U.S. FOOD & DRUG ADMINISTRATION

The Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products

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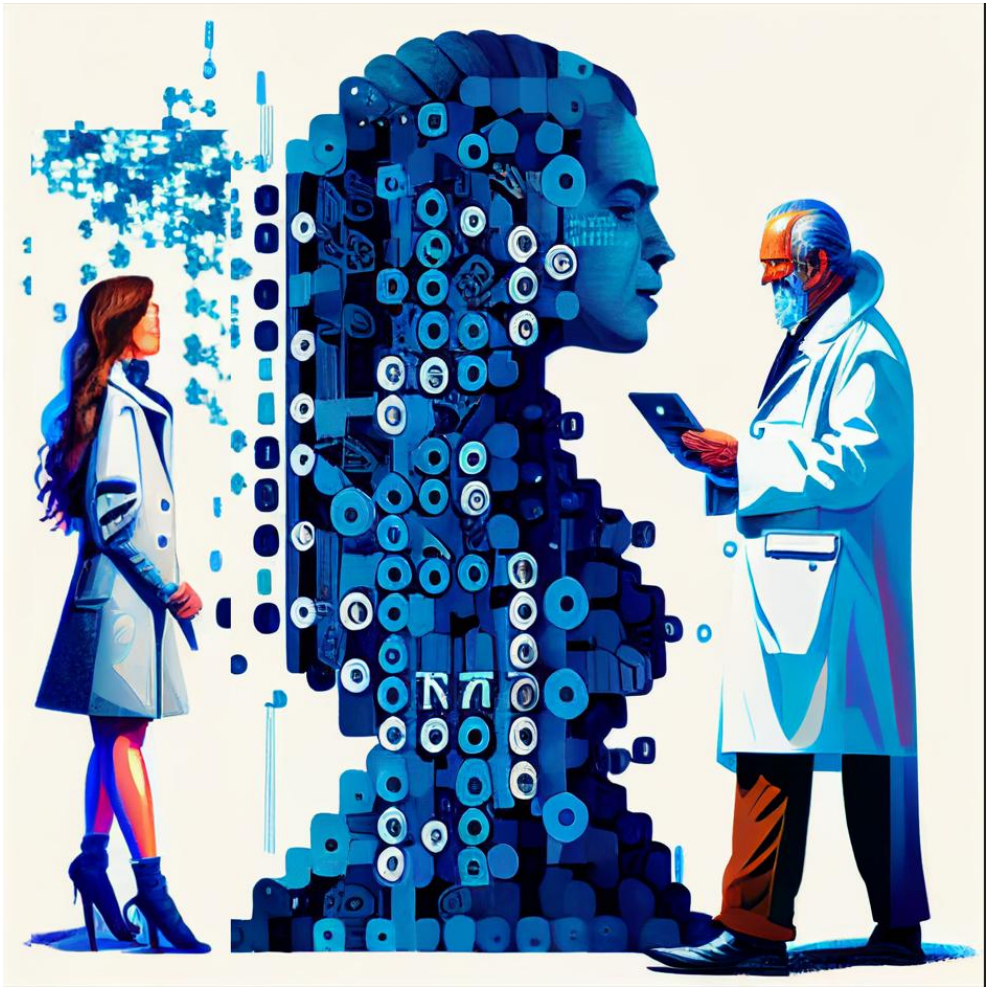
Office of Clinical Pharmacology/OTS/CDER/FDA
CDER AI Council Co-chair
Lead of CDER AI Review Rapid Response (R3) Team

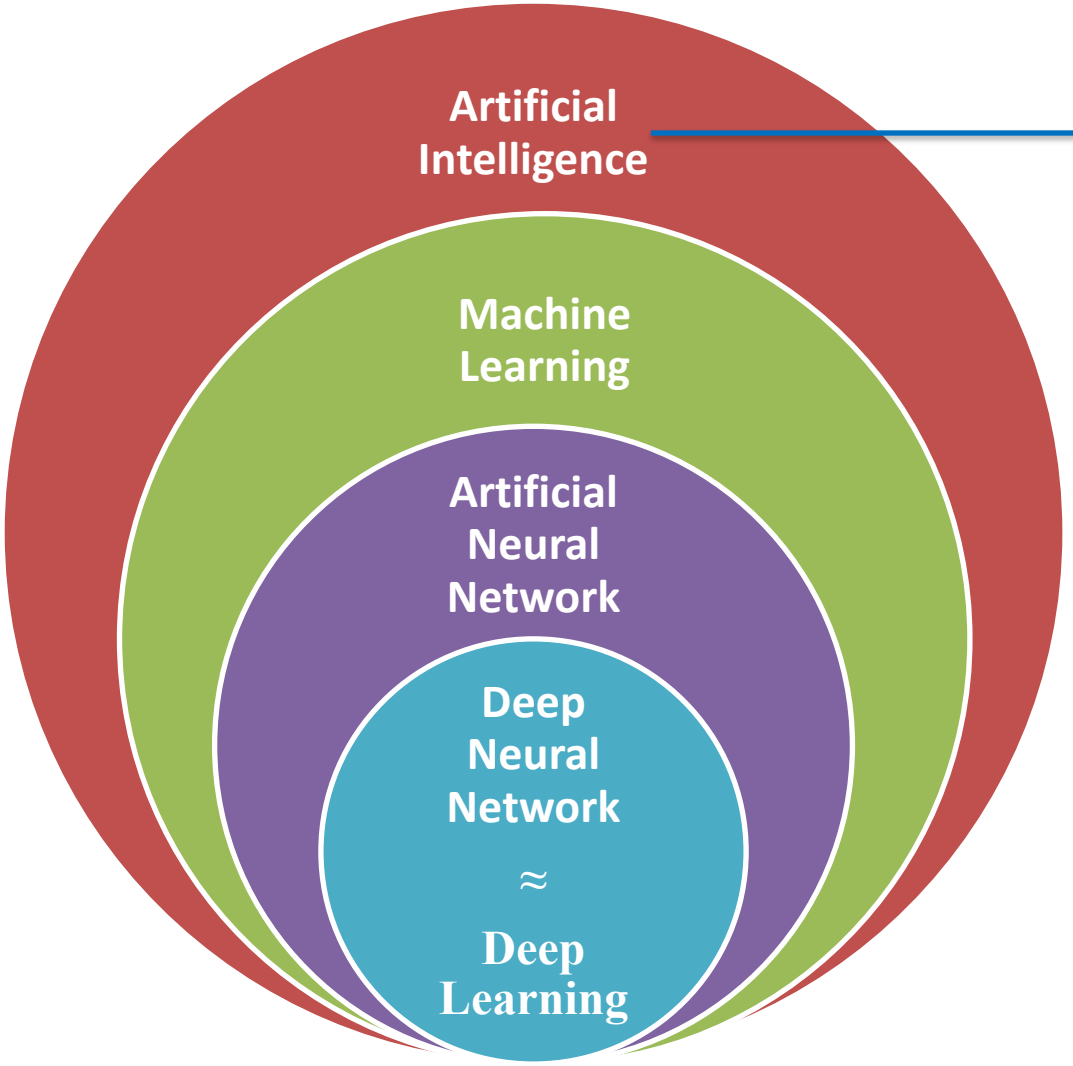
Take-Home Messages

- AI application in drug development is expanding rapidly
- Powerful tools
  - — to improve the efficiency and probability of success of drug development
  - — To advance precision medicine
- Unique challenges
- Risk-based Credibility framework



* Figure generated by Qi Liu using AI – Midjourney

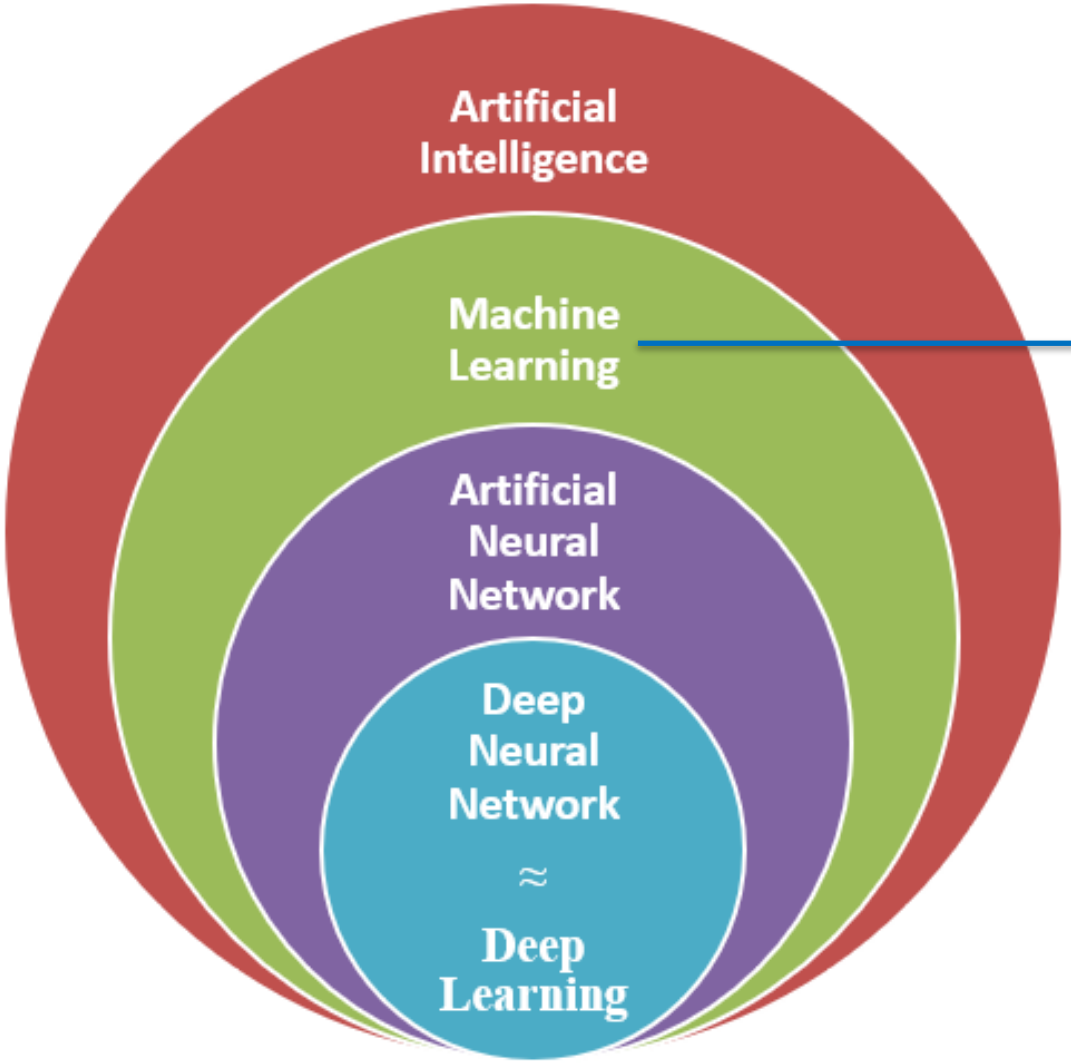
AI and Related terminology



The science and engineering of making intelligent machines -John McCarthy

Artificial intelligence (AI) enables computer systems to perform tasks normally requiring human intelligence.
Artificial Intelligence (AI) | HHS.gov

Machine Learning (ML)

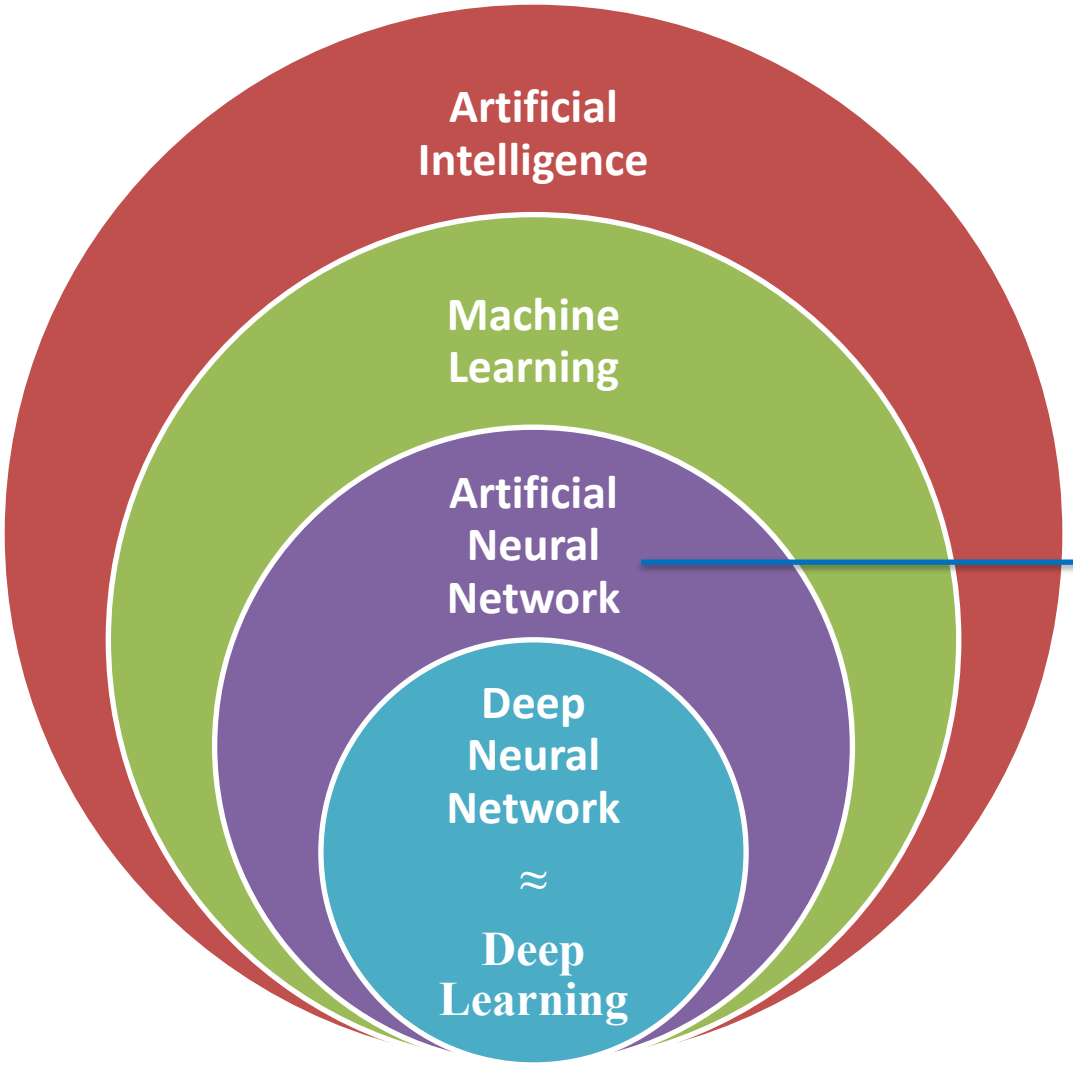


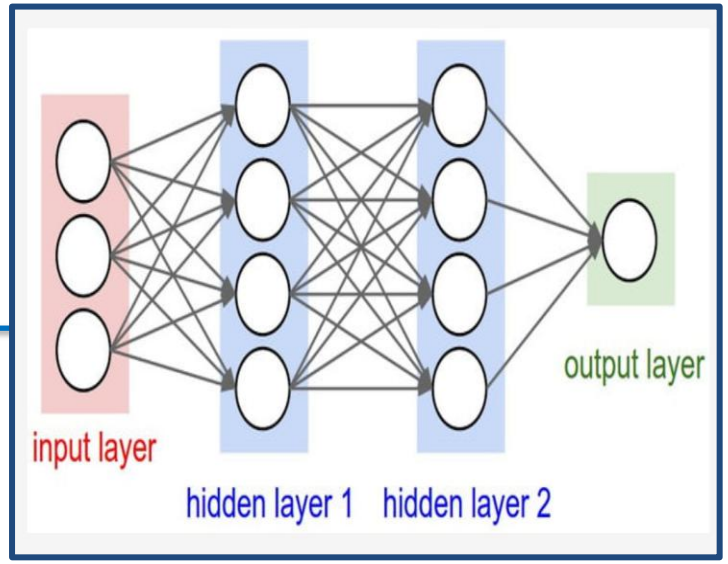
The field of study that gives computers the ability to learn without being explicitly programed - Arthur Samuel

A Computer program learns from experience E with respect to some class of tasks T and performance measure P, if P improves with E - Tom Mitchell

- The algorithm's performance improves with accumulating data.
- ML has a lot of overlap with statistical and pharmacometric modeling.

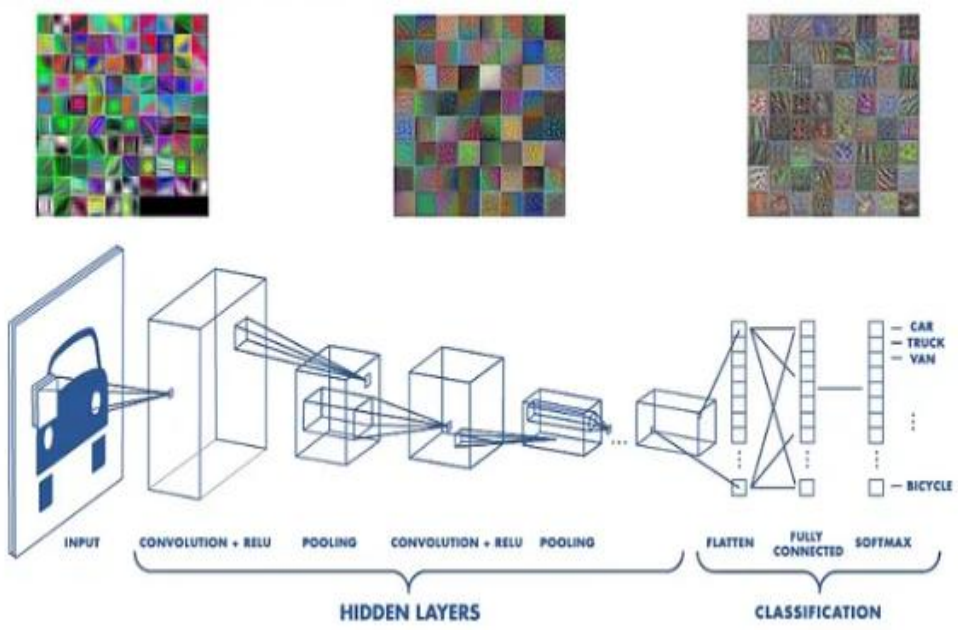
Artificial Neural Network





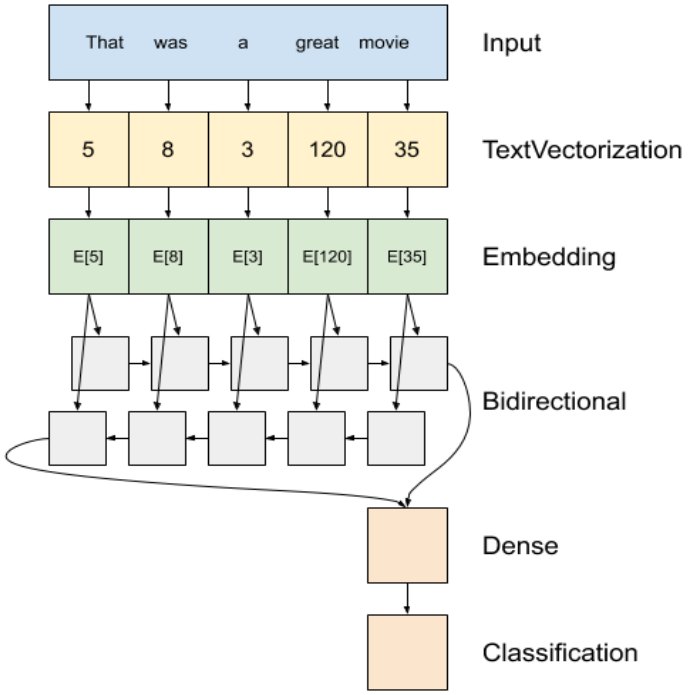
Some Important Types of Artificial Neural Networks

Convolutional Neural Network (CNN)



[Convolutional Neural Network (CNN) In Deep Learning | by Chetan Yeola | Python in Plain English]

Recurrent Neural Network (RNN)



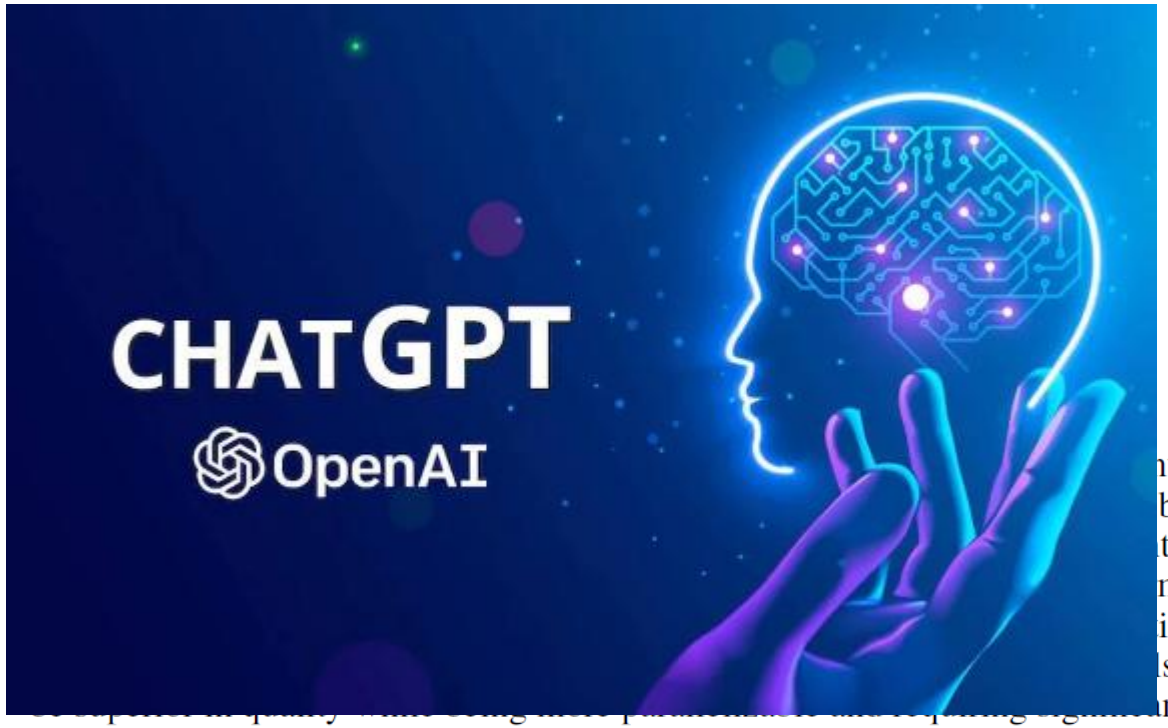
[Text classification with an RNN | TensorFlow]

Some Important Types of Artificial Neural Networks (Continued)

Transformer Neural Network

A transformative game-changer!

Attention Is All You Need



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less time to train. Our model achieves 28.4 BLEU on the WMT 2014 English-to-German translation task, improving over the existing best results, including ensembles, by over 2 BLEU. On the WMT 2014 English-to-French translation task, our model establishes a new single-model state-of-the-art BLEU score of 41.0 after training for 3.5 days on eight GPUs, a small fraction of the training costs of the best models from the literature.

31st Conference on Neural Information Processing Systems (NIPS 2017)

Challenges in the Application of AI

- **Bias**
- **Generalizability**
- **Opacity**
- **Hallucination**
- **Performance Degradation**
- **Privacy**
- **Security**
- **Other…**

→ **Risk and Trustworthiness Issues**

Opportunities for the Application of AI in Drug discovery, Drug Development and Patient Care

Artificial Intelligence/Machine Learning: The New Frontier of Clinical Pharmacology and Precision Medicine by Liu et al. Clin Pharmacol Ther. 2024 (Disclosure: The artwork was generated using OpenAI's GPT4 model.)

Increasing AI Related Submissions at 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

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

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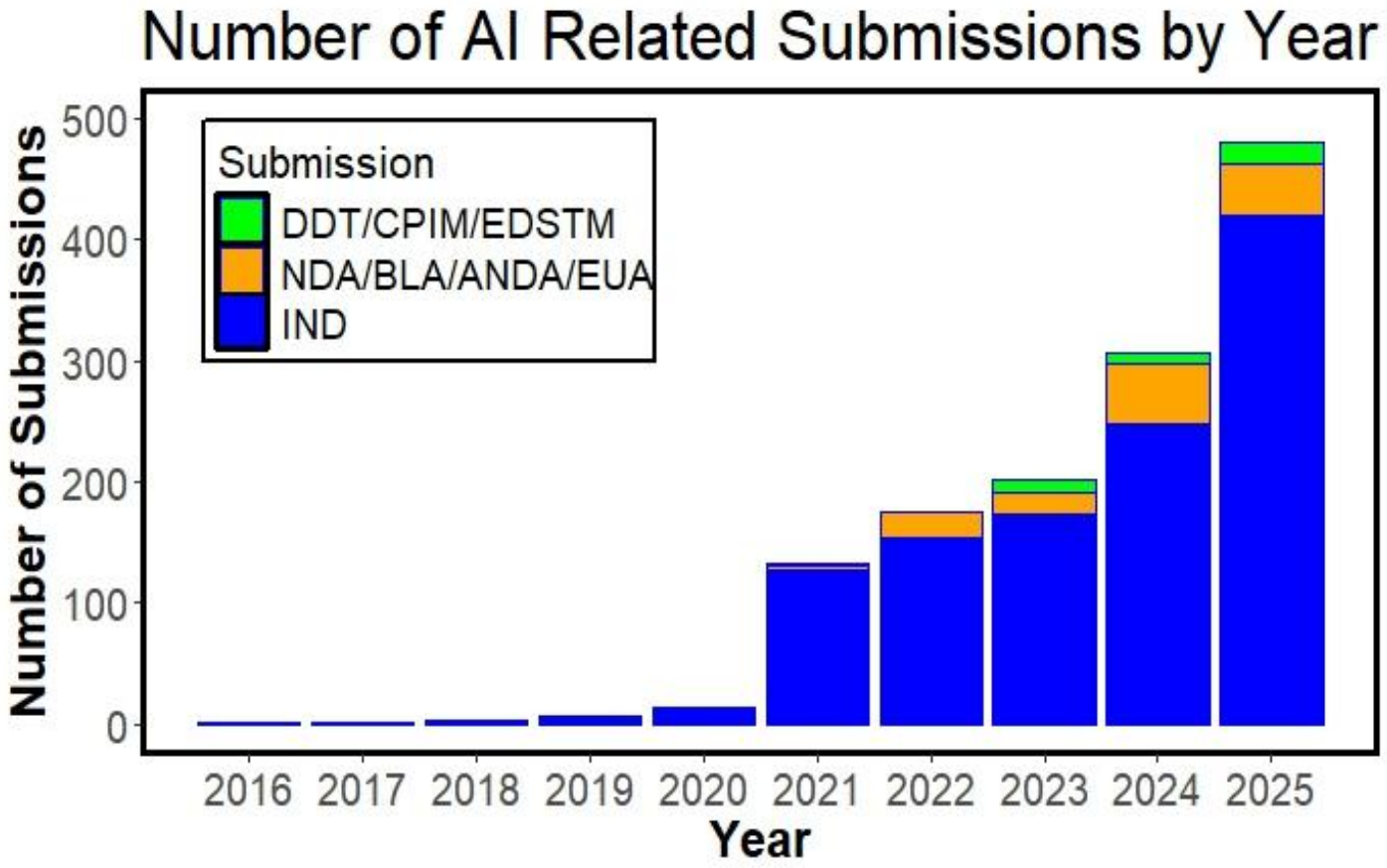
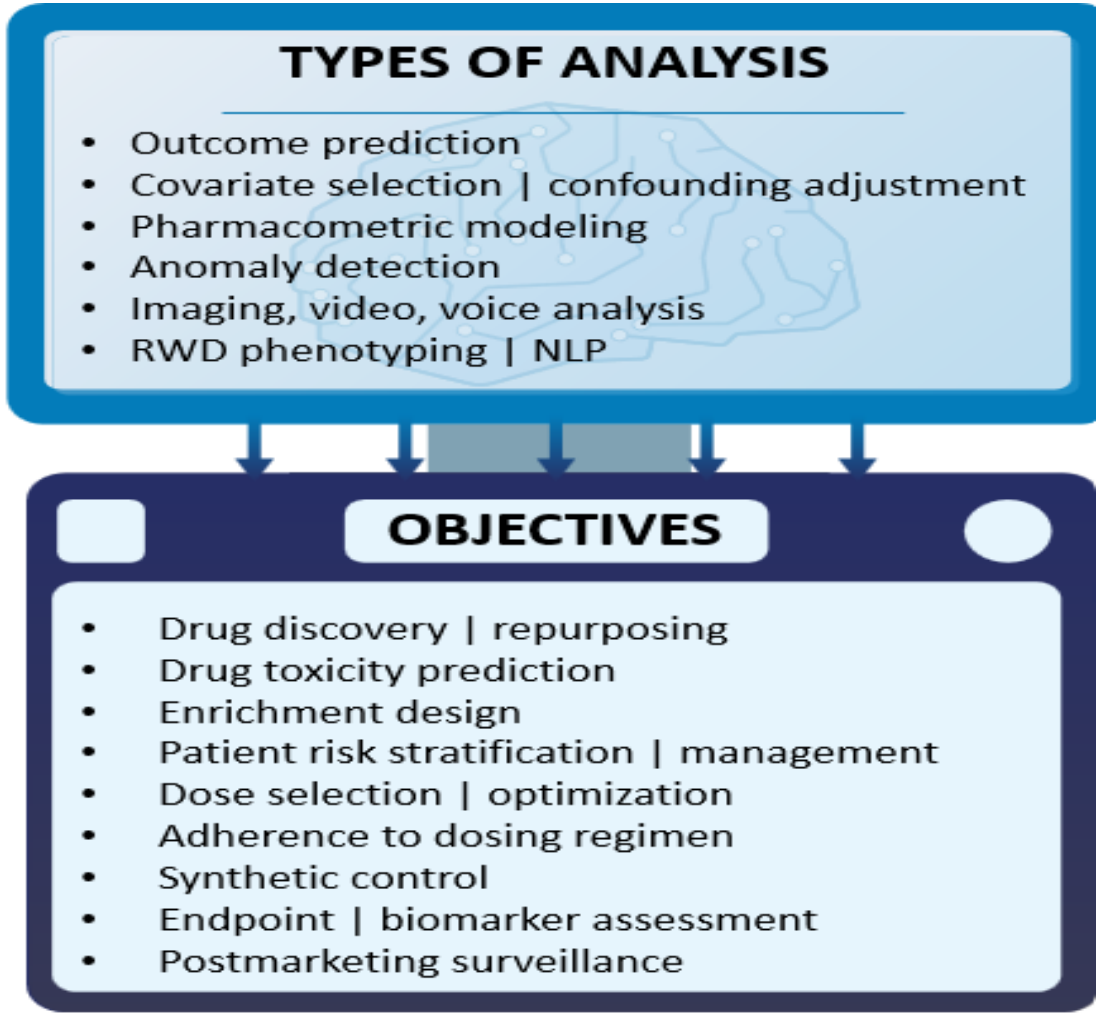
Updated analysis with submissions in 2022-2025



(Figure credit: Dr. Menglun Wang)

Types of AI Related Analyses & Objectives



Liu et al. Clin Pharmacol Ther. 2023

Regulatory Decision-Making Example: ML-based Patient Population Selection

ARTICLE

Using Machine Learning to Determine a Suitable Patient Population for Anakinra for the Treatment of COVID-19 Under the Emergency Use Authorization

Qi Liu[1,†], Raj Nair[2,*,†], Ruihao Huang[1,†], Hao Zhu[1,†], Austin Anderson[2], Ozlem Belen[2], Van Tran[3], Rebecca Chiu[3], Karen Higgins[3], Jianmeng Chen[1], Lei He[1], Suresh Doddapaneni[1], Shiew-Mei Huang[1], Nikolay P. Nikolov[2] and Issam Zineh[1]

Liu et al. CPT doi:10.1002/cpt.3191

https://www.fda.gov/media/163546/download

https://www.fda.gov/drugs/spotlight-cder-science/using-machine-learning-identify-suitable-patient-population-anakinra-treatment-covid-19-under

This was the first time that CDER used AI/ML for a regulatory decision, in this case to identify a population for a drug therapy.

1.1 Patient Population Identification

KINERET is authorized for emergency use for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma suPAR.

In the SAVE-MORE trial used to support the efficacy and safety of KINERET in COVID-19, key exclusion criteria were: pO2/FiO2 ratio < 150 mmHg, requirement for non-invasive ventilation (NIV), requirement for mechanical ventilation (MV), requirement for extra-corporeal membrane oxygenation (ECMO), and < 1500 neutrophils/mm^3.

All enrolled patients were required to have a plasma soluble urokinase plasminogen activator receptor (suPAR) level ≥ 6 ng/mL *[see Clinical Studies (14.1)]*. The suPAR assay is not commercially available in the United States. In order to identify a comparable population as was studied in the SAVE-MORE trial, an alternative patient identification method was developed to select patients most likely to have suPAR ≥ 6 ng/mL based on commonly measured patient characteristics. Patients meeting at least three of the following eight criteria are considered likely to have suPAR ≥ 6 ng/mL at baseline:

1. Age ≥ 75 years
2. Severe pneumonia by WHO criteria[1]
3. Current/previous smoking status
4. Sequential Organ Failure Assessment (SOFA)[2] score ≥ 3
5. Neutrophil-to-lymphocyte ratio (NLR) ≥ 7
6. Hemoglobin ≤ 10.5 g/dL
7. Medical history of ischemic stroke
8. Blood urea > 50 mg/dL and/or medical history of renal disease

Fact Sheet of Kineret ®

FDA Qualified AI-Based Drug Development Tool (DDT)

FDA Qualifies First AI Drug Development Tool, Will Be Used in 'MASH' Clinical Trials

[12/8/2025] The U.S. Food and Drug Administration (FDA) has qualified the first AI drug development tool, the AI-Based Histologic Measurement of NASH (AIM-NASH), to help pathologists assess metabolic dysfunction-associated steatohepatitis (MASH) disease activity in clinical trials. This cloud-based tool helps pathologists score liver biopsy components, including fat infiltration (steatosis), inflammation (hepatocellular ballooning and lobular inflammation), and scarring (fibrosis) stage.

MASH, a significant public health challenge affecting millions of Americans, is a severe form of metabolic-associated fatty liver disease that develops when fat buildup in the liver causes inflammation and scarring. MASH can lead to cirrhosis (severe liver scarring), hepatic decompensation (worsening of liver function), liver cancer, liver transplantation, or death.

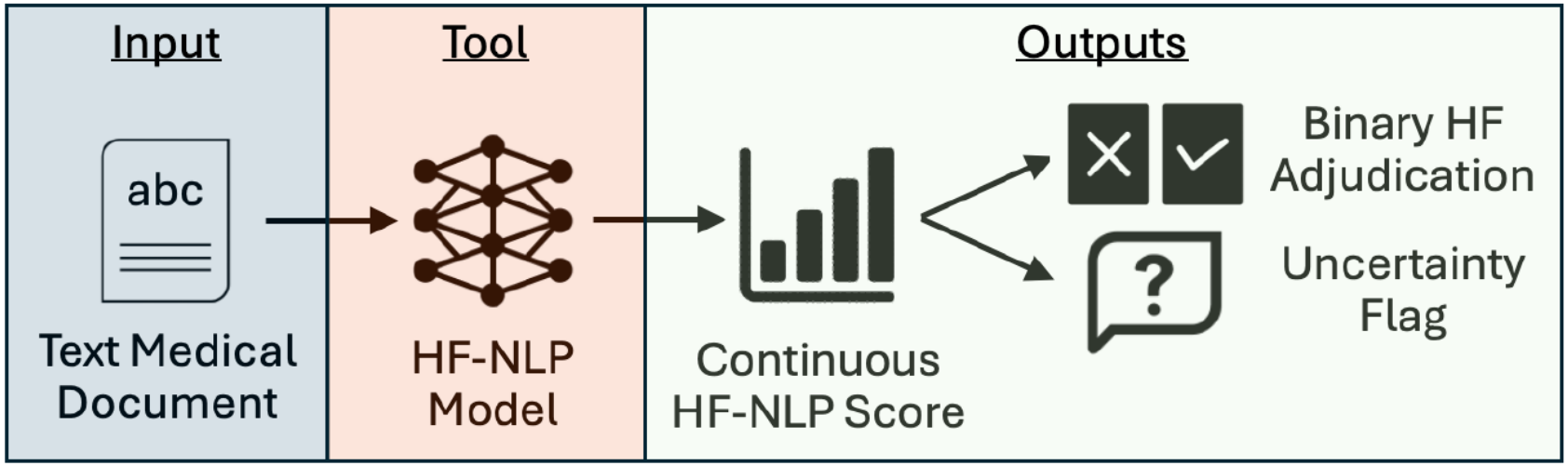
Currently in MASH clinical trials, multiple experts independently assess liver histology, a time-consuming process made complicated by variable scoring. AIM-NASH could help standardize histologic assessment and reduce the time and resources needed for MASH drug development.

FDA Accepted Letter of Intent for AI/Natural Language Processing-Based DDT

FDA has completed its review of the Letter of Intent (LOI) for Drug Development Tool (DDT), DDT-IST-000027, received on April 10, 2024, by the CDER Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic (FD&C) Act.[1]

The LOI is for the Heart Failure Natural Language Processing (HF-NLP) model.

FDA has made a determination to **accept** the LOI into the CDER ISTAND Pilot Qualification Program. Note that projects in the ISTAND Pilot Qualification Program may be eligible to apply for DDT grant programs which are offered for further DDT tool development as funding permits.[2]



https://force-dsc.my.site.com/ddt/s/ddt-project?ddtprojectid=205

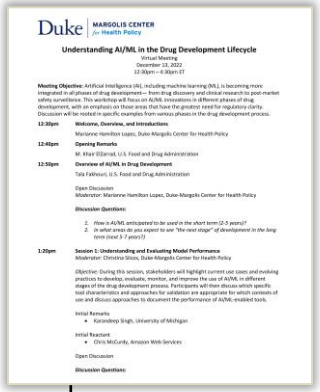
CDER AI Initiatives

2019

- CDER AISC
- AI CoP
- AI Framework WG
- Tracking of AI uses

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:

2. *How is AI/ML anticipated to be used in the short term (2-5 years)?*
3. *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 Silva, Duke-Margolis Center for Health Policy

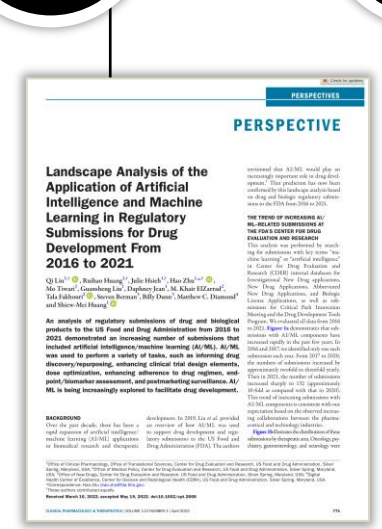
Objective: During this session, stakeholders will highlight current use cases and evolving practices to develop, evaluate, monitor, and improve the use of AI/ML in different stages of the drug development process. Participants will then discuss which specific tool characteristics and approaches for validation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

Liu et al Landscape Analysis

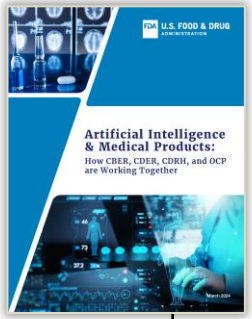
2023

Discussion Papers

CERSI Workshop

2024

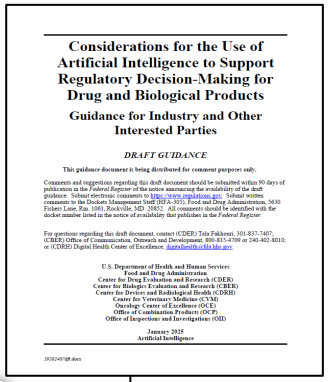
Areas of Focus



2025

CDER AI Council

Draft 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

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 (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@fda.hhs.gov.

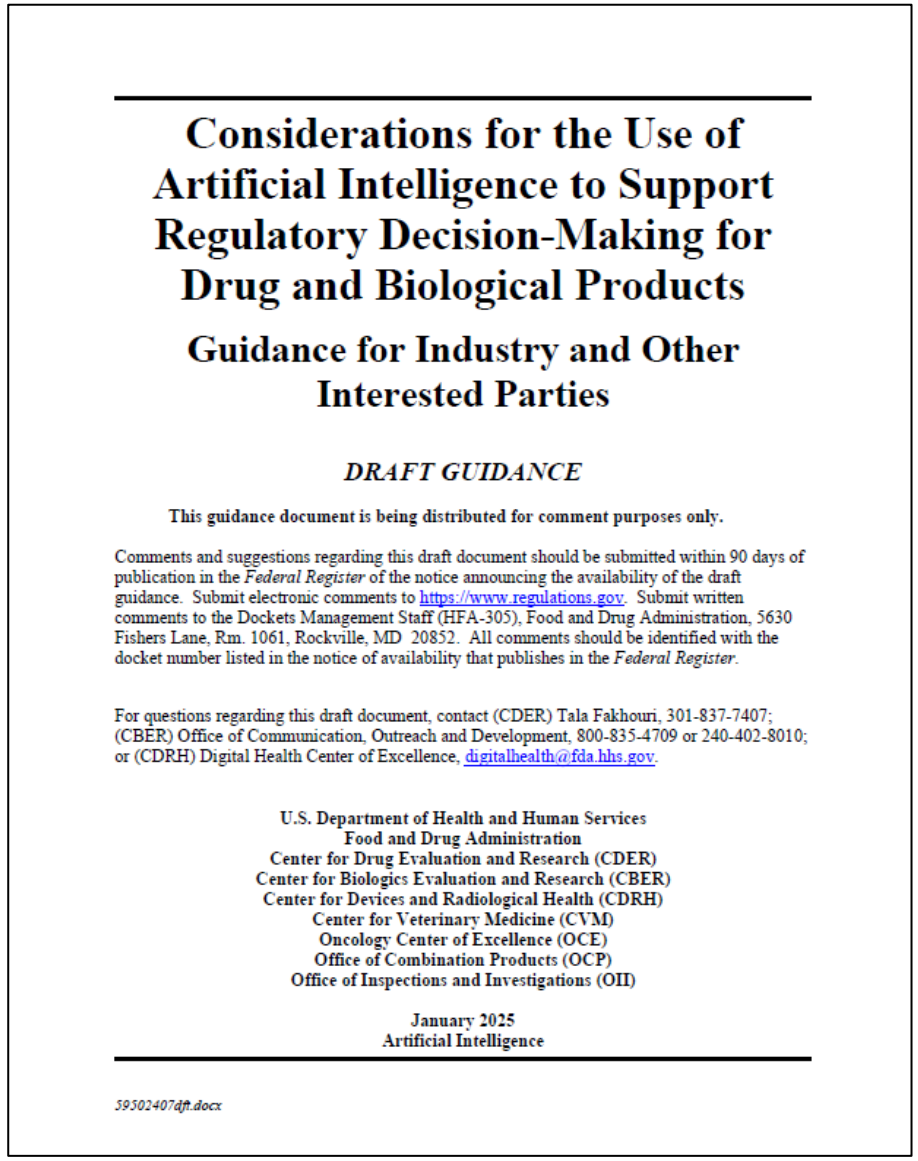
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Oncology Center of Excellence (OCE)
Office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

January 2025
Artificial Intelligence

CTTI Workshop

CTTI Workshop

Considerations for AI Use in Regulatory Decision-Making



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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

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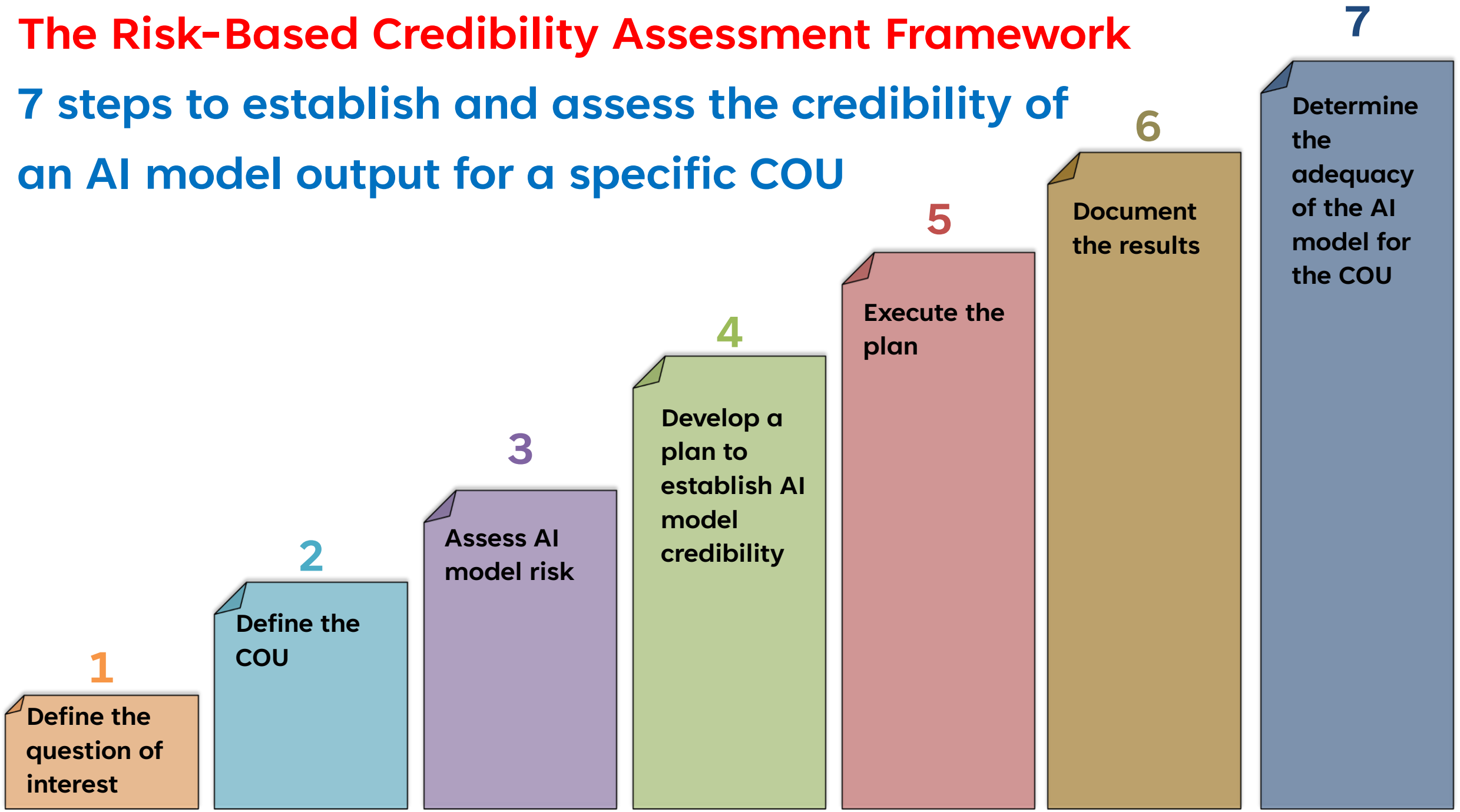
Providing a **risk-based framework** for establishing and evaluating the credibility of AI use in regulatory decision making.

The credibility assessment activities used to establish the credibility of AI model outputs should be commensurate with the AI model risk and tailored to the specific context of use (COU).

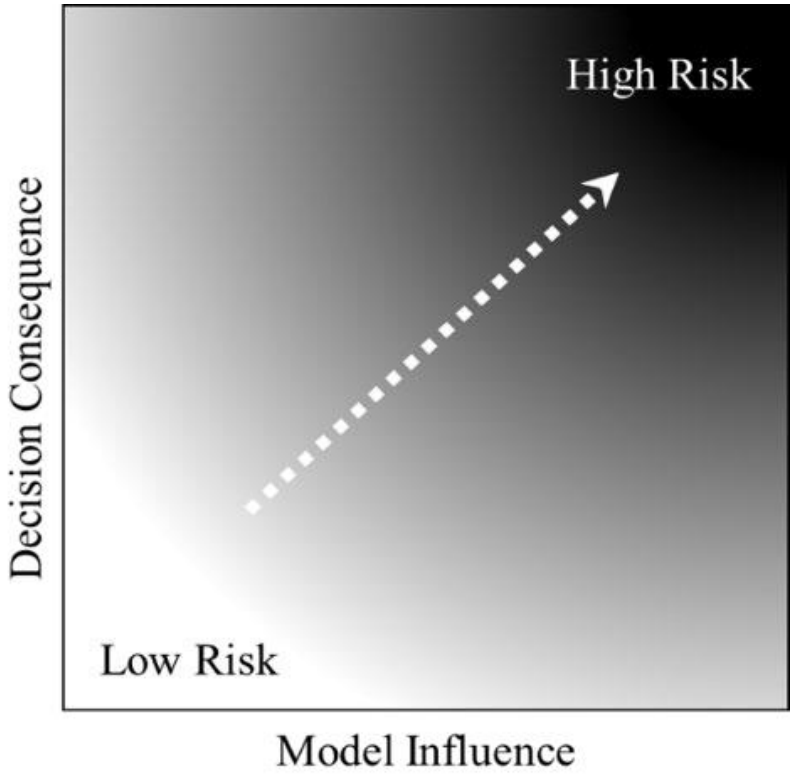
SOURCE: https://www.fda.gov/media/184830/download

The Risk-Based Credibility Assessment Framework

7 steps to establish and assess the credibility of an AI model output for a specific COU



Model Risk Matrix



Model influence: the contribution of the evidence derived from the AI model relative to other contributing evidence used to inform the question of interest

Decision consequence: the significance of an adverse outcome resulting from an incorrect decision concerning the question of interest

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.

AI Research in CDER/OTS/OCP AI Team

Landscape analyses

(PMID: 31925955) (PMID: 35707940)

Methodology Exploration

- Long short-term memory recurrent neural network for pharmacokinetic-pharmacodynamic modeling. (PMID: 33210994)
- A novel approach for personalized response model: deep learning with individual dropout feature ranking. (PMID: 33104924)
- Application of machine learning based methods in exposure-response analysis. (PMID: 35275315)
- Measurement and Mitigation of Bias in Artificial Intelligence (PMID: 38018360)
- Addressing AI's challenges with out-of-distribution data (PMID: 39821661) (PMID: 41127928)
- Interpretable/Explainable ML
- Large Language Model

Application for Therapeutic Optimization/Individuation

- Use ML to predict prognosis or treatment outcome (both efficacy and toxicity) (DOI:10.21203/rs.3.rs-8118762/v1)
- Multi-omics data for precision medicine (PMID: 37965805)

https://orise.orau.gov/FDA/index.html

Moving Forward. Looking Ahead.

- Continue seeking feedback from all stakeholders
- Continue our responsive risk-based regulation approach
- Continue advancing regulatory science
  - Monitor the landscape to detect gaps and opportunities
  - Support regulatory research
- Continue our collaborative approach to advance AI science for the benefits of patients

Acknowledgement

- Ruihao Huang
- Hao Zhu
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- Cecilia Almeida
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- Dianne Paraoan
- Shiew-Mei Huang
- Issam Zineh
- ShaAvhrée Buckman-Garner
- Our current and past fellows
- Our collaborators
- Patients