U.S. FOOD & DRUG ADMINISTRATION

The FDA AI Program: Challenges & Opportunities

Tucker A. Patterson, Ph.D.
Director, National Center for Toxicological Research

EFSA Symposium on Data Readiness for Artificial Intelligence
Parma, Italy – 23 October 2024

Disclaimer: The views expressed are those of the presenter and should not be considered as the official position or policy of U.S. FDA.

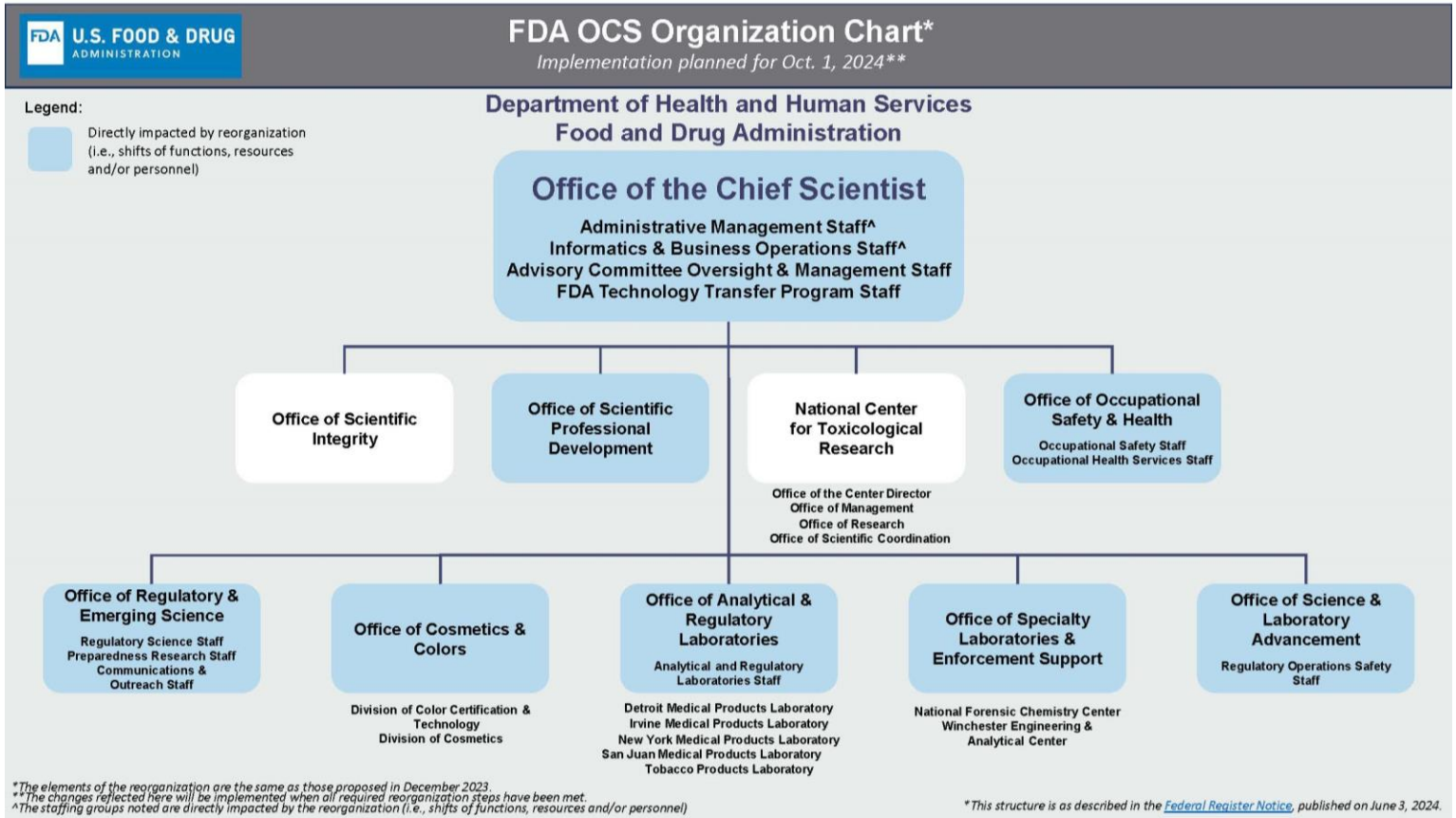
Outline

- Overview of FDA Centers and Regulatory Authorities
- AI at FDA
  - Diverse application and distinct responsibilities across centers
- AI at FDA: two aspects
  - How to regulate a product containing AI
  - How to facilitate FDA's operation through regulatory science research with AI
- AI research at NCTR and our experience to translate AI research for regulatory application
  - To assess AI innovation in real world-applications by working with public
  - To establish a platform with agility to evaluate AI innovation in regulatory applications
  - To qualify AI innovation in the regulatory process

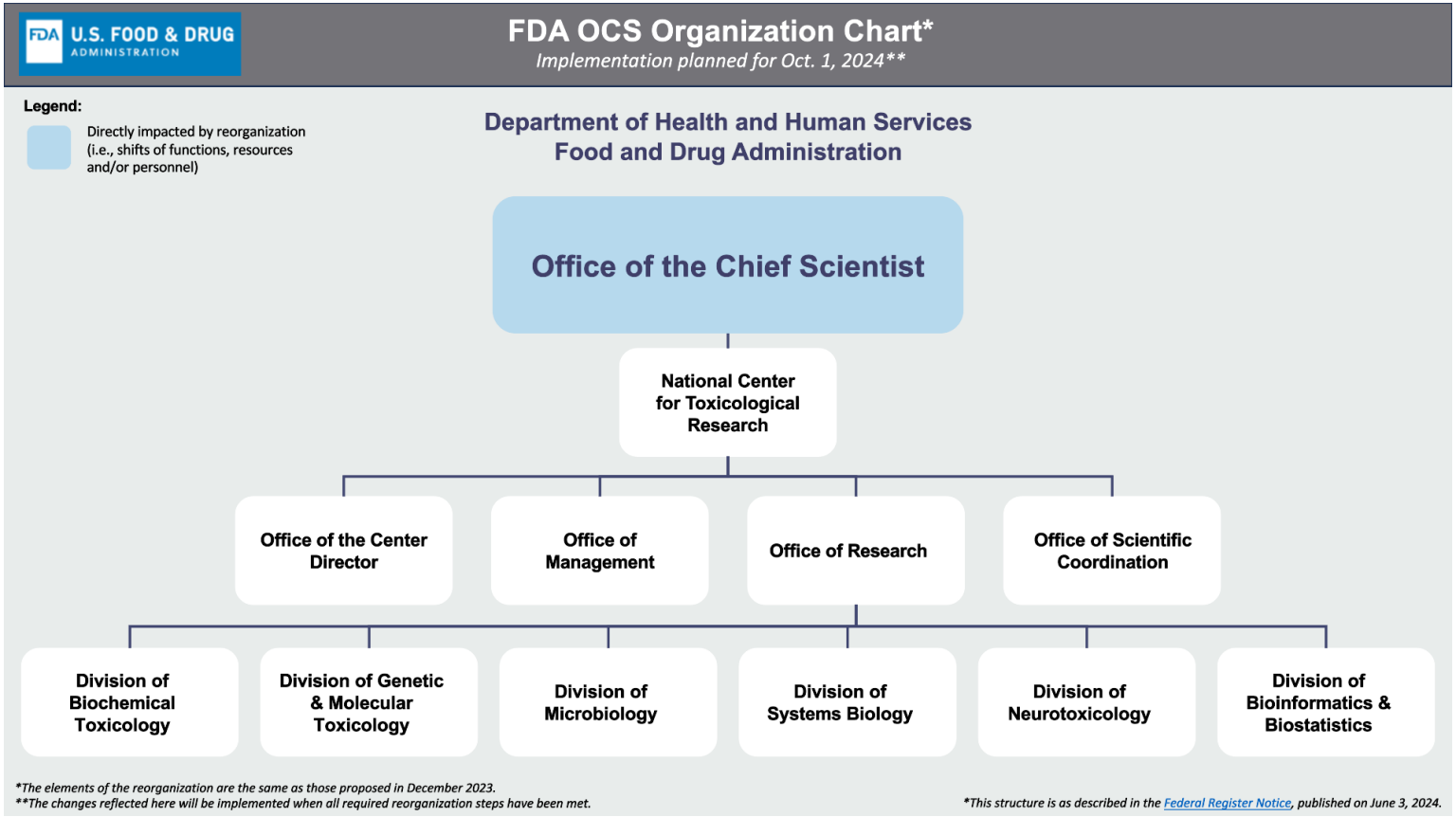
FDA Mission

- FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics and products that emit radiation.
- FDA is also responsible for advancing public health by helping to speed innovations that make medical products more effective, safer and more affordable, and by helping the public get the accurate science-based information they need to use medical products and foods to maintain and improve their health.
- FDA plays a significant role in the Nation's counterterrorism capability - fulfilling this responsibility by ensuring the security of the food supply and fostering development of medical products to respond to deliberate and naturally emerging public health threats.

OCS Organizational Chart (1 October 2024)



National Center for Toxicological Research



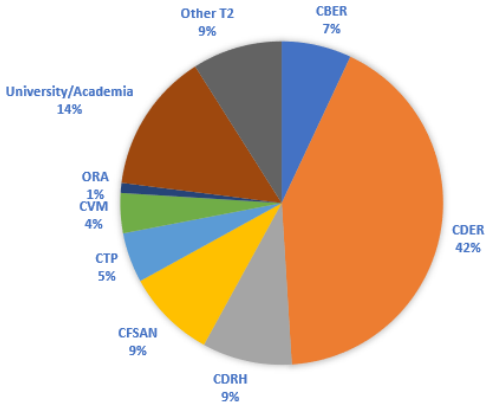
National Center for Toxicological Research

Major functions

- Provide interdisciplinary toxicology research solutions and consultations that support current and anticipate future FDA needs.
- Use multidisciplinary research teams to develop novel translational research approaches that provide FDA methods to address regulatory questions.

Stakeholders

>75% of NCTR Active Research Protocols are Collaborations with FDA Product Centers/Offices



NCTR Staff

Government (FTEs) = 286
Research Scientists = 139
Support Scientists = 65
Administrative = 82

Contractors = 220

ORISE = 45

National Center for Toxicological Research

SPECIALIZED FACILITIES

- Animal
- Bio-imaging
- Inhalation Toxicology Facility
- Nanotechnology Core Facility
- Analytical Chemistry

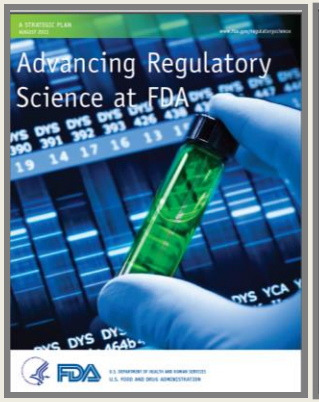
SCIENTIFIC EXPERTISE

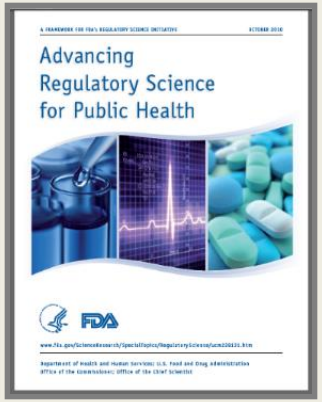
- Animal models including chronic bioassays
- Antimicrobial drug resistance
- Bioinformatics and biostatistics, artificial intelligence
- Computational modeling
- Developmental, reproductive, behavioral toxicology
- Genetic toxicology
- In vivo/In vitro metabolism and PBPK modeling
- Microbiome and host interactions
- Neurochemistry, neuropathology, behavioral studies
- New Approach Methods (NAMs)
- Perinatal and maternal health
- Systems biology
- Translational biomarker discovery
- Virology

FDA Regulates a Diversity of Consumer Products

- Center for Biologics Evaluation and Research (CBER)
- Center for Device and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Center for Food Safety and Nutrition (CFSAN)
- Center for Tobacco Products (CTP)
- Center for Veterinary Medicine (CVM)
- Office of Regulatory Affairs (ORA)
- **National Center for Toxicological Research (NCTR)**

Regulatory Science:
The science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.





FDA Regulates a Diversity of Consumer Products

- Center for Biologics Evaluation and Research (CBER)
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- ~~Office of Regulatory Affairs (ORA)~~
- **National Center for Toxicological Research (NCTR)**
- **Human Foods Program**

Regulatory Science:
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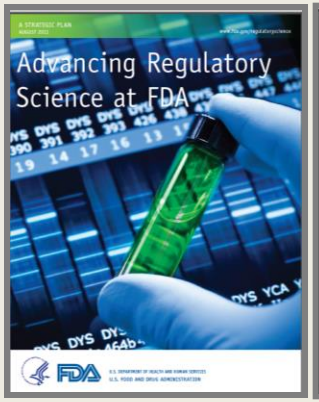
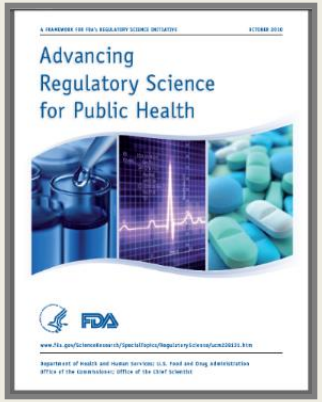
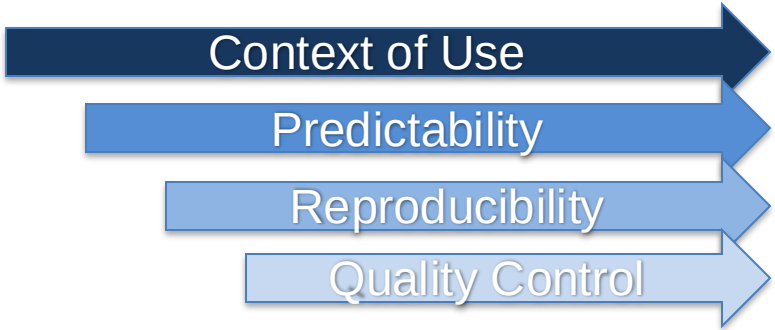




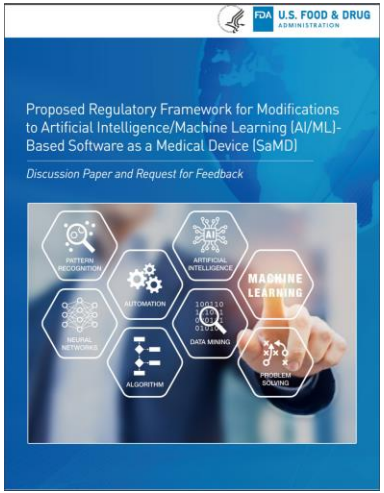
Challenges and Opportunities of AI for FDA

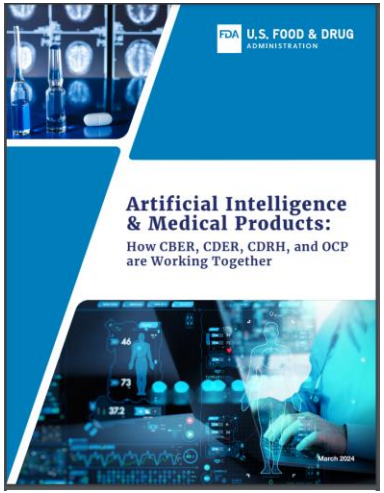
- New technologies hold significant promise.
- However, multiple steps are required to translate new technologies into regulatory use and maintain the same standards of safety, efficacy and quality for FDA-regulated products.



Challenges and Opportunities of AI for FDA

Q1: How to regulate a product that contains AI?





- CDRH:
  - By Aug. 7, 2024, CDRH authorized 950 AI/ML-enabled medical devices.
  - CDRH has developed several guidance documents on AI/ML- based software as a medical device
- CDER: the number of drug applications incorporating AI/ML elements have “increased drastically in the past five years” (2023)

Innovate Healthcare

RADIOLOGY BUSINESS

FOR IMAGING LEADERS IMPROVING ECONOMICS, OPERATIONS & OUTCOMES

American College of Radiology partners with FDA to hasten availability of AI products

Marty Stempniak | October 07, 2024 | Radiology Business | Artificial Intelligence

FDA's TAP

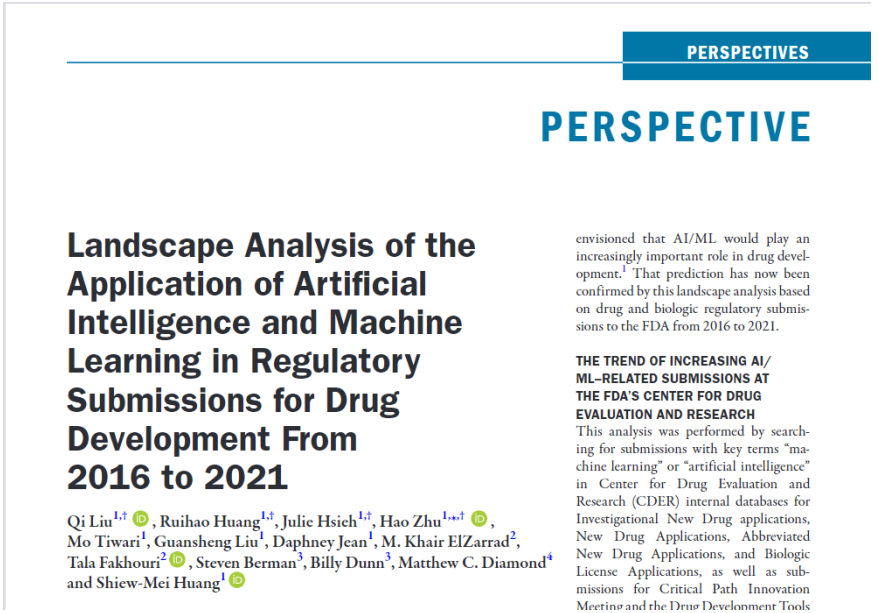
- Initially piloted in 2023 for cardiology & neurology
- Expanding to include radiology & ophthalmology, - orthopedic devices in 2025
- 46 breakthrough devices

Challenges and Opportunities of AI for FDA

Q1: How to regulate a product that contains AI?

CDER Artificial Intelligence Council (AIC) was established in June 2024

- To serve as CDER's executive review and decision-making board for oversight of all CDER AI initiatives
- To coordinate, support, and promote consistency of both internal and external AI-related activities in CDER
- As appropriate, to oversee certain activities, including CDER's internal AI capabilities (i.e., talent, technology, data) and CDER AI policy initiatives for regulatory decision-making (e.g., guidance development)



PERSPECTIVES

PERSPECTIVE

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

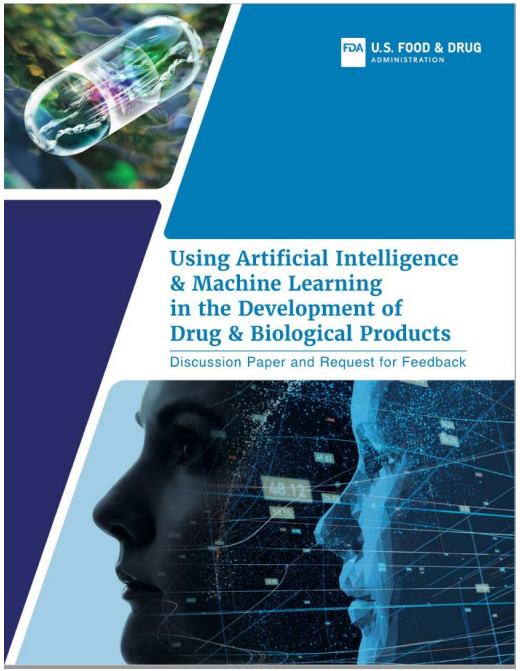
Qi Liu[1,†], Ruihao Huang[1,†], Julie Hsieh[1,†], Hao Zhu[1,*,†], Mo Tiwari[1], Guansheng Liu[1], Daphney Jean[1], M. Khair ElZarrad[2], Tala Fakhouri[2], Steven Berman[3], Billy Dunn[3], Matthew C. Diamond[4] and Shiew-Mei Huang[1]

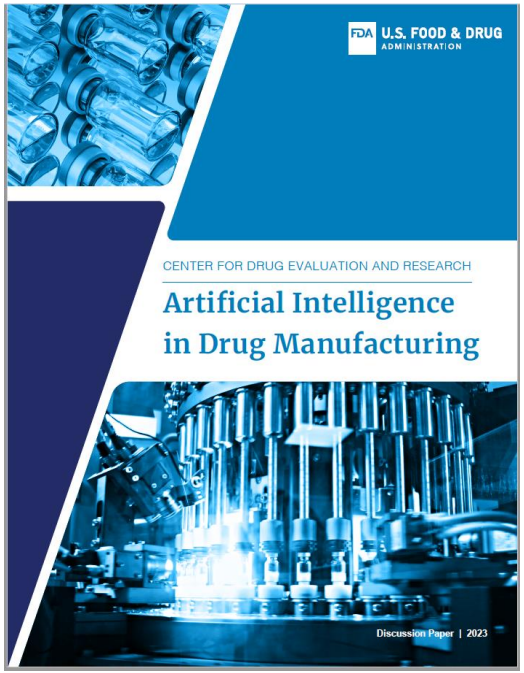
envisioned that AI/ML would play an increasingly important role in drug development.[1] That prediction has now been confirmed by this landscape analysis based on drug and biologic regulatory submissions to the FDA from 2016 to 2021.

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

CDER Releases Two Discussion Papers on AI Application





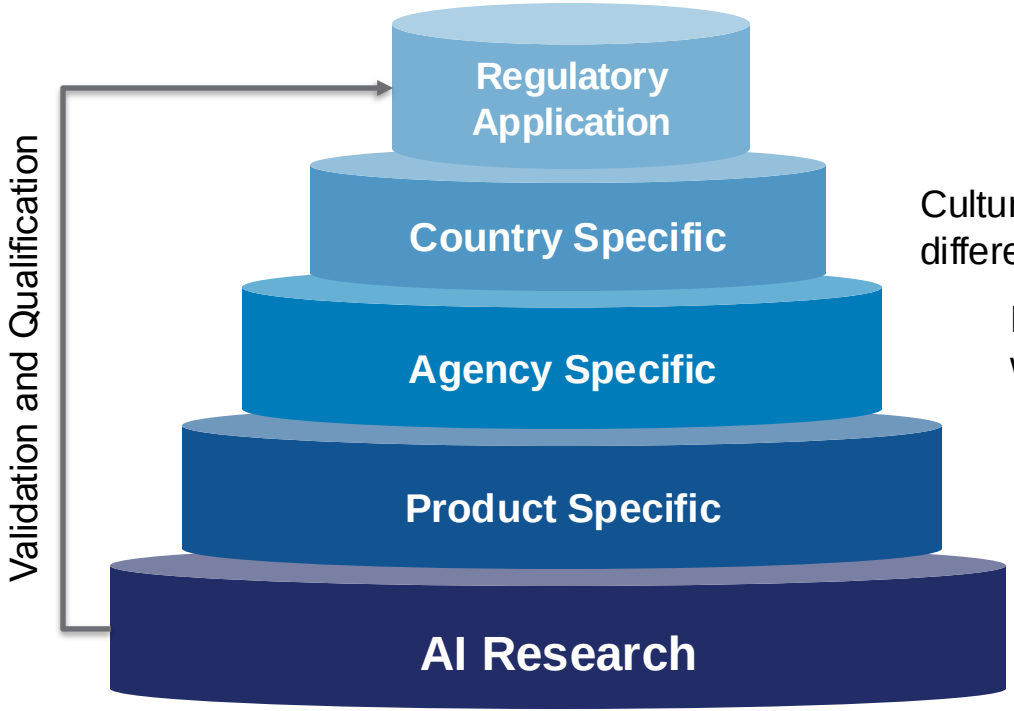
[FDA Releases Two Discussion Papers to Spur Conversation about Artificial Intelligence and Machine Learning in Drug Development and Manufacturing | FDA]

FDA AI Governance and Advisory Board (AIGA)

- On March 28, 2024, the Office of Management and Budget released M-24-10, "Advancing Governance, Innovation, and Risk Management for Agency Use of Artificial Intelligence", directing agencies to advance AI governance and innovation while managing risks from the use of artificial intelligence (AI) in the Federal Government, particularly in cases affecting the rights or safety of the public. The memo specifically directs applicable federal agencies (i.e., HHS) to designate a Chief Artificial Intelligence Officer (CAIO), establish a senior-level AI governance board, and implement processes to manage the risks from the use of AI.

- Ram Iyer is the FDA CAIO who is chairing the FDA AI Governance and Advisory Board (AIGA)
  - The purpose of the AI Governance and Advisory Board is to advance the safe, ethical, and effective deployment of artificial intelligence technologies at the Food and Drug Administration. The Board will provide guidance and make recommendations to FDA leadership on strategies, policies, and procedures related to AI adoption, implementation, and governance across the agency.

The Complex Nature of AI in the Regulatory Landscape



Cultural and regional differences drive different regulatory frameworks

Different agencies have different policies which usually governed by the law

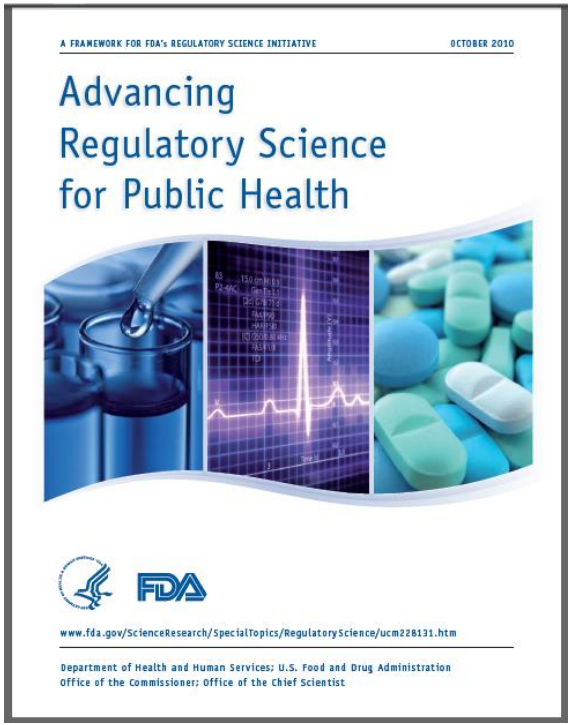
Not all products are created equal; some may require a more stringent policy for AI application

How do we translate AI research into regulatory application?

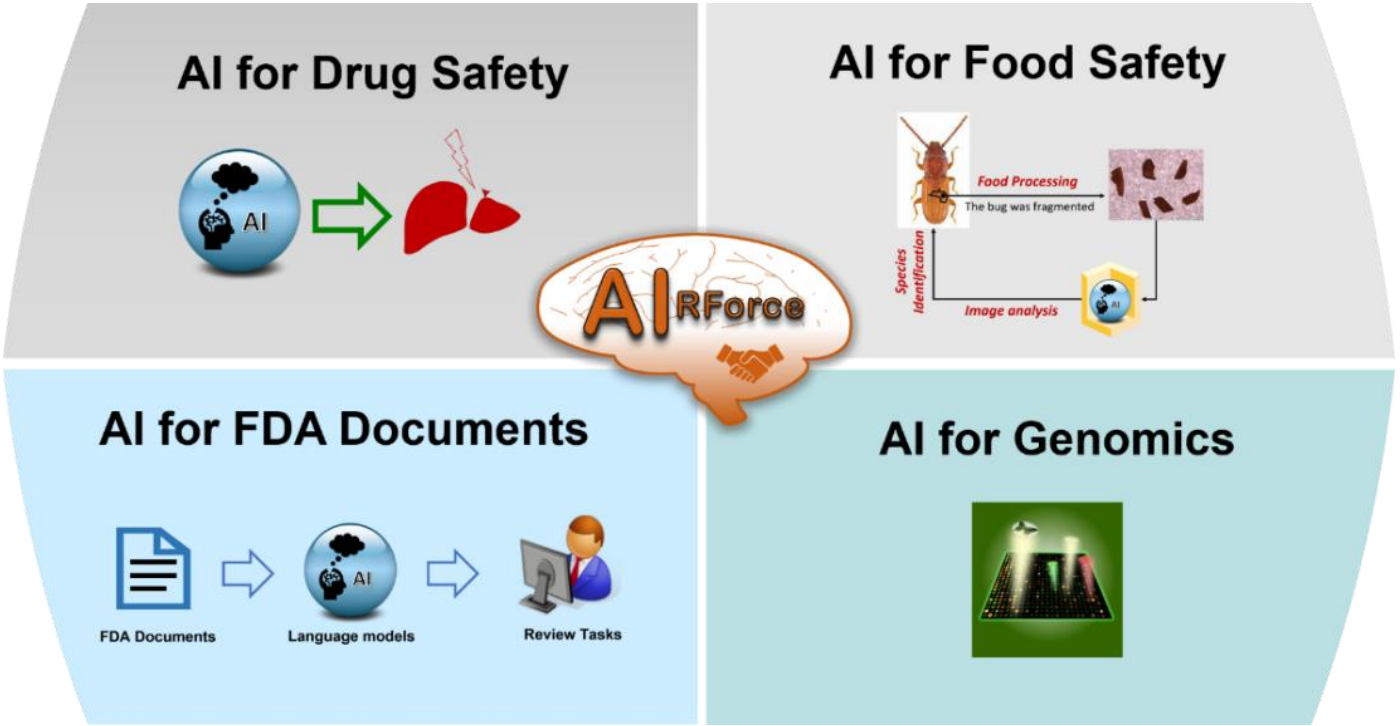
Challenges and Opportunities of AI for FDA

Q1: How to improve the Agency's operation through regulatory science research?

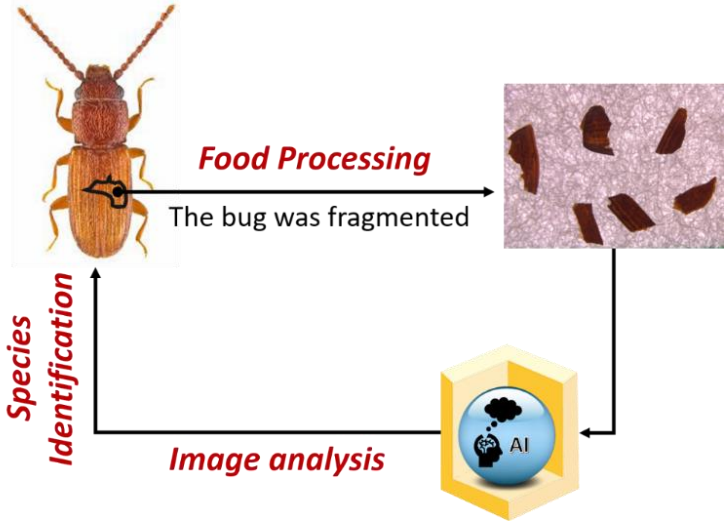
- *Regulatory science* is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.



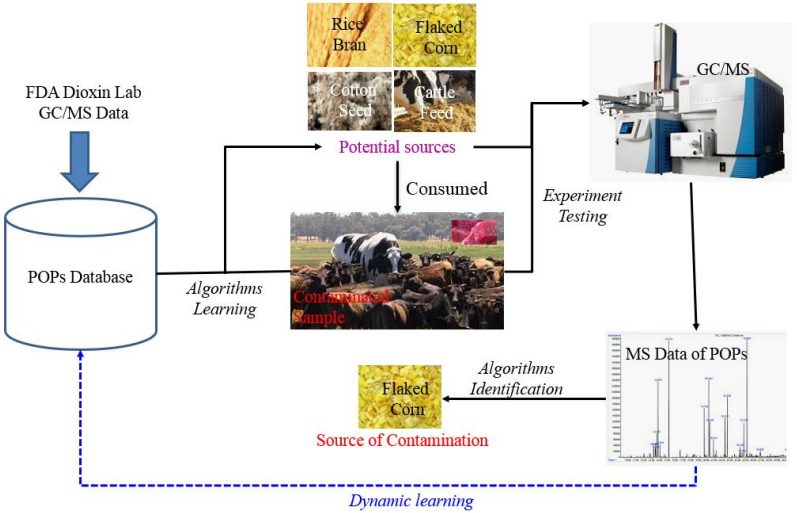
AI Projects at NCTR



AI for Food Safety (with ORA)



Species identification using image analysis with AI for storage pest fragments containing food products



Machine learning for automated pattern recognition of persistent organic pollutants in foods and feeds

FDA/NCTR AI Program for Toxicology (AI4TOX)

BERTox	LLMs for FDA documents to improve regulatory efficiency, enhance information retrieval, and maintain institutional memory at FDA
safetai	Predictive models for safety endpoints critical to drug safety review, particularly in IND Application review at CDER
Animal GAN	Virtual animals to generate animal study results with generative AI to advance 3Rs for animal use and digital twin
TransIAi	Generative AI models to translate experiment findings across different domains such as across organs, in vitro-to-in vivo (IVIVE), and between genomic technologies
PathologAI	AI-driven digital pathology for preclinical histopathology images

https://www.fda.gov/about-fda/nctr-research-focus-areas/artificial-intelligence

FDA-Industry Collaboration Mechanisms

Material/Data Transfer Agreement (MTA/DTA)

- A contractual agreement used to transfer (send, receive), define, and limit use of proprietary material or data for Recipient's non-commercial research use; may be one-way or two-way

Research Collaboration Agreement (RCA)

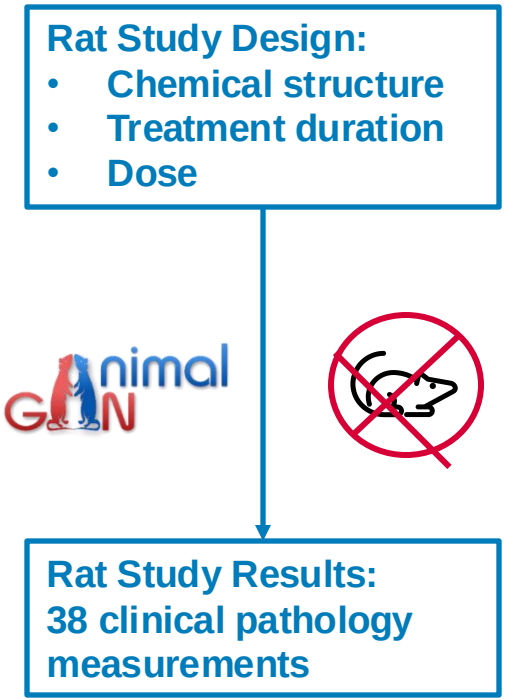
- A contractual agreement of limited scope and duration used to define terms and conditions for both Parties on a specific research project collaboration; also covers the transfer of Material(s) and confidential information; equal partners

Cooperative Research and Development Agreement (CRADA)

- A contractual agreement of limited scope and duration used to define terms and conditions for both Parties on a specific research project collaboration; also covers the transfer of Material and confidential information; equal partners
    - Allows for funding to FDA and/or
    - There is a reasonable risk of IP stemming from collaboration; offers license option for resulting inventions

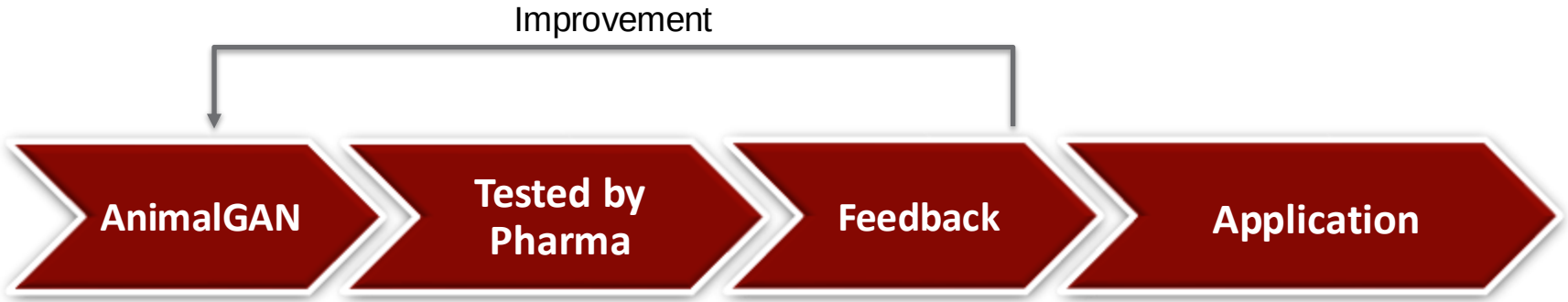
Virtual Animal models to Generate Animal Study Results with Generative AI

- **Why?** Animal studies assess safety of consumer products, but they are expensive and can pose ethical concerns. Can AI learn from past animal study data to generate animal study results of new untested compounds without using animals?
- **How? AnimalGAN** was developed using a Generative Adversarial Networks (GANs) framework (a DeepFake algorithm) to learn from the legacy animal data to produce new animal data *without using animals*.
- **Impact:** AnimalGAN can aid in assessing animal toxicity, potentially reducing or replacing animal testing in specific contexts.



Chen X., Liu Z., and Tong W. **A Generative Adversarial Network Model Alternative to Animal Studies for Clinical Pathology Assessment**. *Nature Communications*. 2023, 14:7141.

AnimalGAN – Evaluated in Drug Development in Collaboration with Pharma



Tested on proprietary compounds through various mechanisms:

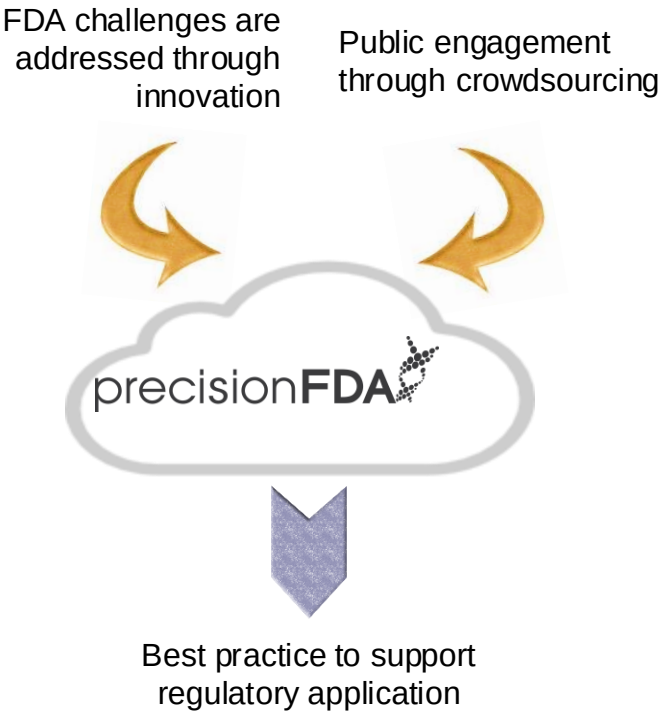
- RCA with AbbVie
- RCA with BI
- MTA with GSK

Potential applications:

- To support drug development
- To facilitate drug safety review at FDA

PrecisionFDA: Working with Public

- PrecisionFDA was initially established as a computational platform to support the FDA Precision Medicine Initiative.
- It has evolved to address the challenges associated with digital technologies such as AI/ML.
- FDA has launched 41 challenges with over 850 total challenge submissions.
- Currently, PrecisionFDA is conducting a **Democratizing and Demystifying AI challenge series** to explore and illustrate how AI can support FDA's mission.

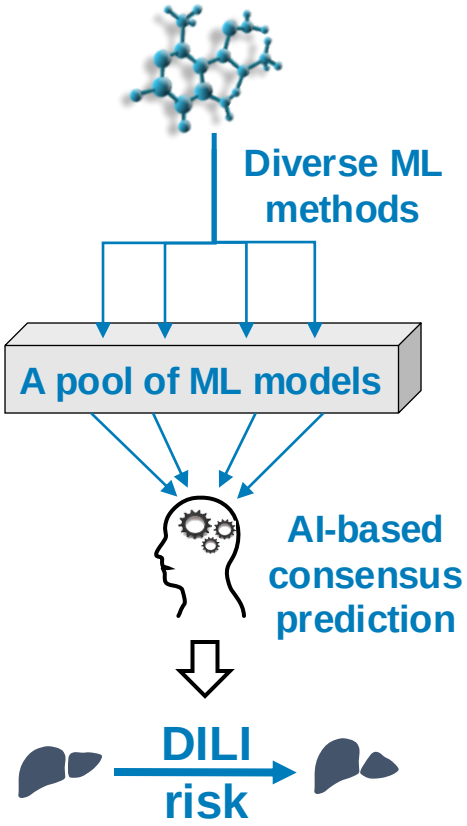


Initiative to Support Drug Review

Objective: To develop a set of AI models for safety endpoints critical to drug safety review, particularly in IND Application review with an *in-house deep learning algorithm*.

Ongoing projects: AI models for 5 toxicity endpoints

1. DeepDILI for liver toxicity (published)
2. DeepCarc for carcinogenicity (published)
3. DeepAmes for mutagenicity (published)
4. DeepCardio for cardiotoxicity (submitted)
5. DeepKidney for kidney toxicity (ongoing)



- Li T., Liu Z., Thakkar S., Roberts R., and Tong W., **DeepAmes: A Deep Learning-Powered Ames Test Predictive Model with Potential for Regulatory Application.** *Regulatory Toxicology and Pharmacology*. 2023, 144:105486.
- Li T., Tong W., Roberts R., et al. **DeepCarc: Deep Learning-Powered Carcinogenicity Prediction Using Model-Level Representation**. *Frontiers in Artificial Intelligence*. 2021, 4:757780.
- Li T., Tong W., Roberts R., et al. **DeepDILI: Deep Learning-Powered Drug-Induced Liver Injury Prediction Using Model-Level Representation**. *Chemical Research in Toxicology*. 2021, 34(2):550-565.

SafetAI – Evaluated with Regulatory Data in the RAPID Environment for Regulatory Application

AI innovative applications from all FDA centers (such as SafetAI)

CDER Innovation Board - consisting of representatives from all the FDA centers - reviews the application

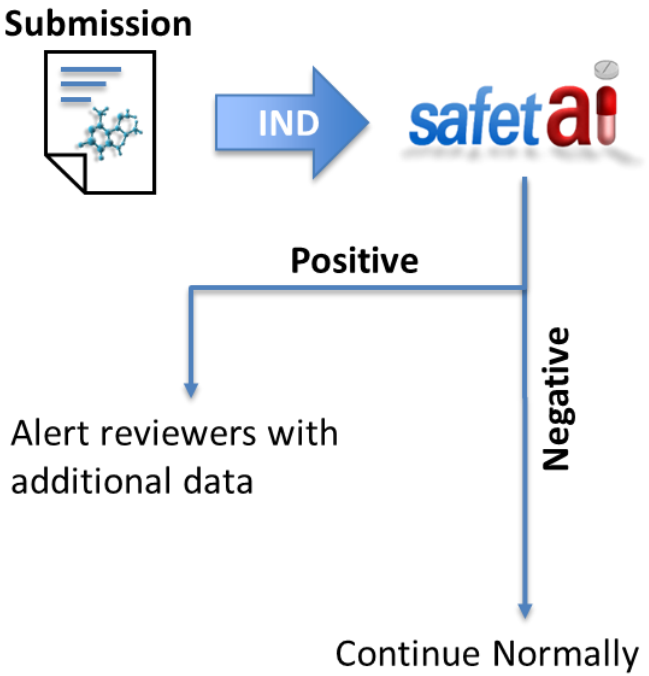
An IB-approved application is deployed in RAPID, a sandbox:

- RAPID stands for **R**eal World **A**pplication **P**latform for **I**nnovation and **D**evelopment
- It is managed by CDER with both IT and administrative support
- An AI algorithm can be tested on regulatory data to assess its value in FDA

FDA-wide implementation

Pilot in RAPID to Define Context-Of-Use

- **Objective:** Assist IND review of new drug candidates
- **Key considerations:**
  1. prediction accuracy,
  2. applicability domain, and
  3. prediction confidence
- **Additional consideration – Adaptability and life-cycle maintenance:** Should a model be treated as a static or evolving model over the new data?



FDA Innovative Science and Technology Approaches for New Drugs (ISTAND)

- To qualify Drug Development Tools (DDTs) that don't fit the definition of a biomarker and clinical outcome assessment, e.g.,
  - Computational approaches:
    1) Use of artificial intelligence (AI)-based algorithms to evaluate patients, develop novel endpoints, or inform study design and
    2) Use of novel digital health technologies (e.g., wearables) for patient assessment
  - Scientific tools and technologies that use human biology to predict human outcomes to help reduce and replace animal testing as part of drug development.
- Qualification is intended to provide a pathway for new nonanimal approaches to be integrated into drug development and regulatory decision-making.
- Once qualified, DDTs will be available to use in any drug development program for the qualified context of use. Additionally, the qualified DDT can generally be included in IND, NDA, or BLA applications without needing FDA to reconsider and reconfirm its suitability.

FDA's ISTAND Pilot Program accepts submission of organ-on-a-chip technology designed to predict DILI

- 24 September 2024 - CDER accepted the first letter of intent (LOI) into the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program for an organ-on-a-chip technology, a type of micro-physiological system (MPS), to study drug-induced liver injury (DILI) for certain drug candidates.

- This accepted LOI is for a human Liver-Chip drug development tool (DDT) used to assess the risk of DILI in adults to create relevant data for a drug's investigational new drug (IND) submission.


FDA U.S. FOOD & DRUG ADMINISTRATION
Women of CDER Artificial Intelligence Interest Group,
Data Science and Software Development Working Group
& Modeling and Simulation Working Group
present
Artificial Intelligence
for Regulatory Review
AIR 2024
NOV 12
8:30AM - 4:30PM EDT
NOV 13
8:20AM - 4:30PM EDT
In-person
Great Room (Bldg 31, Section A)
White Oak Conference Center
Silver Spring, MD
or
Join virtually
via Zoom [passcode: $V*2vh]
AIR Recognition Awards
presented by
Robert Califf, MD
Opening Remarks by
Namandjé N. Bumpus, MD
and Patrizia Cavazzoni, MD

Summary

- FDA is responsible for regulating a broad range of consumer products
- AI has diverse applications across centers depending on the regulated product
- The challenges and opportunities of AI at FDA are two-fold:
  - How to regulate a product containing AI
  - How to facilitate FDA's operation through regulatory science research with AI
- FDA has established several mechanisms to facilitate:
  - Collaboration with public and private sectors through the PrecisionFDA platform and bilateral collaborative mechanisms
  - Collaboration with regulatory divisions in the RAPID environment to evaluate AI innovation in regulatory applications
  - Collaboration with ISTAND to qualify AI innovation to support drug development and review


FDA
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