Responsive Regulation of Artificial Intelligence in Drug Development

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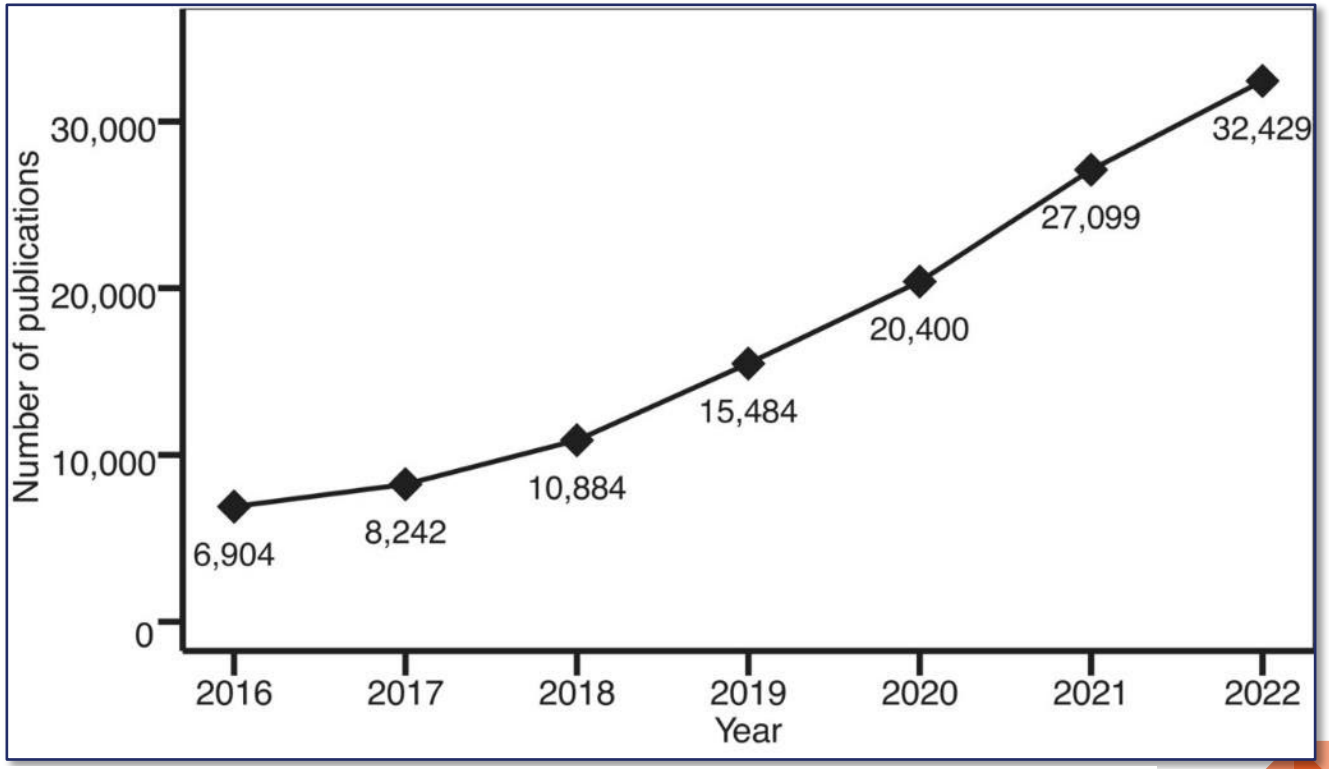
Learning Objectives

- Learn about AI use across the drug development process
- Learn about FDA's experience with AI in regulatory submissions
- Learn about FDA's Center for Drug Evaluation and Research (CDER's) policy milestone for AI
- Learn about CDER's work to address Executive Order 14110 on Safe, Secure, and Trustworthy Development and Use of AI
- Future Direction

PubMed Search Query Results for: AI, Generative AI, or LLMs from 2016 to 2022



REFERENCE: Naik K, Goyal RK, Foschini L, et al. Current Status and Future Directions: The Application of Artificial Intelligence/Machine Learning for Precision Medicine. Clin Pharmacol Ther. 2024;115(4):673-686. doi:10.1002/cpt.3152

AI Across the Drug Development Process

Discovery

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

Nonclinical Research

- PK/PD and toxicologic studies
- Dose range finding

Clinical Research

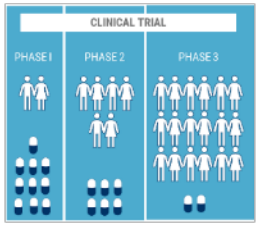


Image source: cbinsights.com

- 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)

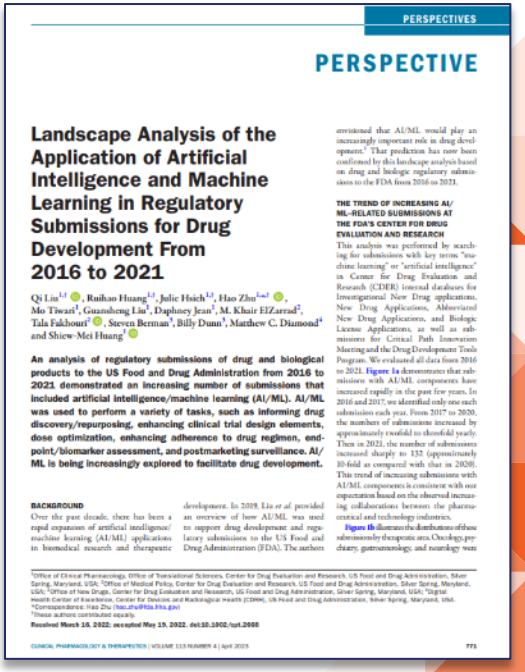
FDA's CDER has Received Over 300 Submissions with AI Components

	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[2,*,†], 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

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [2]Office of Medical Policy, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [3]Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [4]Digital Health Center of Excellence, Center for Devices and Radiological Health (CDRH), US Food and Drug Administration, Silver Spring, Maryland, USA.
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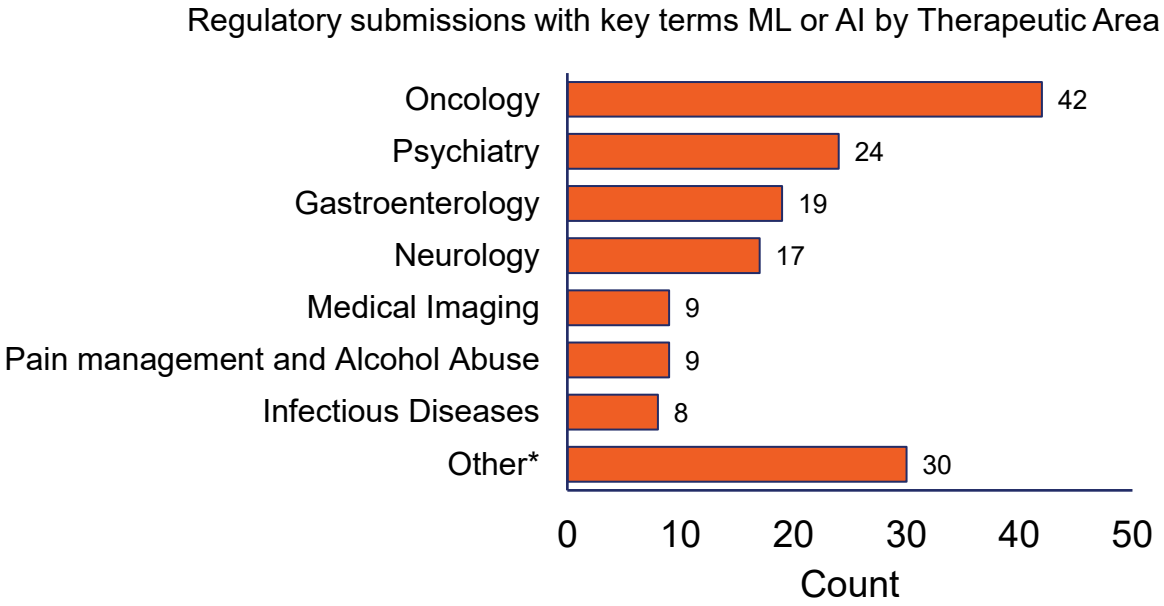

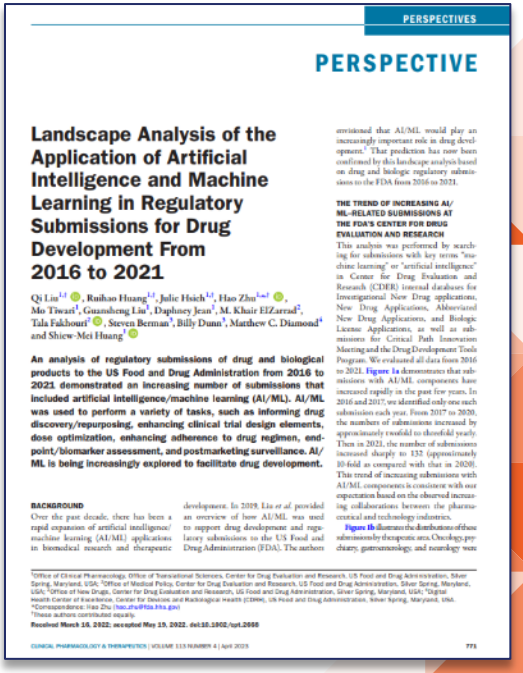

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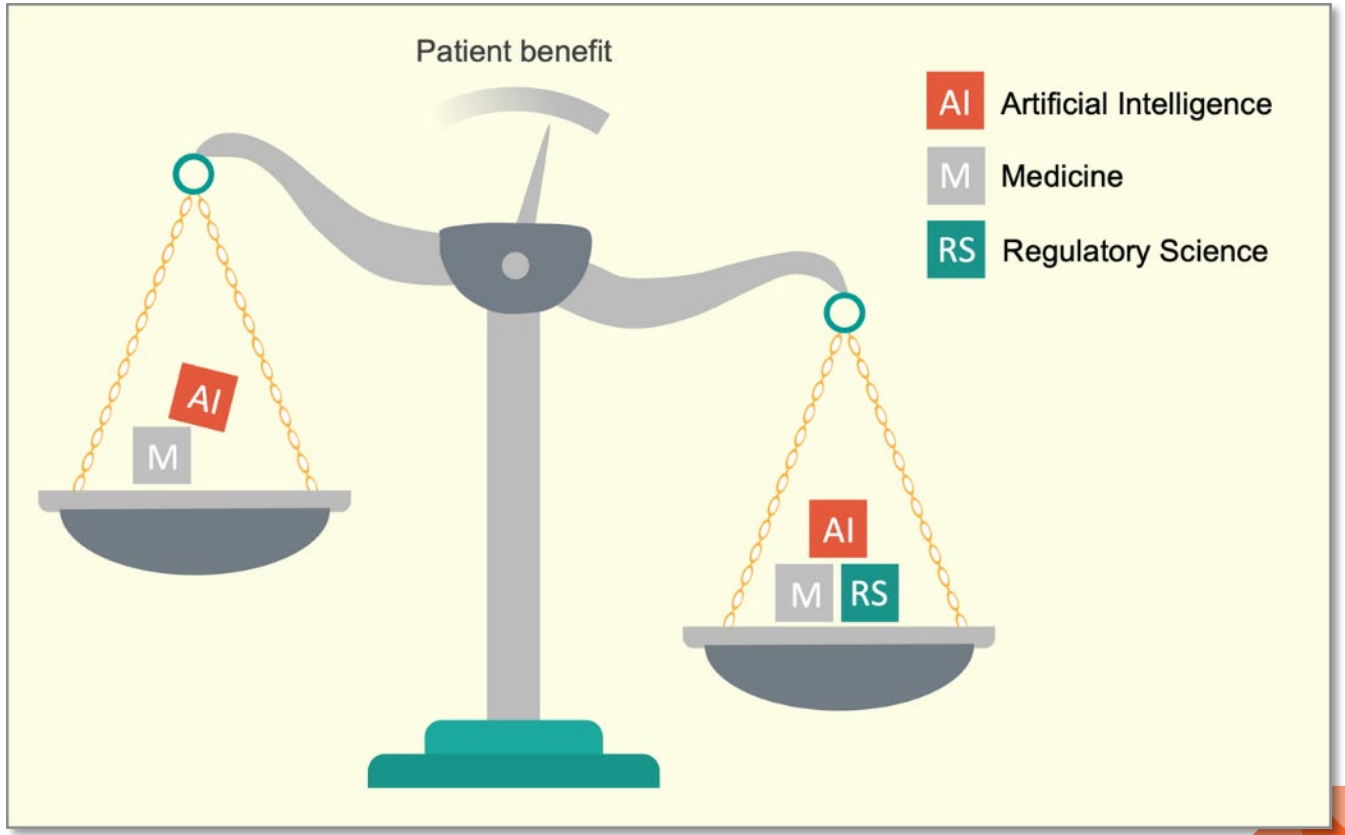
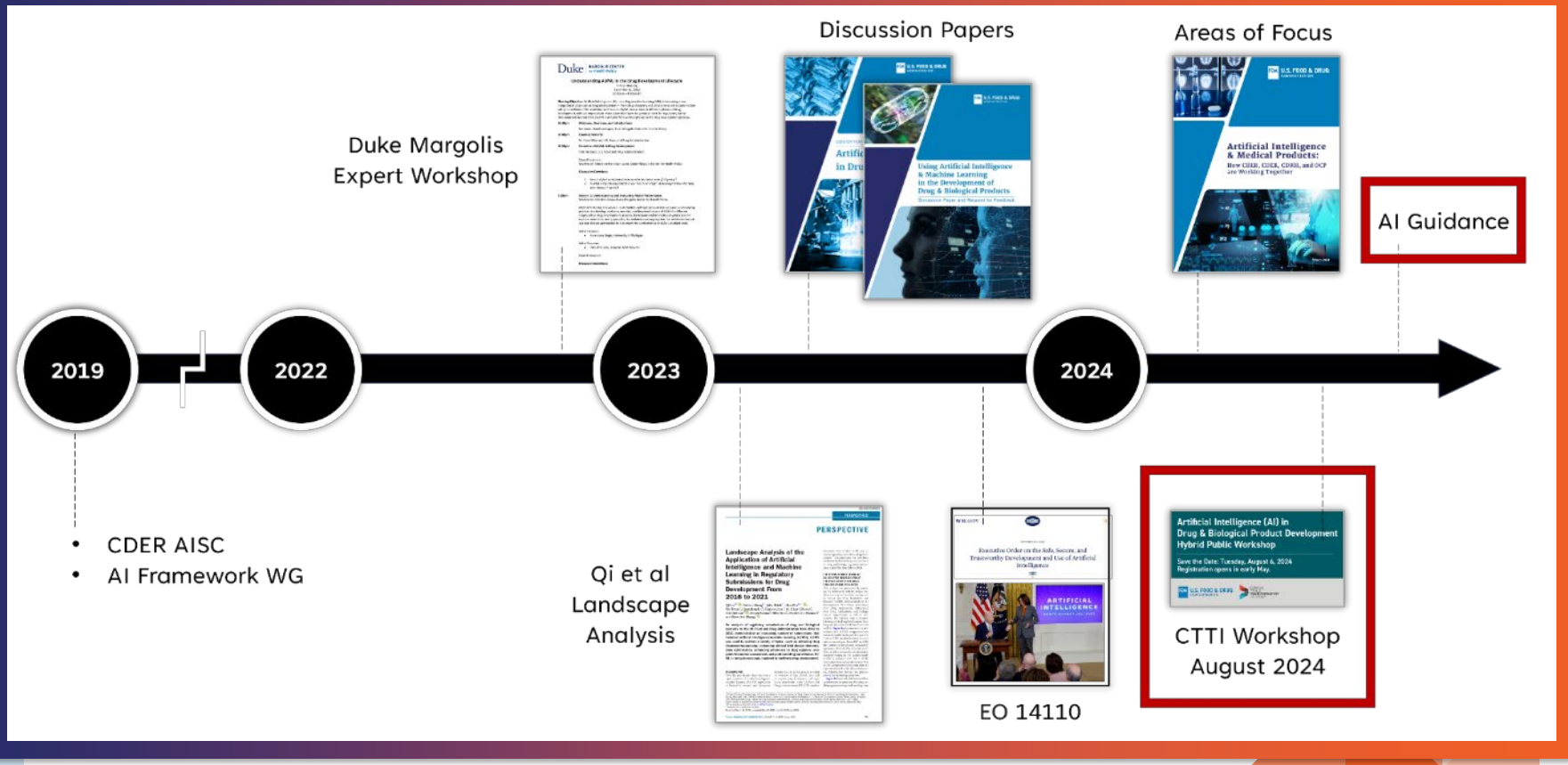
FDA is Advancing AI Regulatory Science



Source: : https://www.nature.com/articles/s41746-022-00721-7

CDER AI Policy Milestones

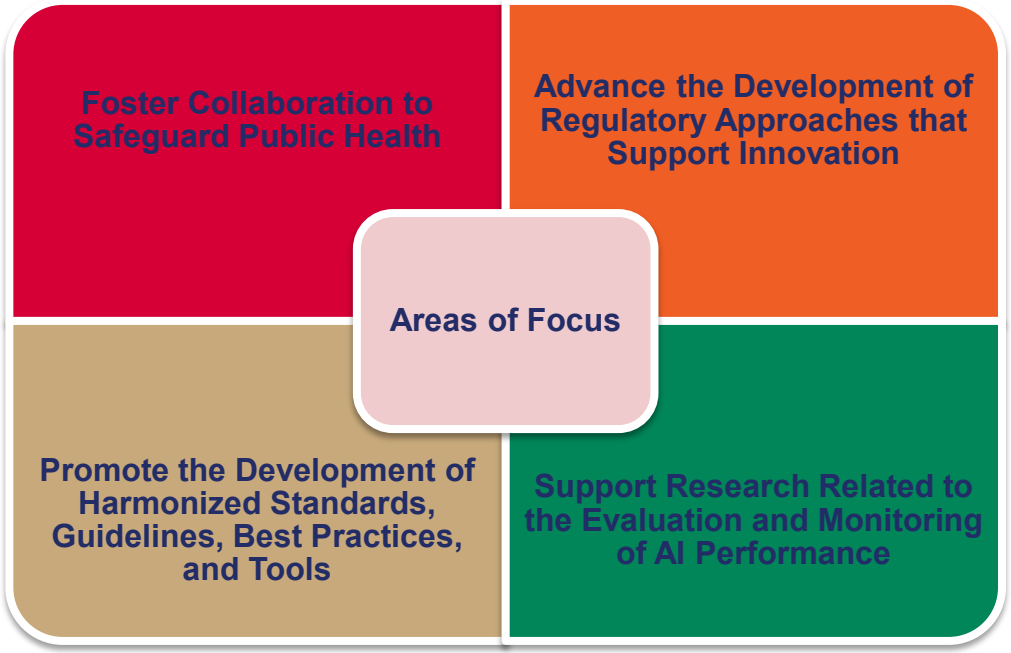


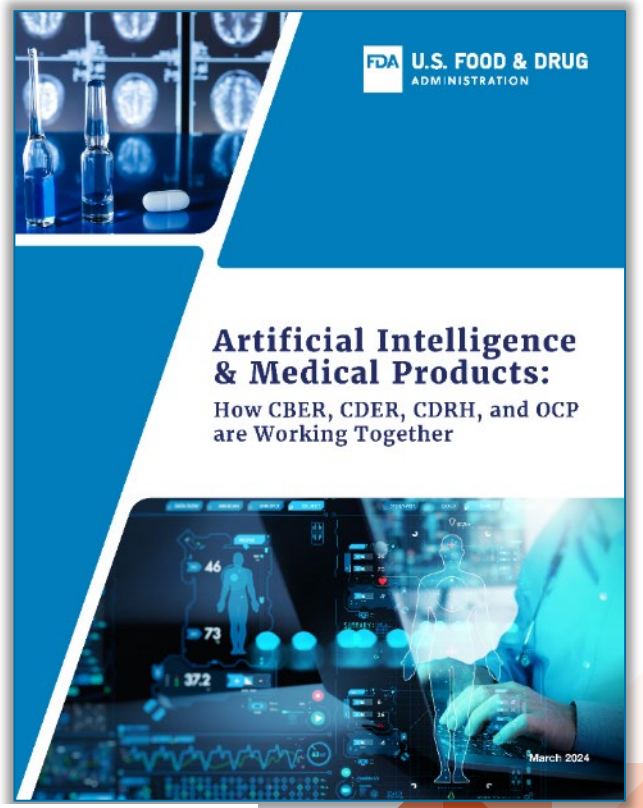
EO 14110 on Safe, Secure, and Trustworthy Development and Use of AI

- Government-wide effort to guide responsible AI development and deployment through federal agency leadership, regulation of industry, and engagement with international partners
- Includes 150 requirements* with 8 requirements for HHS
- Includes specific language related to drugs and devices regulations, including: “define the objectives, goals, and high-level principles required for appropriate regulation throughout each phase of drug development”

*For more EO by the numbers, see https://hai.stanford.edu/news/numbers-tracking-ai-executive-order

Four Areas of Focus to Advance Regulatory Science for AI

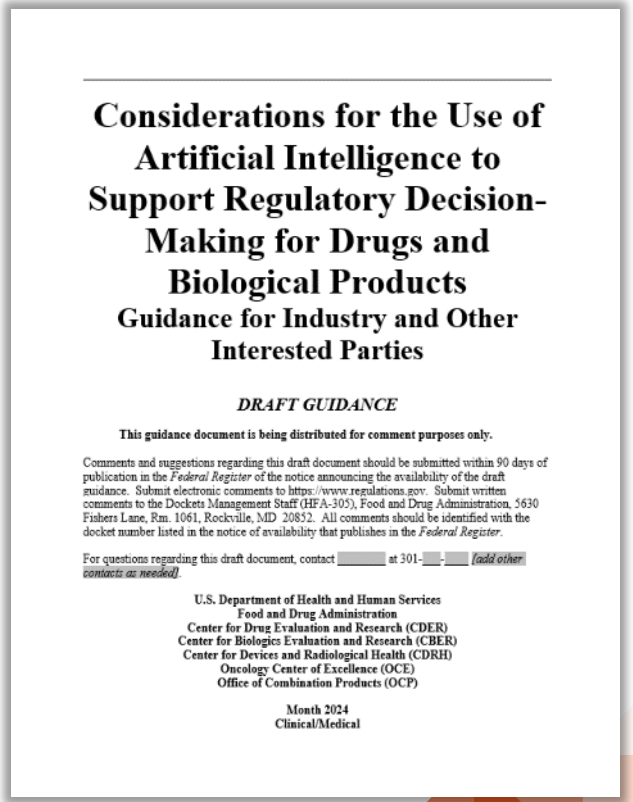




SOURCE: https://www.fda.gov/media/177030/download?attachment

Considerations for AI Use in Regulatory Decision Making

- Guidance to be published in 2024
- AI used to produce data or information to support regulatory decision making
- Informed by:
  - FDA's experience with reviewing over 300 submissions with AI
  - Over 800 comments received on the 2023 discussion papers
  - Current regulatory science research



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] *[add other contacts as needed]*.

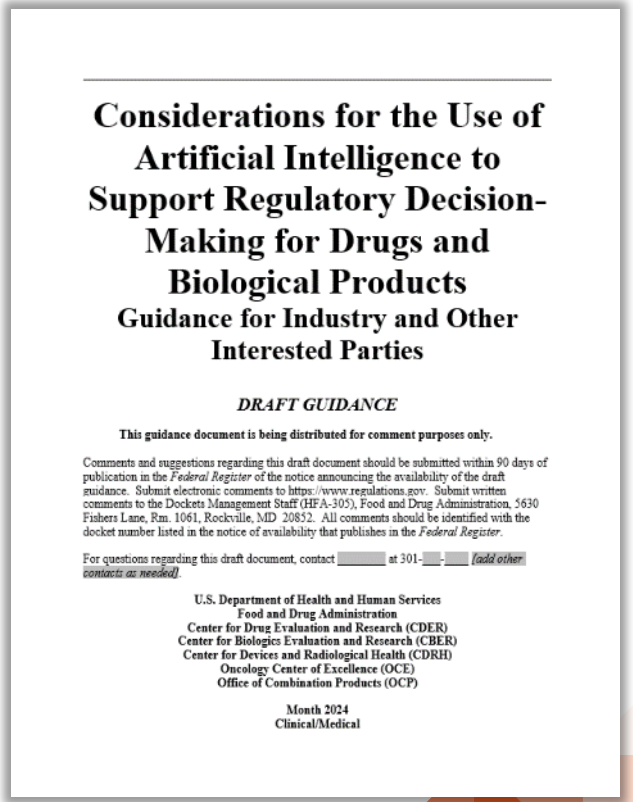
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Combination Products (OCP)

Month 2024
Clinical/Medical

SOURCE: https://www.fda.gov/media/134778/download

Considerations for AI Use in Regulatory Decision Making

- Provides a risk-based framework for establishing and evaluating the credibility of AI use in regulatory decision making
- Help ensure that AI models used to answer regulatory questions are sufficiently credible for a particular context of use and are supported with the appropriate level of evidence



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Office of Combination Products (OCP)

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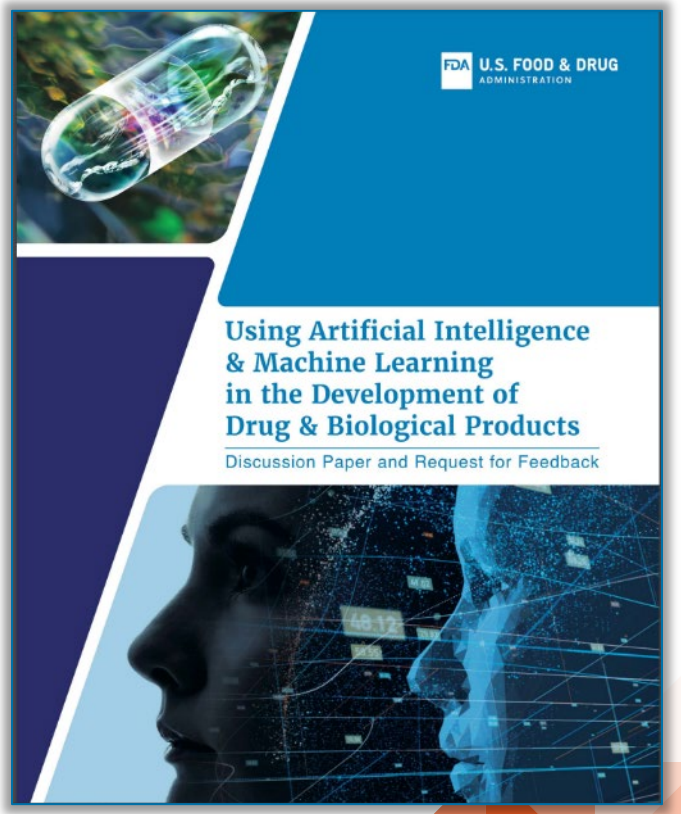
Considerations for AI Use in Regulatory Decision Making

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



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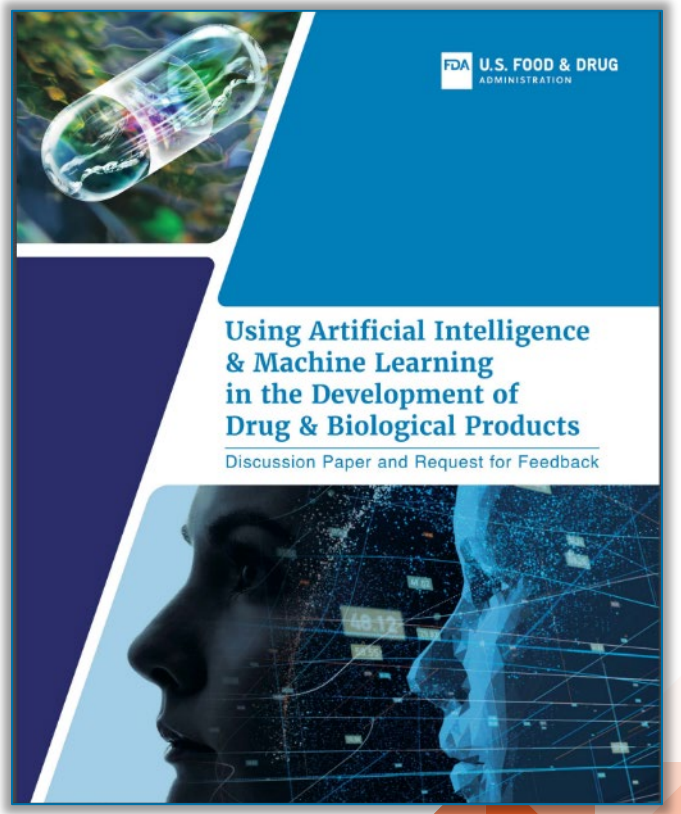
Considerations for AI Use in Regulatory Decision Making

- Goal is 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



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Responses to the 2023 Discussion Paper Inform Guidance Content

- 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 for drug development

What's Next?
Short Term Goals

- Once the guidance is published, we hope to get critical feedback on the proposed approach
  - Update to the guidance
  - Inform future guidance development
- Develop best practices that can be shared with all interested parties (i.e., GMLP)
- Continue to help develop consistent terminology that can facilitate the work of multidisciplinary teams
- Continue to engage with all interested parties to remain responsive to the changing technological landscape
- FDA CTTI Workshop August 6th, 2024

What's Next?
Long Term Goals

- Continue our responsive risk-based regulation approach
  - An iterative approach that keeps the pace with this rapidly evolving technology
- Continue advancing regulatory science in this area
  - Monitor and evaluate trends and emerging issues to detect gaps and opportunities
  - Support regulatory science for evaluating AI models and ensuring the development of robust AI technologies
- Continue our collaborative approach
  - Continue engaging all parties across the AI ecosystem (i.e., academia, industry, biotech, international regulators, etc.)

Poll Question #1

Evaluation of machine learning model performance requires an evaluation of the data used to develop the model because these models are data-driven.

A. True

B. False

Poll Question #2

A risk-based credibility assessment framework means that the level of oversight, the rigor of the assessments and the acceptance criteria for an AI model, and the amount of documentation will depend on AI model risk.

A. True

B. False