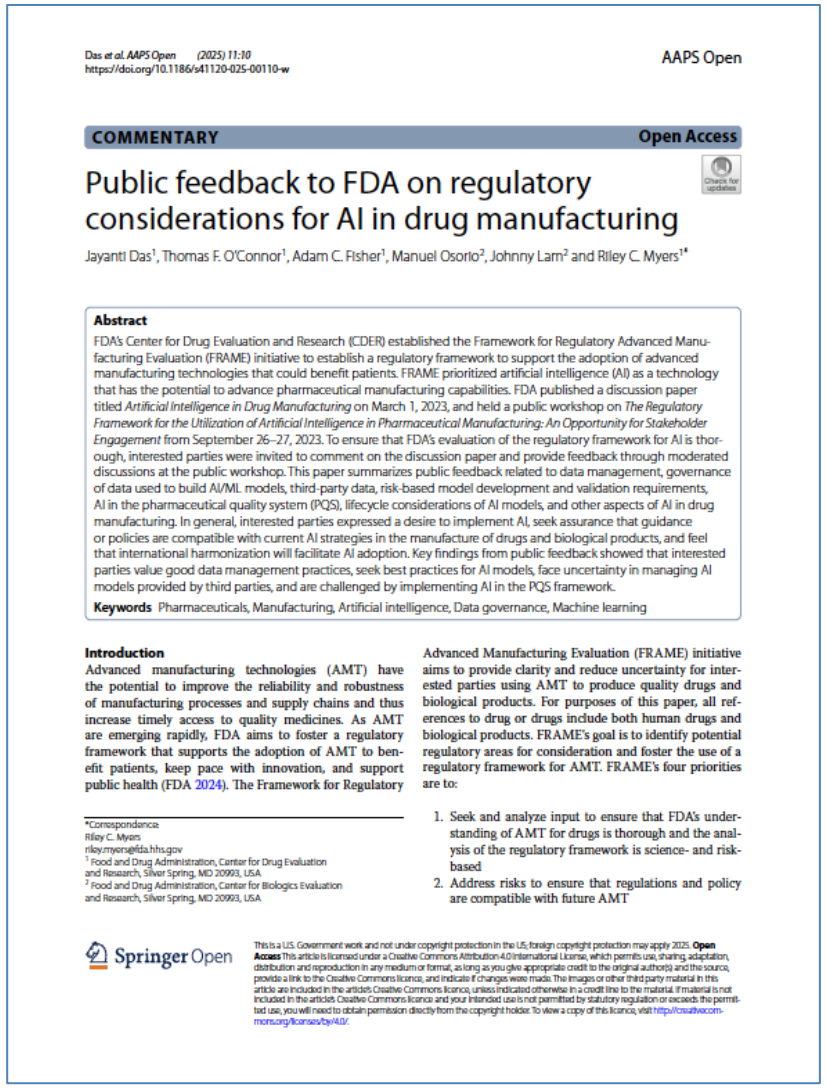
An opportunity for **interested parties** to share and discuss key topics **with regulators**

[1]https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-framework-regulatory-advanced-manufacturing-evaluation-frame-initiative

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

Artificial Intelligence in Drug Manufacturing: Public Feedback to FDA



Das et al. AAPS Open (2025) 11:10
https://doi.org/10.1186/s41120-025-00110-w

AAPS Open

COMMENTARY Open Access

Public feedback to FDA on regulatory considerations for AI in drug manufacturing

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

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 the discussion paper and provide feedback through moderated discussions at the public workshop. This paper summarizes public feedback related to data management, governance of data used to build AI/ML models, third-party data, risk-based model development and validation requirements, AI in the pharmaceutical quality system (PQS), lifecycle considerations of AI models, and other aspects of AI in drug manufacturing. In general, interested parties expressed a desire to implement AI, seek assurance that guidance or policies are compatible with current AI strategies in the manufacture of drugs and biological products, and feel that international harmonization will facilitate AI adoption. Key findings from public feedback showed that interested parties value good data management practices, seek best practices for AI models, face uncertainty in managing AI models provided by third parties, and are challenged by implementing AI in the PQS framework.

Keywords Pharmaceuticals, Manufacturing, Artificial intelligence, Data governance, Machine learning

Introduction

Advanced manufacturing technologies (AMT) have the potential to improve the reliability and robustness of manufacturing processes and supply chains and thus increase timely access to quality medicines. As AMT are emerging rapidly, FDA aims to foster a regulatory framework that supports the adoption of AMT to benefit patients, keep pace with innovation, and support public health (FDA 2024). The Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative aims to provide clarity and reduce uncertainty for interested parties using AMT to produce quality drugs and biological products. For purposes of this paper, all references to drug or drugs include both human drugs and biological products. FRAME's goal is to identify potential regulatory areas for consideration and foster the use of a regulatory framework for AMT. FRAME's four priorities are to:

1. Seek and analyze input to ensure that FDA's understanding of AMT for drugs is thorough and the analysis of the regulatory framework is science- and risk-based
2. Address risks to ensure that regulations and policy are compatible with future AMT

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Public feedback summary:

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.

Key Findings from feedback:

- Industry values good data management practices
- Industry seeks best practices for machine-learning models, including development, validation and maintenance of AI models
- Industry may face uncertainty when managing third-party AI models
- Industry is challenged by implementation of AI in the pharmaceutical quality system framework

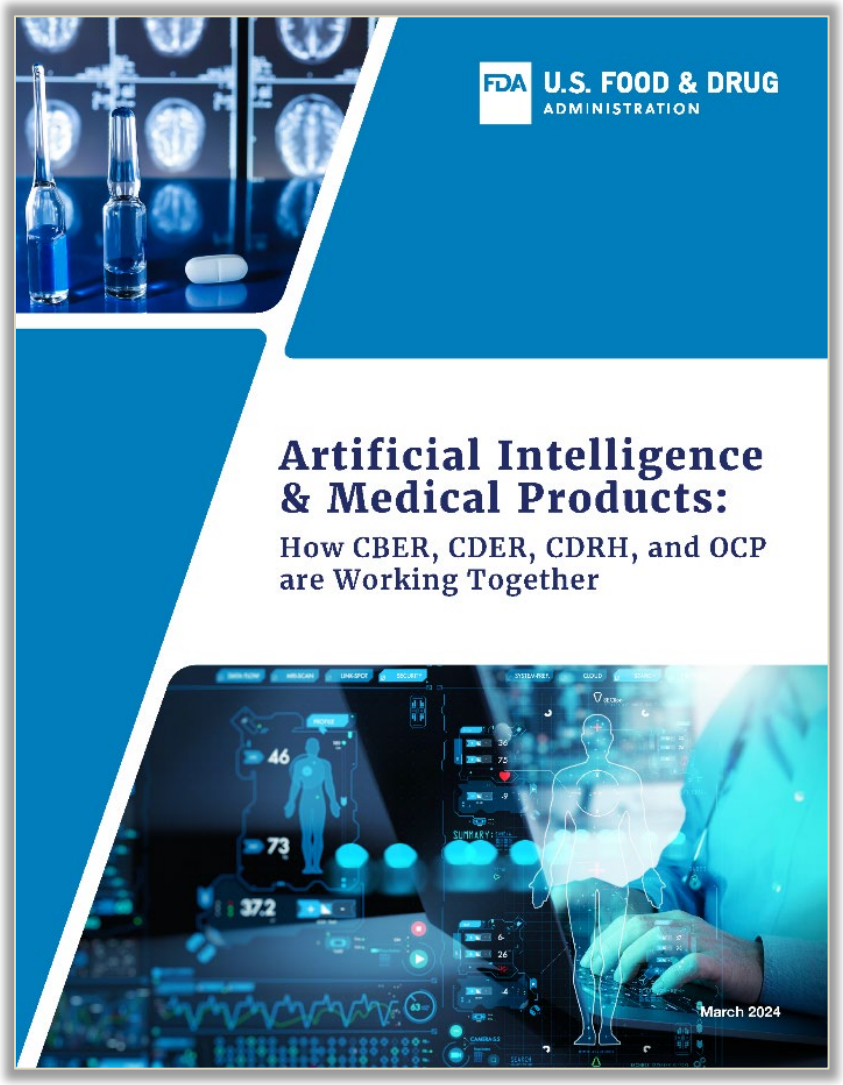
https://link.springer.com/article/10.1186/s41120-025-00110-w

Artificial Intelligence at FDA

Advancing AI Regulatory Science

Areas of Focus

- Foster Collaboration to Safeguard Public Health
- Advance the Development of Regulatory Approaches that Support Innovation
- Promote the Development of Harmonized Standards, Guidelines, Best Practices, and Tools
- Support Research Related to the Evaluation and Monitoring of AI Performance



SOURCE: https://www.fda.gov/media/177030/download?attachment

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AI Across the Product Life Cycle

Discovery

- Drug Target Identification, Selection, and Prioritization
- Compound Screening and Design

Nonclinical Research

- PK/PD and toxicologic studies
- Dose range finding

Clinical Research

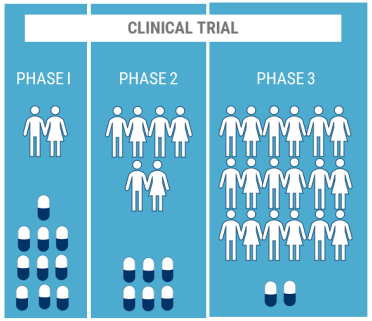


Image source: cbinsights.com

- Dose range finding
- Site selection
- Recruitment and Retention
- Adherence
- Data collection, management, and analysis
- RWD analyses
- Clinical endpoint assessment

Manufacturing and Postmarket Safety Monitoring

- Advanced pharmaceutical manufacturing
- Post-market safety surveillance or pharmacovigilance (PV)

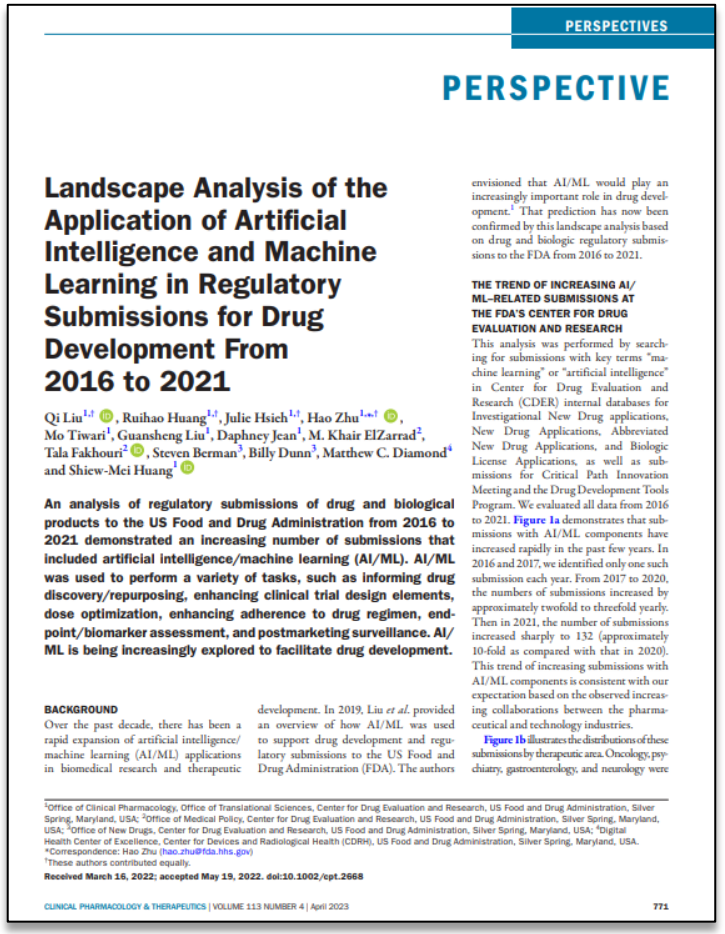
FDA's CDER has Received >500 Submissions with AI

	Year					
Submission Type (n)	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
IND	1	1	2	5	11	128
NDA, ANDA, BLA	-	-	1	2	2	2
DDT, CPIM	-	-	-	-	1	2

	Year					
Drug Development Stage (n)	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**
Discovery and Development	-	-	-	-	1	3
Preclinical Research	-	-	-	-	-	8
Clinical Research	1	1	3	5	12	118
Post-Market Safety Monitoring	-	-	-	2	1	3

ABBREVIATIONS: Investigational New Drug (IND); New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Biologics License Application (BLA); Drug Development Tool (DDT) Qualification Programs, Critical Path Innovation Meeting (CPIM)

SOURCE: Internal databases maintained by the FDA Center for Drug Evaluation and Research (CDER)



PERSPECTIVES

PERSPECTIVE

Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021

Qi Liu[1,†], Ruihao Huang[1,†], Julie Hsieh[1,†], Hao Zhu[1,*,†], Mo Tiwari[1], Guansheng Liu[1], Daphney Jean[1], M. Khair ElZarrad[2], Tala Fakhouri[2], Steven Berman[3], Billy Dunn[3], Matthew C. Diamond[4] and Shiew-Mei Huang[1]

An analysis of regulatory submissions of drug and biological products to the US Food and Drug Administration from 2016 to 2021 demonstrated an increasing number of submissions that included artificial intelligence/machine learning (AI/ML). AI/ML was used to perform a variety of tasks, such as informing drug discovery/repurposing, enhancing clinical trial design elements, dose optimization, enhancing adherence to drug regimen, endpoint/biomarker assessment, and postmarketing surveillance. AI/ML is being increasingly explored to facilitate drug development.

BACKGROUND

Over the past decade, there has been a rapid expansion of artificial intelligence/machine learning (AI/ML) applications in biomedical research and therapeutic development. In 2019, Liu *et al.* provided an overview of how AI/ML was used to support drug development and regulatory submissions to the US Food and Drug Administration (FDA). The authors envisioned that AI/ML would play an increasingly important role in drug development.[1] That prediction has now been confirmed by this landscape analysis based on drug and biologic regulatory submissions to the FDA from 2016 to 2021.

THE TREND OF INCREASING AI/ML-RELATED SUBMISSIONS AT THE FDA'S CENTER FOR DRUG EVALUATION AND RESEARCH

This analysis was performed by searching for submissions with key terms "machine learning" or "artificial intelligence" in Center for Drug Evaluation and Research (CDER) internal databases for Investigational New Drug applications, New Drug Applications, Abbreviated New Drug Applications, and Biologic License Applications, as well as submissions for Critical Path Innovation Meeting and the Drug Development Tools Program. We evaluated all data from 2016 to 2021. Figure 1a demonstrates that submissions with AI/ML components have increased rapidly in the past few years. In 2016 and 2017, we identified only one such submission each year. From 2017 to 2020, the numbers of submissions increased by approximately twofold to threefold yearly. Then in 2021, the number of submissions increased sharply to 132 (approximately 10-fold as compared with that in 2020). This trend of increasing submissions with AI/ML components is consistent with our expectation based on the observed increasing collaborations between the pharmaceutical and technology industries.

Figure 1b illustrates the distributions of these submissions by therapeutic area. Oncology, psychiatry, gastroenterology, and neurology were

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*Correspondence: Hao Zhu (hao.zhu@fda.hhs.gov)
†These authors contributed equally.

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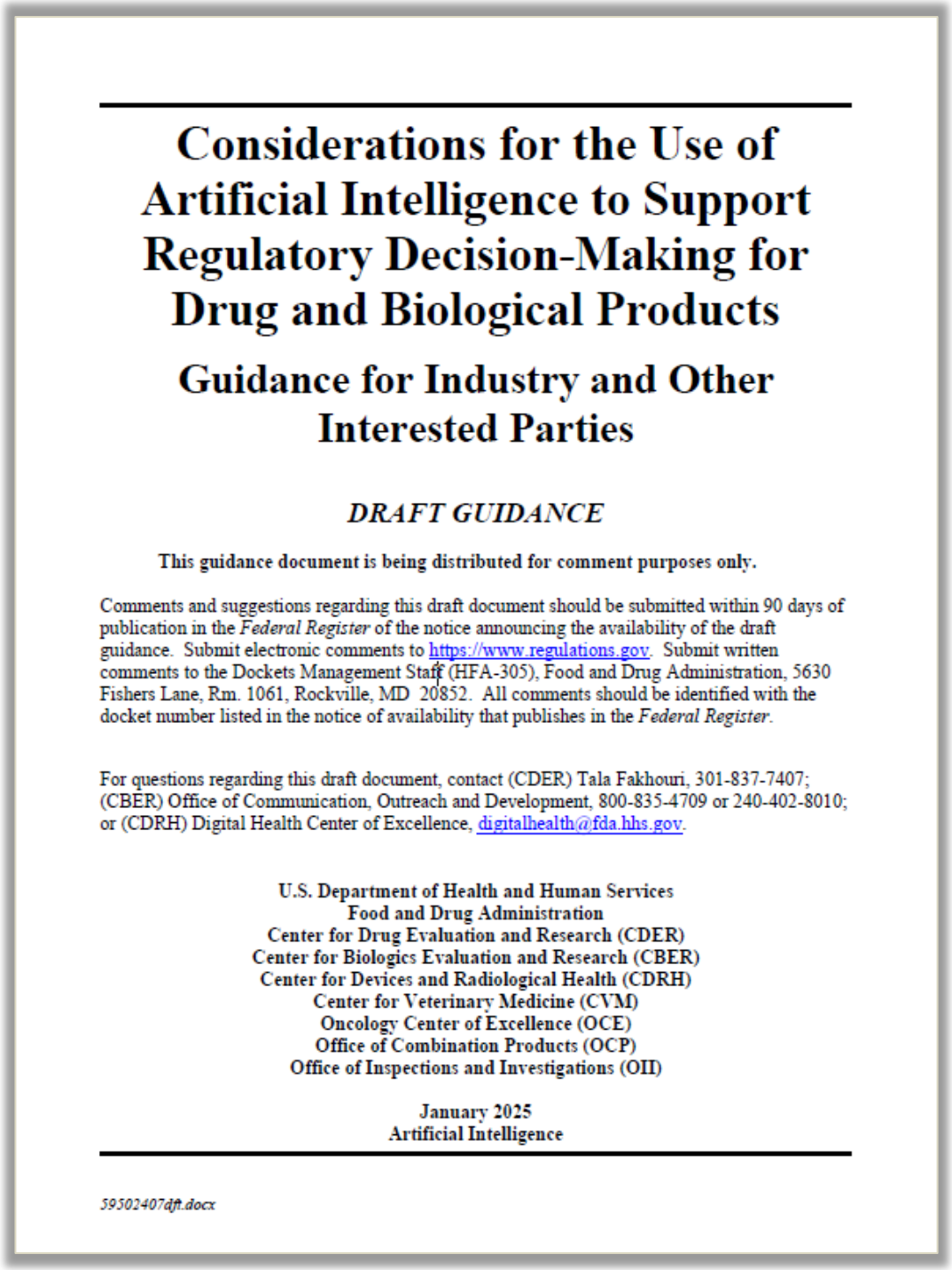
REFERENCE: Liu Q, Huang R, Hsieh J, et al. Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021. Clin Pharmacol Ther. 2023;113(4):771-774. doi:10.1002/cpt.2668

Some 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)



Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry and Other Interested Parties

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January 2025
Artificial Intelligence

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- Provides recommendations on the use of AI to produce information or data to support regulatory decision-making regarding safety, effectiveness, or quality for drugs.

- Provides a risk-based credibility assessment framework to establish and evaluate the credibility of an AI model for a particular context of use (COU):
  - Sufficiently credible for a particular context of use
  - Supported with the appropriate level of evidence

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- Considers the meaning of artificial intelligence (AI) and context of use (COU) for purpose of guidance
- Topic of guidance is primarily a risk-based creditability assessment framework (RCAF) to establish the credibility of an AI model for a particular COU

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- AI used to produce information that supports regulatory decision-making for safety, effectiveness, or quality of drugs; not for drug discovery or operational efficiencies

- RCAF intended to help those to plan, gather, organize, and document information to establish credibility of AI models when used to product information/data to support regulatory decision-making

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- Provides examples regarding AI uses to support regulatory decision-making
- Outlines unique challenges inherent to AI, including training data, interpretability, and data and model drift

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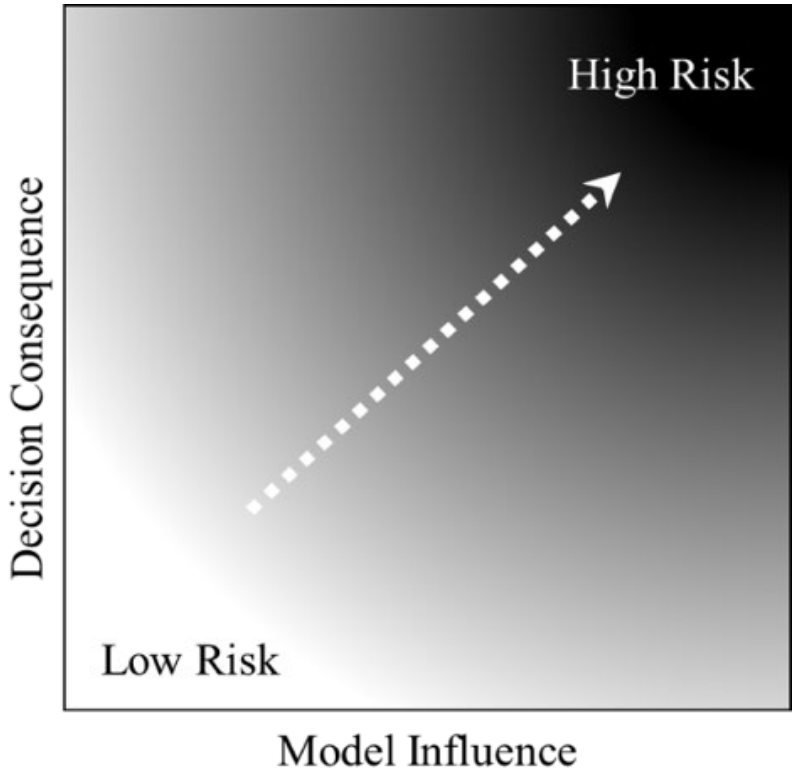
- Informed by the structure of the ASME V&V40
- Consistent with the CDRH guidance on AI-enabled medical devices

CONSIDERATIONS FOR AI USE IN THE DRUG PRODUCT LIFE CYCLE

A. A Risk-Based Credibility Assessment Framework

1. *Step 1: Define the Question of Interest*
2. *Step 2: Define the Context of Use for the AI Model*
3. *Step 3: Assess the AI Model Risk*
4. *Step 4: Develop a Plan to Establish AI Model Credibility Within the Context of Use*
    a. Describe the model and the model development process
        i. Describe the model
        ii. Describe the data used to develop the model
        iii. Describe the model training
    b. Describe the model evaluation process
5. *Step 5: Execute the Plan*
6. *Step 6: Document the Results of the Credibility Assessment Plan and Discuss Deviations From the Plan*
7. *Step 7: Determine the Adequacy of the AI Model for the Context of Use*

A Risk-Based Approach, Anchored in the Context of Use



Depending on model risk, the level and stringency of "credibility evidence" may differ

Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for model influence and decision consequence are determined independently.

SOURCE: https://www.fda.gov/media/184830/download

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Life Cycle Maintenance of the Credibility of AI Model Outputs in Certain COU

- Life cycle maintenance refers to the management of changes to AI models to ensure the model remains fit for use over the drug product life cycle for its COU and a set of planned activities

- A risk-based approach for life cycle maintenance may help sponsors assess the impact of a change or changes to the AI model performance.

- Detailed plans about life cycle maintenance should be made available for review as a component of the manufacturing site's pharmaceutical quality system.

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Early Engagement

- FDA strongly encourages sponsors and other interested parties to engage early with FDA to set expectations regarding the appropriate credibility assessment activities for the proposed model based on model risk and COU.

- Various options can be used to engage with the Agency, depending on how the sponsor or other interested parties intend to use the AI model.

  - Sponsors may request appropriate formal meetings (**INTERACT**, **pre-IND**) to discuss the use of AI for a **specific development program**

  - Engagement options other than formal meetings

Engagement Options Other Than Formal Meetings

1. Center for Clinical Trial Innovation (C3TI)
2. Complex Innovative Trial Design (CID) Meeting Program
3. Drug Development Tools (DDTs) and Innovative Science and Technology Approaches for New Drugs (ISTAND)
4. Digital Health Technologies (DHTs) Program
5. Emerging Drug Safety Technology Program (EDSTP)
6. CDER's Emerging Technology Program (ETP) and **CBER's Advanced Technologies Team (CATT)**
7. Model-Informed Drug Development (MIDD) Paired Meeting Program
8. Real-World Evidence (RWE) Program

Inquiries to CBER Regarding Artificial Intelligence

Engaging with CBER

- **FDA Web Sites**
  - Focus Area: Artificial Intelligence | FDA
  - Artificial Intelligence and Medical Products | FDA

- **CBER Web Site**
  - Artificial Intelligence and Machine Learning (AI/ML) for Biological and Other Products Regulated by CBER | FDA

- For specific uses in regulatory submissions:
  - Contact assigned RPM or Office with product responsibility *well in advance of intended use*
  - Request a formal meeting
- For broader application in manufacturing, or novel products: ★
  - CBER Advanced Technologies Team (CATT)
- For general AI inquiries:
  - OCOD@fda.hhs.gov

Closing Thoughts

- Whenever appropriate, all centers are coordinating and collaborating on AI efforts, with leverage of multi-disciplinary expertise
- FDA evidentiary standards are the same, independent of the technology
- A risk-based approach towards the application of AI in drug development is critical to foster innovation and protect the public
- AI in drug and biological product development has great potential, and we must ensure its safe and effective application
- AI is also driving advances and innovations in regulatory science
- Early engagement with FDA and CBER is highly encouraged

Contact Information

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- Regulatory Questions:

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- OTP Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm
- Phone: 1-800-835-4709 or 240-402-8010
- Consumer Affairs Branch: ocod@fda.hhs.gov
- Manufacturers Assistance and Technical Training Branch: industry.biologics@fda.gov
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