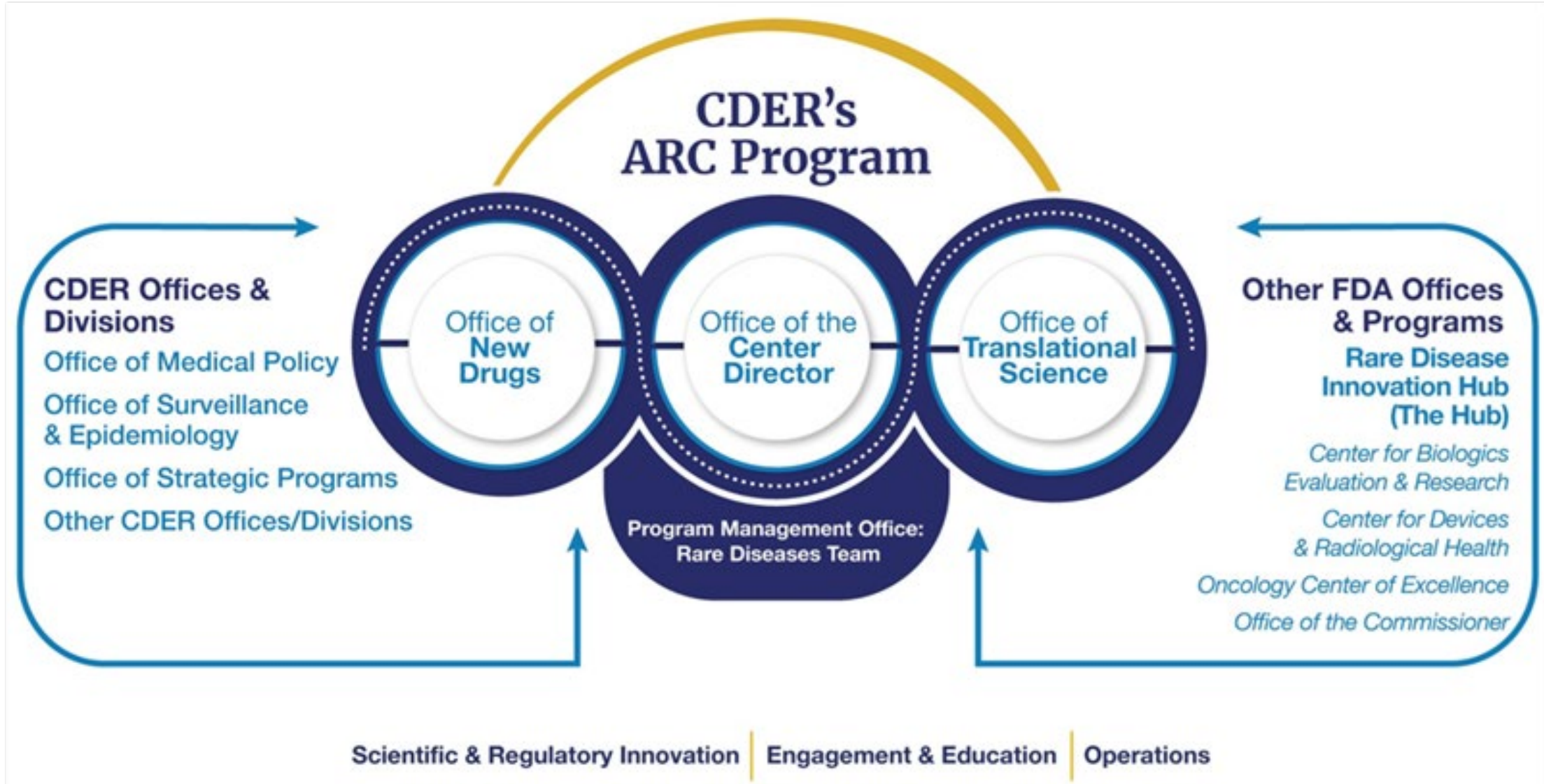
U.S. FOOD & DRUG ADMINISTRATION

LEADER 3D: Learning and Education to ADvance and Empower Rare Disease Drug Developers

Accelerating Rare disease Cures (ARC) Program

Andrea Bell-Vlasov, Ph.D.
Science Policy Analyst, CDER Rare Diseases Team

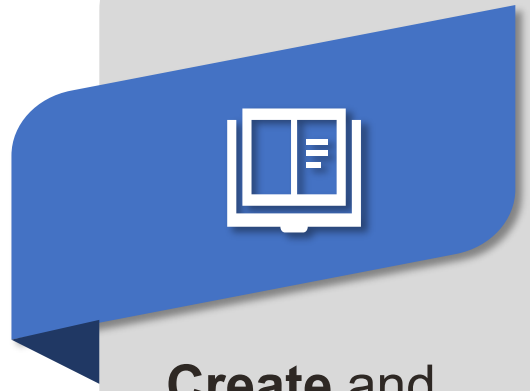
Accelerating Rare disease Cures (ARC) Program



What is LEADER 3D?

CDER seeks input from stakeholders who **design or conduct** rare disease drug development programs

Identify **knowledge gaps** for stakeholders about the regulatory process of rare disease drug development



Create and **expand** educational resources for stakeholders

LEADER 3D Educational Content

LEADER 3D Public Report

Public report summarizing landscape assessment/ feedback from rare disease drug developers

Six Case Studies and User Guide

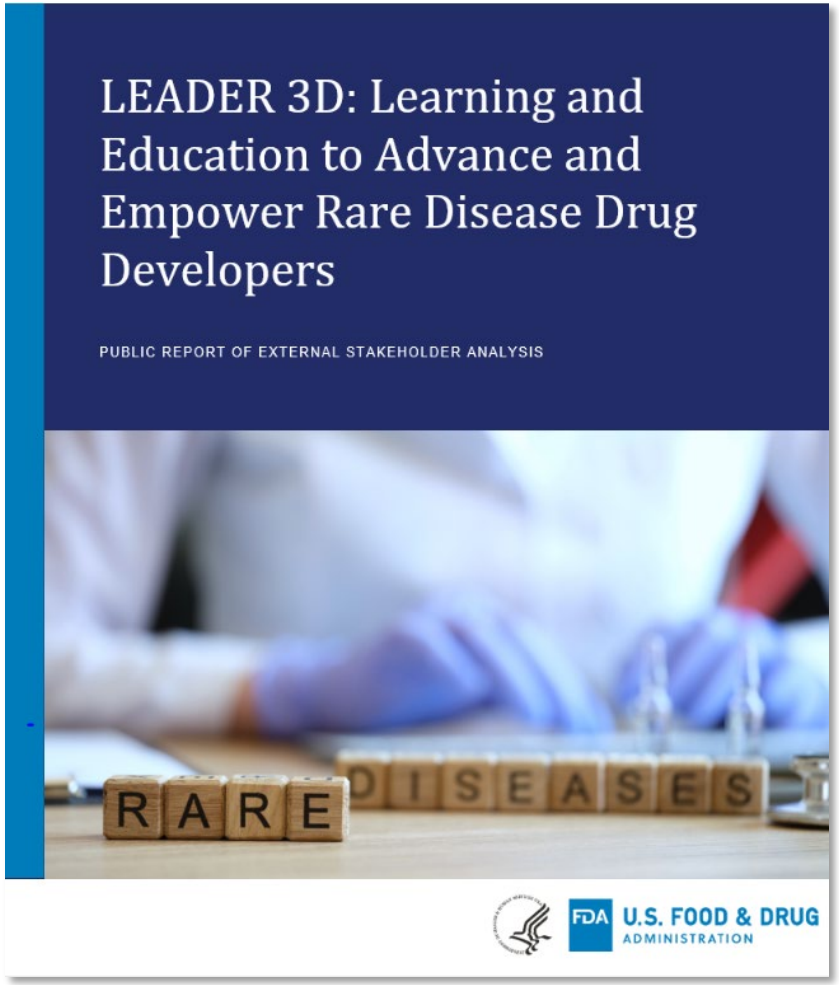
Based on topics of interest highlighted by rare disease drug developers in the LEADER 3D public report

3 Foundational Videos

Based on topics of interested highlighted in the LEADER 3D public report

LEADER 3D: Public Report

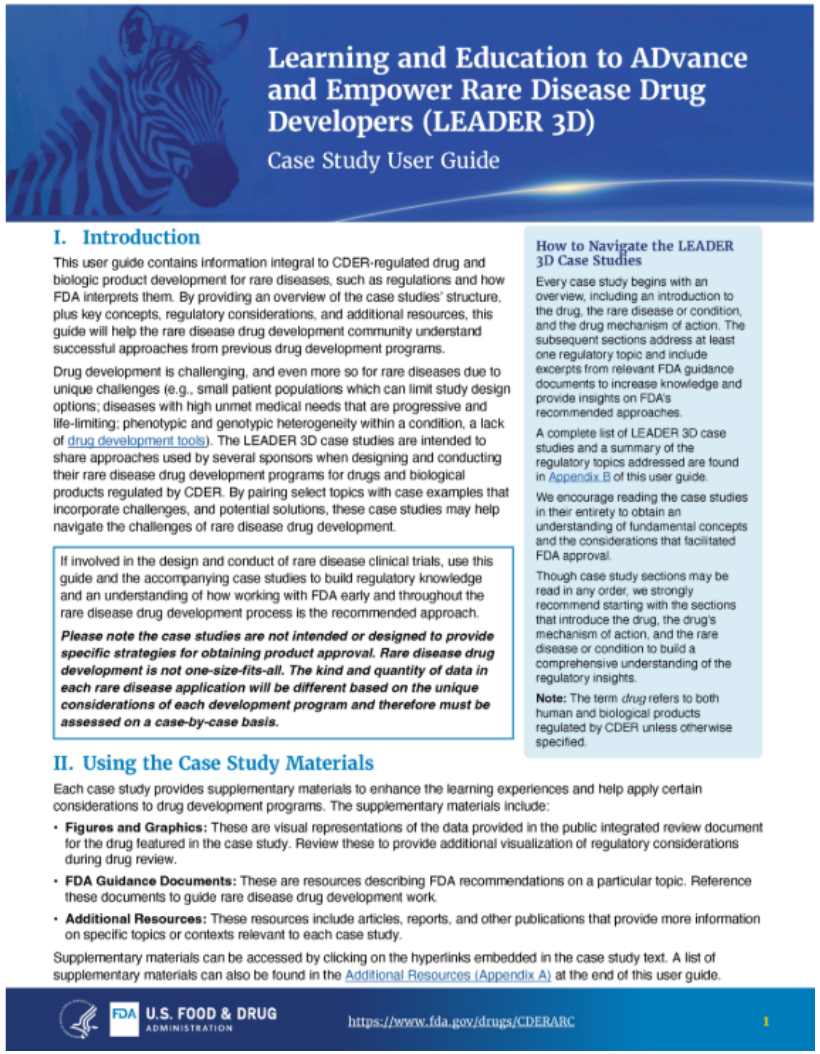
- Topics analyzed from feedback included:
  - Nonclinical studies
  - Dose-Finding
  - Natural History Studies and Registries
  - Novel Endpoint and Biomarker Development
  - Clinical Trial Design and Analysis
  - Rare Disease Drug Development Regulatory Considerations



LEADER 3D Case Studies

- Case study topics include but are not limited to:
  - Development of a novel clinical outcome assessment
  - Leveraging external controls, surrogate endpoints, biomarkers, in a rare disease clinical investigation
  - Example of a clinical dose escalation strategy
  - Example of a single adequate and well-controlled clinical trial with confirmatory evidence

Case Study User Guide



Learning and Education to ADvance and Empower Rare Disease Drug Developers (LEADER 3D)

Case Study User Guide

I. Introduction

This user guide contains information integral to CDER-regulated drug and biologic product development for rare diseases, such as regulations and how FDA interprets them. By providing an overview of the case studies' structure, plus key concepts, regulatory considerations, and additional resources, this guide will help the rare disease drug development community understand successful approaches from previous drug development programs.

Drug development is challenging, and even more so for rare diseases due to unique challenges (e.g., small patient populations which can limit study design options; diseases with high unmet medical needs that are progressive and life-limiting; phenotypic and genotypic heterogeneity within a condition, a lack of drug development tools). The LEADER 3D case studies are intended to share approaches used by several sponsors when designing and conducting their rare disease drug development programs for drugs and biological products regulated by CDER. By pairing select topics with case examples that incorporate challenges, and potential solutions, these case studies may help navigate the challenges of rare disease drug development.

If involved in the design and conduct of rare disease clinical trials, use this guide and the accompanying case studies to build regulatory knowledge and an understanding of how working with FDA early and throughout the rare disease drug development process is the recommended approach.

Please note the case studies are not intended or designed to provide specific strategies for obtaining product approval. Rare disease drug development is not one-size-fits-all. The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and therefore must be assessed on a case-by-case basis.

How to Navigate the LEADER 3D Case Studies

Every case study begins with an overview, including an introduction to the drug, the rare disease or condition, and the drug mechanism of action. The subsequent sections address at least one regulatory topic and include excerpts from relevant FDA guidance documents to increase knowledge and provide insights on FDA's recommended approaches.

A complete list of LEADER 3D case studies and a summary of the regulatory topics addressed are found in Appendix B of this user guide.

We encourage reading the case studies in their entirety to obtain an understanding of fundamental concepts and the considerations that facilitated FDA approval.

Though case study sections may be read in any order, we strongly recommend starting with the sections that introduce the drug, the drug's mechanism of action, and the rare disease or condition to build a comprehensive understanding of the regulatory insights.

Note: The term *drug* refers to both human and biological products regulated by CDER unless otherwise specified.

II. Using the Case Study Materials

Each case study provides supplementary materials to enhance the learning experiences and help apply certain considerations to drug development programs. The supplementary materials include:

- **Figures and Graphics:** These are visual representations of the data provided in the public integrated review document for the drug featured in the case study. Review these to provide additional visualization of regulatory considerations during drug review.
- **FDA Guidance Documents:** These are resources describing FDA recommendations on a particular topic. Reference these documents to guide rare disease drug development work.
- **Additional Resources:** These resources include articles, reports, and other publications that provide more information on specific topics or contexts relevant to each case study.

Supplementary materials can be accessed by clicking on the hyperlinks embedded in the case study text. A list of supplementary materials can also be found in the Additional Resources (Appendix A) at the end of this user guide.

- **<u>Disclaimer:</u>** *Case studies are not intended or designed to provide specific strategies for obtaining product approval. Rare disease drug development is not one-size-fits-all. The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and therefore must be assessed on a case-by-case basis.*

Read Case Study User Guide First

Anatomy of the Case Studies

Fosdenopterin (Nulibry)

Use of a Single Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence to Demonstrate Substantial Evidence of Effectiveness for a Rare Disease

Prior to reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. Please note this case study is not intended or designed to provide specific strategies for obtaining product approval. **Rare disease drug development is not one-size-fits-all.** The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

Introduction

This case study discusses the demonstration of substantial evidence of effectiveness for the U.S. Food and Drug Administration's (FDA) approval of fosdenopterin (Nulibry). For further details on this case study, please refer to the Integrated Review.

Fosdenopterin is a substrate replacement therapy for cyclic pyranopterin monophosphate (cPMP). It is used to treat molybdenum cofactor deficiency (MoCD) Type A—a rare, life-threatening, autosomal recessive disease. Most children with MoCD succumb to the disease within the first years of life (median survival at 36 months).

For all drugs approved in the U.S., Section 505(d) of the Federal Food, Drug and Cosmetic (FD&C) Act (21 U.S.C. § 355(d), states that a drug's effectiveness must be established by substantial evidence. The statute defines substantial evidence as "evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." Reflecting the importance of independent substantiation of experimental results, FDA generally requires two adequate and well-controlled investigations, each convincing on its own, to establish effectiveness.[1] However, the law also states, "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled investigation and confirmatory evidence are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence."[2] Although the topic of establishing safety is not discussed in this case study, please note that FDA approval is not solely based on demonstration of substantial evidence of effectiveness but also on a determination that a drug is safe for its intended use, among other things.

FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of draft FDA guidance documents which, when final, will represent the Agency's current thinking on topics within the case study. For up-to-date guidance documents, please search Guidance Documents for Rare Disease Drug Development | FDA.

In this case study, the Applicant engaged with the FDA early in planning for their new drug application. Meeting with the FDA early in the drug development process is crucial so that potential issues may be addressed prior to pivotal clinical studies.

Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry* (September 2023)

When a meeting is needed, a written request must be submitted to the FDA via the electronic gateway, or to CDER via the CDER NextGen Portal, as applicable. Requests should be addressed to the appropriate center and review division or office, and if previously assigned, submitted to the relevant application (e.g., investigational new drug application [IND], new drug application [NDA], biologics license application [BLA]).

If necessary, noncommercial IND holders may also submit the meeting request via the appropriate center's document room.

[1] For further information regarding characteristics of adequate and well-controlled investigations, see 21 CFR 314.126.

[2] See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

Fosdenopterin (Nulibry)

In this case study, to demonstrate substantial evidence of effectiveness for fosdenopterin, the Applicant engaged with the Agency early in planning for their New Drug Application submission to discuss (1) the study design and analysis plan for their one adequate and well-controlled clinical investigation and (2) the types of confirmatory evidence that would be submitted to establish substantial evidence of effectiveness.

The single adequate and well-controlled clinical investigation is an analysis of data pooled from a cohort of 13 treated participants drawn from 2 clinical trials and a retrospective non-interventional (observational) study compared to an external control consisting of 18 genotype-matched untreated participants from a retrospective natural history study (NHS).

The two types of confirmatory evidence included (a) pharmacodynamic (PD) evidence and (b) evidence from a relevant animal model.

Introduction to the Rare Condition

MoCD Type A is a rare (1 in 200,000) and rapidly progressive, life-threatening disease with an autosomal recessive pattern of inheritance. MoCD typically presents acutely in the neonatal period or early infancy and is characterized by intractable seizures, metabolic acidosis, failure to thrive, feeding difficulties, and axial hypotonia with limb hypertonia. The estimated U.S. prevalence of MoCD Type A is 45 to 54 patients, all under 10 years of age.

Variants in the molybdenum cofactor synthesis 1 (MOCS1) gene lead to a deficiency of cyclic pyranopterin monophosphate (cPMP), which is necessary for the synthesis of molybdenum cofactor (Figure 1.A).

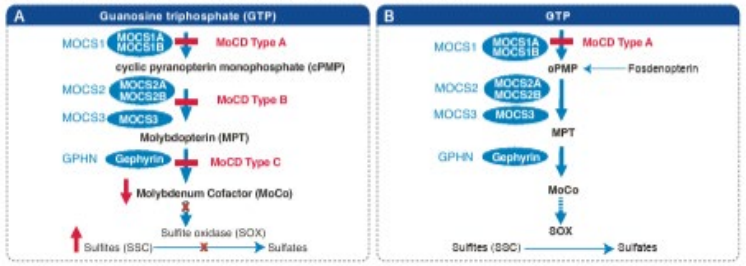
FDA Guidance Corner

Guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023)

Many rare diseases are serious conditions with no approved treatments, leaving substantial unmet medical needs for patients. FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses even within a condition.

Further complexity is added depending on what is known about a disease's natural history and pathophysiology. **As such, no one program can be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.**

Figure 1: (A) *Molybdenum cofactor (MoCo) biosynthetic pathway. MoCo is synthesized from Guanosine triphosphate (GTP). The schematic shows the enzymes (in blue circles) and their respective genes MOCS1, MOCS2, MOCS3, and GPHN that are involved in each step of the MoCo biosynthetic pathway. The three different types of diseases associated with MoCD (Types A, B, and C) and their respective genetic alterations (red boxes) are also indicated in the pathway.* ***(B)*** *MOA of fosdenopterin. Fosdenopterin replaces the deficient cPMP caused by variants in the MOCS1 gene (MoCD Type A), thereby restoring MoCo biosynthesis and SOX activity in converting toxic sulfites to sulfates.*



Fosdenopterin (Nulibry)

Conclusion

For approval of a marketing application, the FDA requires establishing substantial evidence of effectiveness for the drug, among other requirements.

The effectiveness of fosdenopterin for treating MoCD Type A was established based on the survival benefit observed in one adequate and well-controlled clinical investigation and was supported by additional confirmatory evidence. The confirmatory evidence came from:

1. Extensive, longitudinal sampling of urinary SSC, a human PD biomarker and;
2. Supportive PD data from a knockout animal model of MoCD showing improved survival and a reduction of plasma and brain SSC levels when treated with fosdenopterin (Figure 2).

Despite the limited number of study participants, the Applicant was able to meet FDA's standard for substantial evidence of effectiveness for fosdenopterin in the treatment of MoCD Type A using data from one adequate and well-controlled investigation and confirmatory evidence.

Critical Thinking Questions for a Rare Disease Drug Development Program

Will the Development Plan Establish Substantial Evidence of Effectiveness?

Rare disease drug developers should discuss the rationale for their proposed approach to demonstrate substantial evidence of effectiveness with FDA early in the development of their therapy. When planning for and designing a clinical investigation(s) for a rare disease medical product, we encourage consideration of the following questions:

1. **What is the development plan to demonstrate substantial evidence of effectiveness?**
   - If the plan does not include two adequate and well-controlled clinical investigations, what is the scientific justification for the proposed development approach?
2. **When planning to use a one adequate and well-controlled clinical investigation plus confirmatory evidence approach, consider the following questions:**
   - What is the plan for designing an adequate and well-controlled investigation?
   - Is a clinically meaningful endpoint(s) being measured? How reliable and objective is the endpoint(s)?
   - Will a biomarker be utilized?
   - What type of control group is being considered in the clinical investigation?
   - What is the anticipated treatment effect of the medical product?

   Please note that the quantity of confirmatory evidence may be impacted by the design and results of the one adequate and well-controlled clinical investigation.
3. **What is the description of the confirmatory evidence? (Prior to initiating clinical investigations, consider the following questions that pertain to confirmatory evidence):**
   - Is there an available animal model for the rare disease?
   - Is there a biomarker in animals that reliably predicts response to treatment in humans?
   - Are the methods of analysis analytically validated?

We recommend speaking to the Agency to reach alignment regarding the design of the one adequate and well-controlled clinical investigation and related confirmatory evidence.

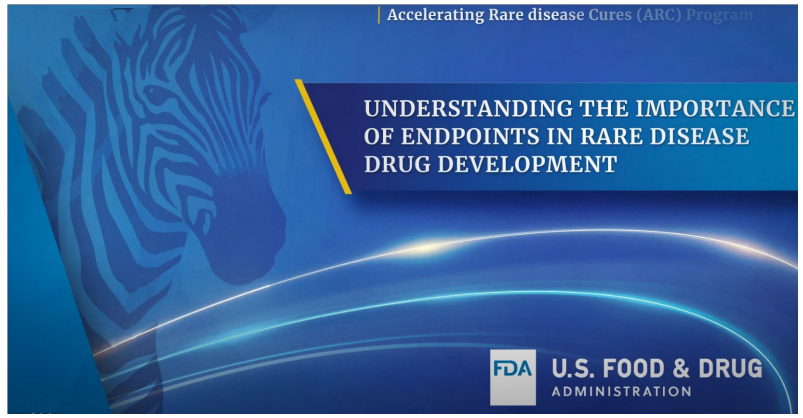
Key Takeaways

- There are circumstances when it might be appropriate for sponsors to use data from an established animal model or pharmacodynamic/mechanistic data as confirmatory evidence to support substantial evidence of effectiveness.
- If contemplating using confirmatory evidence to support an FDA application, please talk with the FDA early in the drug development process. For information on how to interact with the FDA, please read the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023).
- For recommendations regarding confirmatory evidence, read the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023).

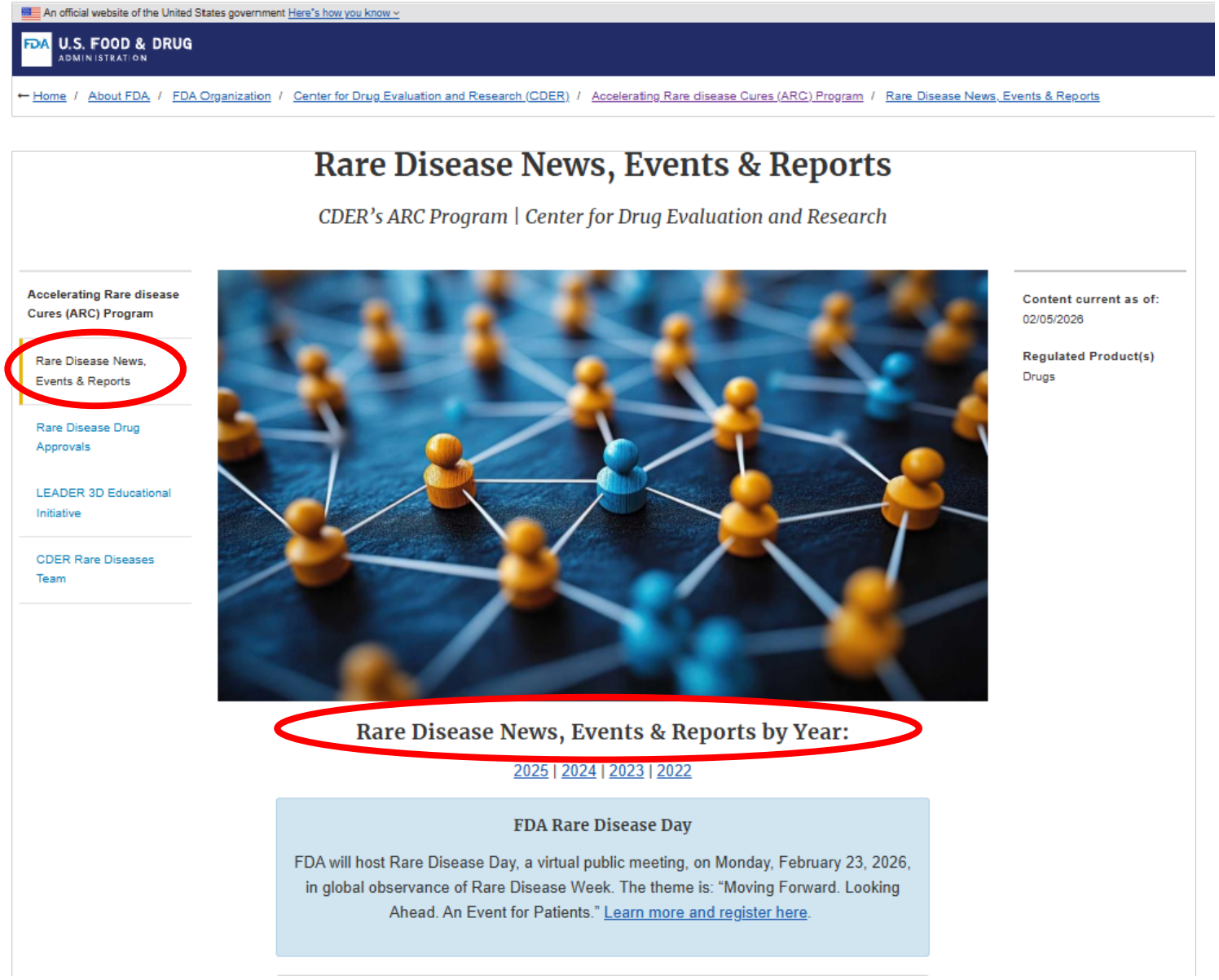
When final, these guidance documents will represent the Agency's current thinking.

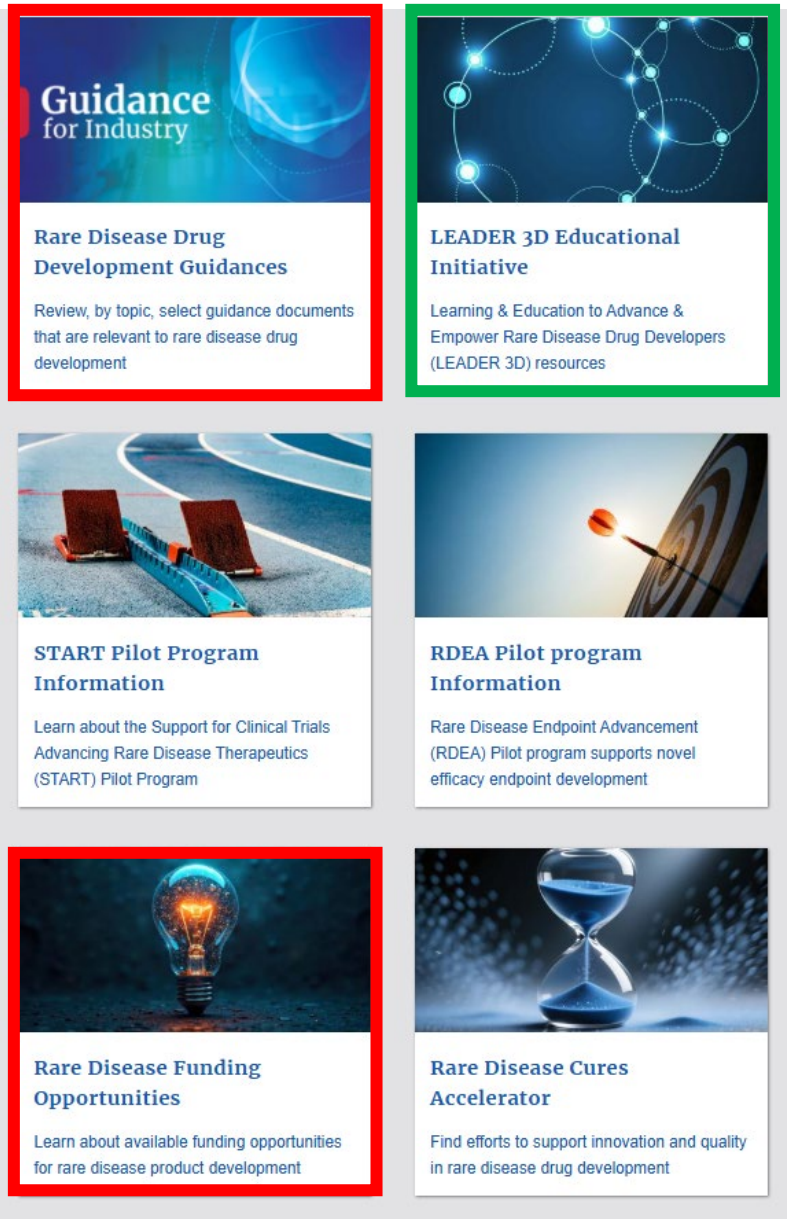
Educational Videos

- Clinical study design considerations for rare disease clinical trials
- Importance of endpoints in rare disease drug development
- Considerations for the use of natural history data in rare disease clinical trials

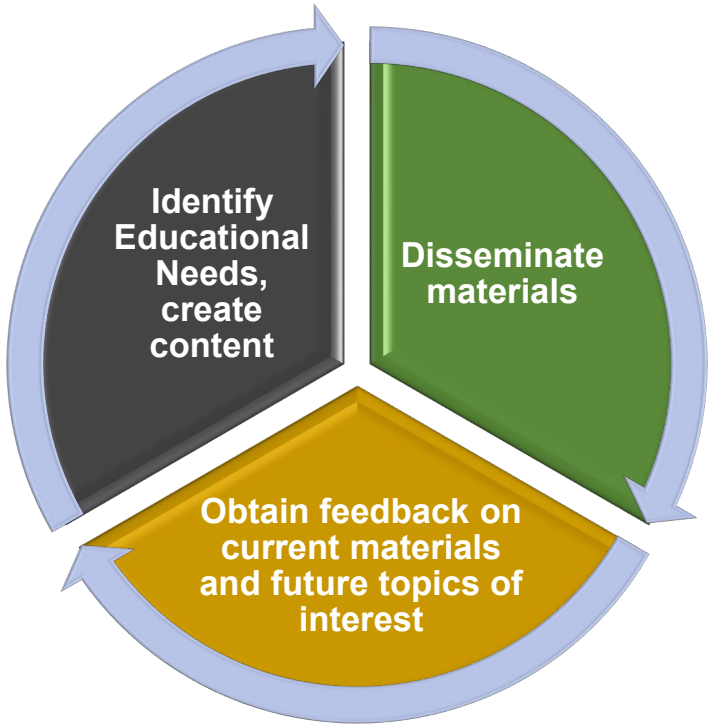


ARC Website: Available Resources for Rare Disease Drug Development





LEADER 3D Requires an Iterative Process



Go to **Regulations.gov** and enter: FDA-2026-N-1584

OTHER

Opportunity for Public Comment on Rare Disease Educational Materials from the Center for Drug Evaluation and Research's Accelerating Rare disease Cures Program and the Rare Disease Innovation Hub

Posted by the **Food and Drug Administration** on Feb 11, 2026

Docket (FDA-2026-N-1584) / Document

Comment Period Ends: **Apr 3, 2026 at 11:59 PM EDT**

https://www.regulations.gov/document/FDA-2026-N-1584-0001

LEADER 3D Website

- LEADER 3D Website: https://www.fda.gov/about-fda/accelerating-rare-disease-cures-arc-program/learning-and-education-advance-and-empower-rare-disease-drug-developers-leader-3d

LEADER 3D Initiative

Find educational resources for rare disease drug development

ARC Website and Newsletter

- https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program

- https://public.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_757

The Purpose = The Patients

U.S. FOOD & DRUG ADMINISTRATION

Building on Patients and Caregivers Input:

Perspectives on Safety Considerations and Early Enrollment into Cell and Gene Therapy Clinical Trials for Rare Diseases

Najat Bouchkouj, MD

Associate Director for Pediatrics

Office of Therapeutic Products, CBER

Approved Gene Therapies: Almost all for Rare Diseases

2017	2018	2019	2020	2021	2022	2023	2024	2025
Kymriah		Zolgensma	Tecartus	Breyanzi	Carvykti	Vyjuvek	Lenmeldy	Encelto
Yescarta				Abecma	Zynteglo	Elevidys	Beqvez	Zevaskyn
Luxturna					Skysona	Roctavian	Tecelra	Papzimeos
					Hemgenix	Lyfgenia	Aucatzyl	Itvisma
					Adstiladrin	Casgevy	Kebilidi	Waskyra

Patient Engagement Initiatives: PDUFA* VII

FDA's commitment:

- Enhance patient engagement in cell and gene therapy (CGT) development

2024 CBER Patient and Care Partner Listening Meetings

- **Safety Considerations for Approved CGT**
  - Decision-making factors | Long-term studies & registries
- **Early Enrollment into CGT Clinical Trials**
  - Pre-symptomatic and early-stage disease (children & adults)

2024 CBER Patient and Care Partner Listening Meetings | FDA

🎯 **Key objectives:**

- Understand patient perspectives on safety and risk tolerance
- Inform patient-centered trial design and regulatory approaches
- Enhance patient-focused drug development efforts

**PDUFA: Prescription Drug User Fee Act*

What We Heard: Patient & Care Partner Priorities

- **Efficacy/Safety & Decision-Making:**
  - Transparent risk information in plain language
  - Long-term efficacy data and impact on future treatment options
  - Quality of life outcomes, not just data on toxicity
- **Early Enrollment:**
  - Strong support - Majority of patients/caregivers willing to accept risks
  - Early intervention may prevent irreversible damage
  - Need for surrogate endpoints and adaptive trial designs
- **Long-Term Follow-Up:**
  - **Barriers:** Travel, costs, time burden, data uncertainty
  - **Solutions:** Telehealth, local labs, mobile apps, real-time data sharing, registries

Value of Patient Voice:
Critical Partnership Throughout Product Lifecycle

🤝 Community Engagement

- Over one-third of participants referred through advocacy networks

📢 Information Translation

- Patient organizations: Important source for treatment information

🔬 Regulatory Science Contributions

- Early trial design input, patient-centered endpoints

📊 Data Infrastructure

- Disease registries, long-term follow-up facilitation

Translating Patient Input into Regulatory Action

- Integrating patient and care partner perspectives into regulatory science to accelerate safe, effective CGT
- FDA's commitment to patient-centered regulatory framework for CGT throughout the entire product lifecycle from clinical trial design to long-term postmarket surveillance

Postapproval Methods to Capture Safety and Efficacy Data for Cell and Gene Therapy Products | FDA

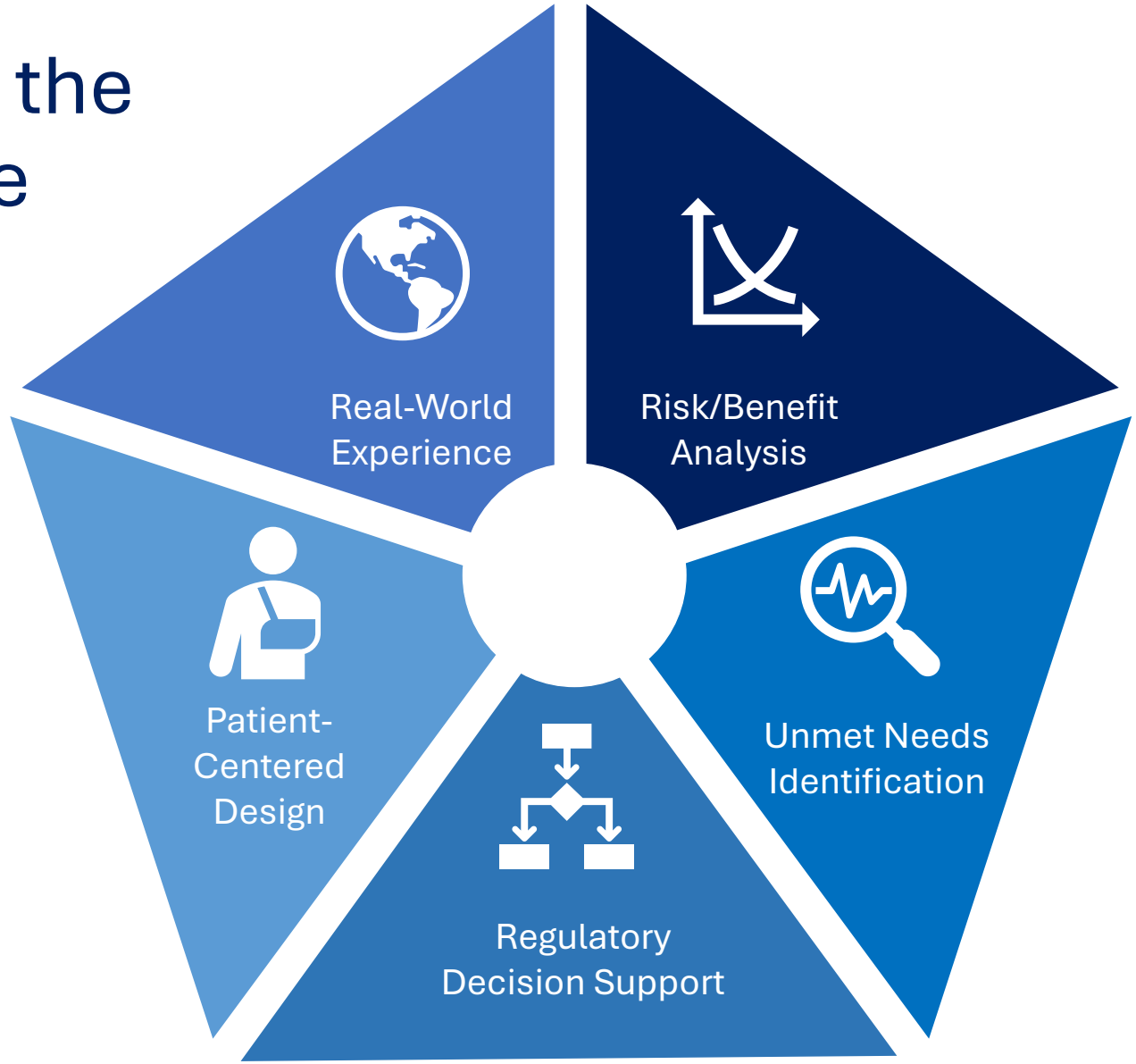
U.S. FOOD & DRUG ADMINISTRATION

The role of digital health tools in accelerating and decentralizing clinical trials for devices

Cynthia Grossman, Ph.D.
Director, Division of Patient-Centered Development, CDRH

Patients are at the Heart of All We Do

The value of the patient voice



Devices Support People Living with Rare Diseases

Assistive respiratory and mobility devices such as wheelchairs and ventilators

Newborn screening tests

Treatment devices for inherited arrhythmia syndromes & hepatocellular carcinoma

Tests to aid in diagnosing and selecting patients for therapeutic treatment

CDRH Programs

Assure patients have safe, effective, and high-quality medical devices

Foster innovation and ensure patient safety from device concept to retirement

Collaboration and Engagement

Breakthrough devices program

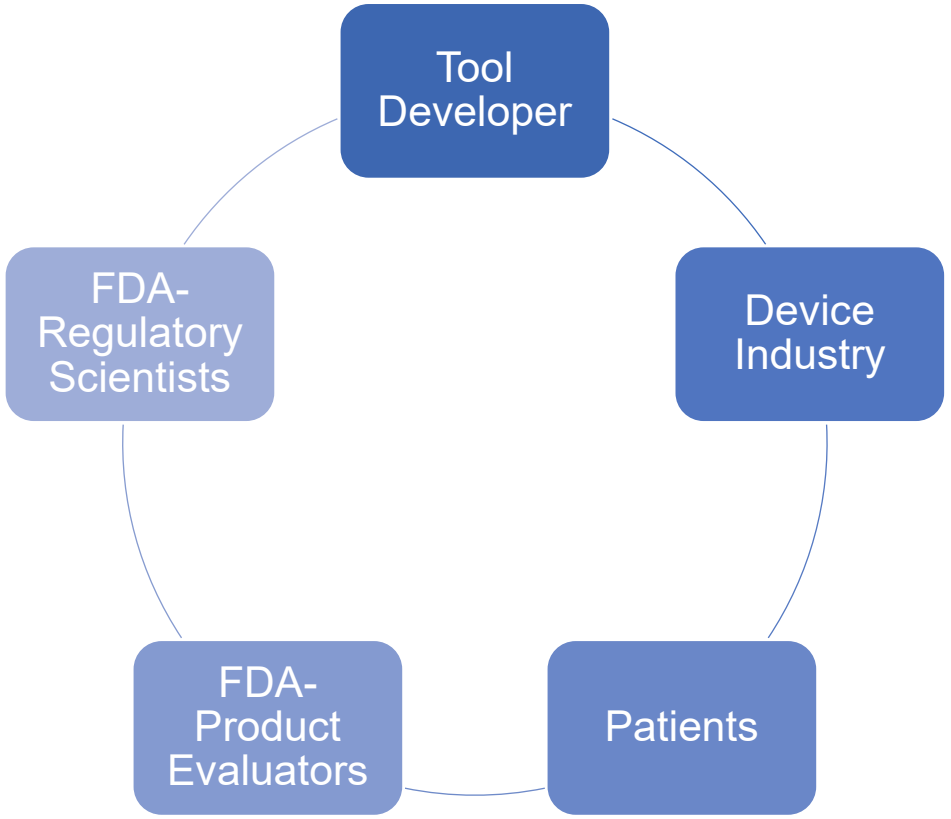
Humanitarian use device program

Patient and Caregiver Connection

Rare disease patients, caregivers, and other professional experts directly and compliantly engage in CDRH activities

Medical Device Development Tool Program (MDDT)

Promotes Efficient Medical Device Development



Benefit of Qualifying Tools

- Fosters innovation
- Encourages collaboration
- Helps reduce resource expenditure
- Can apply in multiple device submissions
- Promotes efficiency in CDRH regulatory review resources
- Minimizes uncertainty in regulatory review process for industry

Patient-Generated Health Data

Patient-Generated Health Data (PGHD)

health-related data that are **created**, **recorded**, or **gathered** by or from patients or caregivers **outside** of the clinical setting

PGHD | *Sources*

- Mobile Applications
- Wearable & Remote Monitoring Devices
- Online Social & Health Communities
- Patient-Driven Registries

WORKSHOP | VIRTUAL

Co-sponsored Public Workshop – Using Patient-Generated Health Data in Medical Device Development: Case Examples of Implementation Throughout the Total Product Life Cycle

JUNE 26 - 27, 2024

Session II: From Rarity to Clarity: PGHD's Role in Rare Diseases

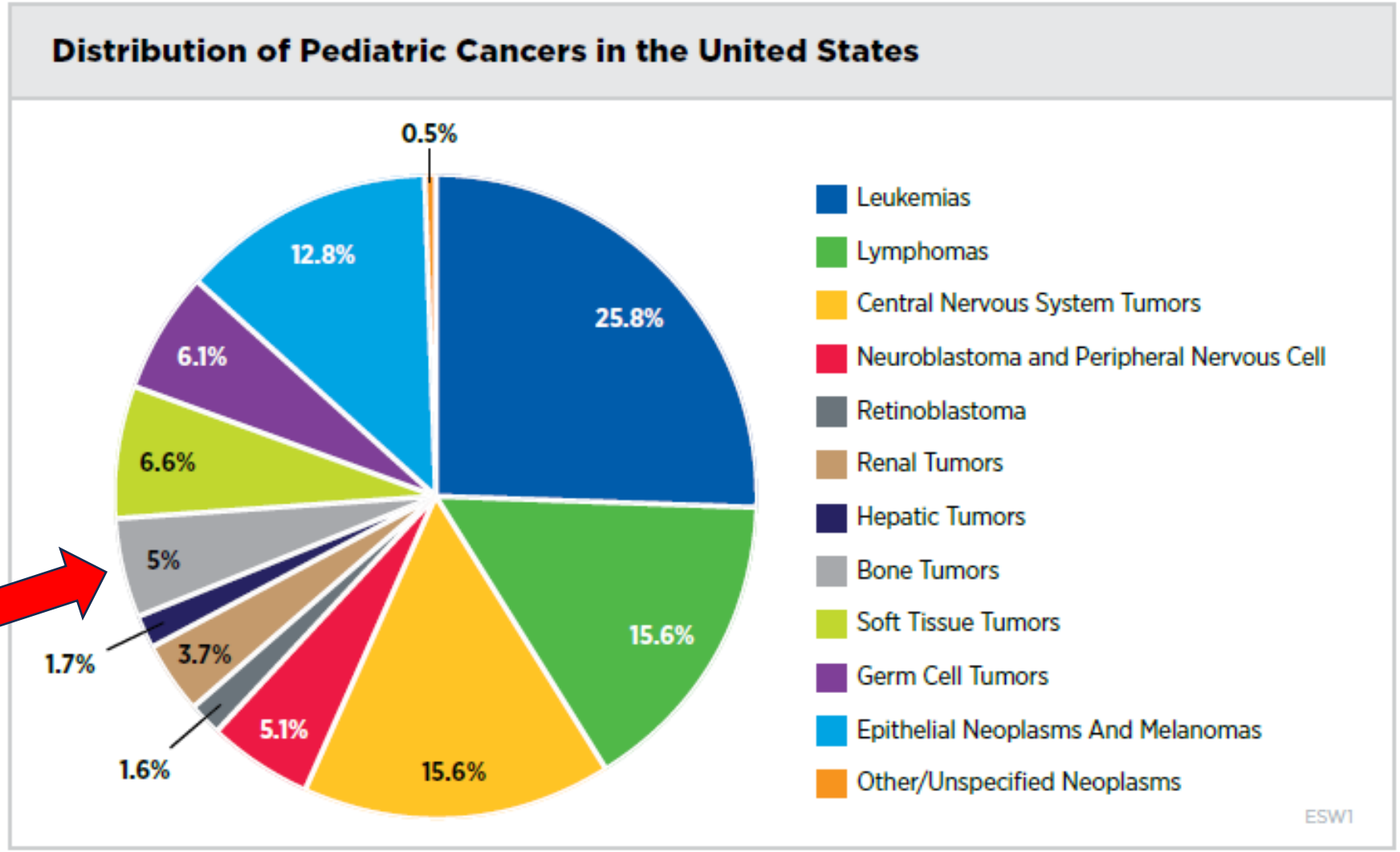
U.S. FOOD & DRUG ADMINISTRATION

FDA/Osteosarcoma Institute (OSI) Workshop: Advancing Osteosarcoma Drug Development – Connecting Research and Regulatory Pathways for Improved Outcomes

Kristin Wessel, MD
Medical Officer, Division of Oncology 2
Office of Oncologic Diseases, Office of New Drugs, CDER

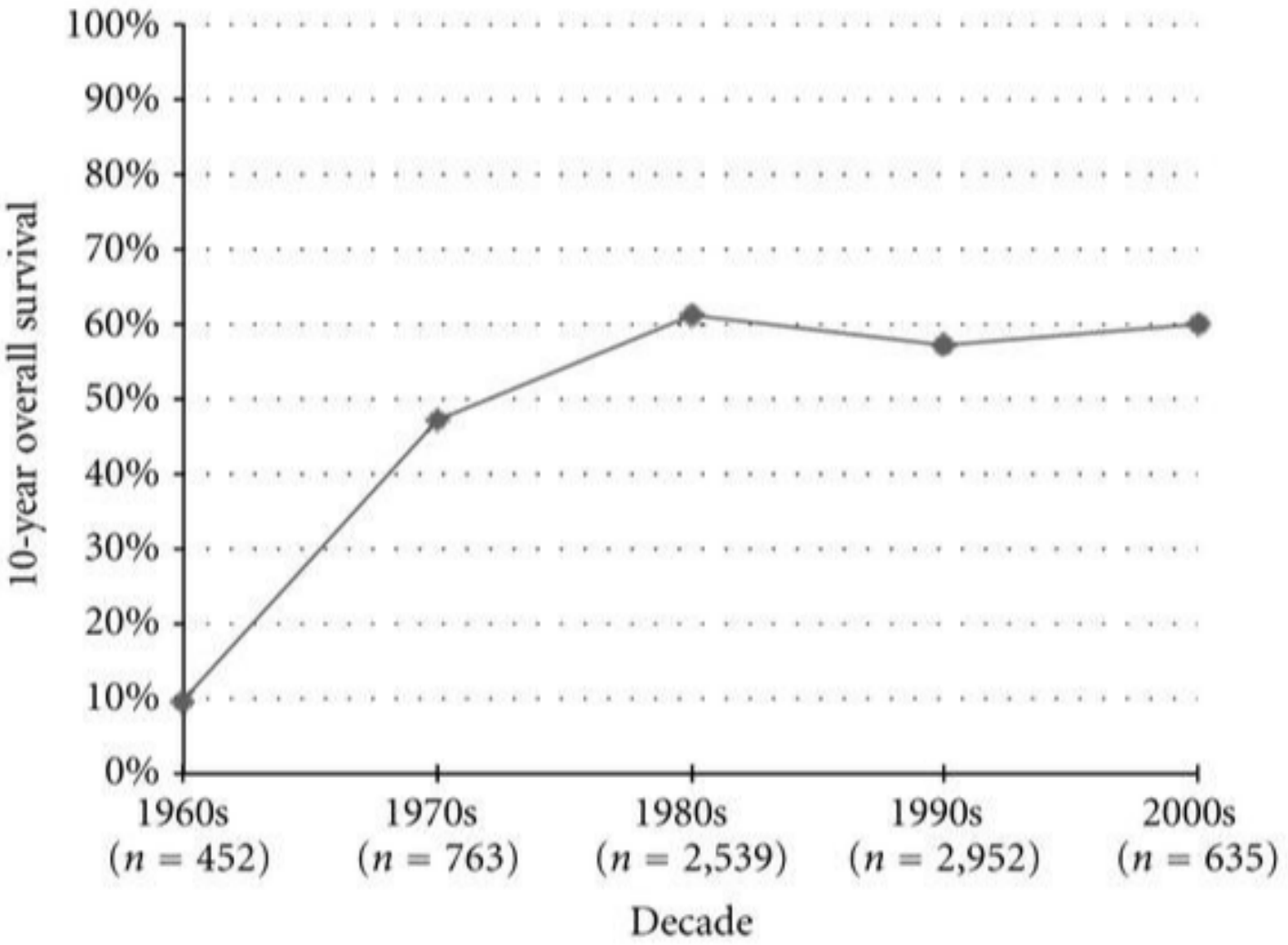
Osteosarcoma: A rare cancer with unmet need

No drugs approved by FDA since 1988 (methotrexate)



AACR Pediatric Cancer Report 2025

Osteosarcoma survival rate by decade



Survival rate for metastatic or recurrent disease ~20%

Alison, et al *Sarcoma* 2012

Progress in rare cancers requires many stakeholders

FDA/OSI workshop goals

- To **convene key stakeholders** to share perspectives on the challenges to, and identify opportunities for, advancing clinical development of therapies for osteosarcoma through collaboration and communication.

- To **identify opportunities to increase efficiency** within drug development.

- To **develop strategies to address the most significant challenges** in clinical trials design and implementation in osteosarcoma.

Key patient/advocate insights

- Acute and long-term **toxicities** from osteosarcoma treatment significantly impact quality of life
- **Equitable access** to specialized treatment centers and clinical trials is important
- New therapies that **improve overall survival** needed
- Continued **coordination** among all stakeholders is vital

How FDA facilitates drug development in osteosarcoma

- Multistakeholder engagement
- Expedited programs for promising new treatments
- Patient listening sessions
- Clear communication of regulatory expectations
- Coordination with international regulatory bodies (e.g., EMA)

Outcomes from the Rare Disease Innovation, Science, and Exploration (RISE) Public Workshop Series

Amy Comstock Rick, J.D.

Director, Strategic Coalitions for the Rare Disease Innovation Hub

Rare Disease Innovation Hub (RDIH)

- **Mission:** Create a focal point that will further enhance the synergy between CBER and CDER and strengthen collaborations across FDA to accelerate development of rare disease therapies, especially for those diseases with smaller populations.
- **RDIH Steering Committee:**
  - Leadership CBER & CDER
  - Director, CDRH
  - CDER ARC Lead
  - CBER Rare Disease Program Lead
  - Director, OOPD
  - Director, OCE

RDIH 2025 Strategic Agenda Goals

- **Goal 1:** Further advance regulatory science of rare disease therapies
- **Goal 2:** Enhance and strengthen coordination and alignment between medical product centers, with particular focus on CDER and CBER
- **Goal 3:** Create a centralized point of contact for external partners

https://www.fda.gov/media/185144/download?attachment

RDIH 2025 Strategic Agenda – Goal One

Further Advance Regulatory Science of Rare Disease Therapies

- Rare disease Innovation, Science, Exploration (RISE) Workshops
  - *On The RISE: Controls in Rare Disease Trials for Small and Diminishing Populations,* Sept. 3, 2025
  - *Individualized Therapies on the RISE,* Nov. 20, 2025
    - 2,000+ attendees
    - 50% from industry
  - Federal Register Docket – continuous proposal submissions
  - *RISE Together: Data Sharing Across the Rare Disease Ecosystem*, March 30, 2026
  - RISE #4 & 5 TBD

RDIH 2025 Strategic Agenda – Goal Two

Enhance and Strengthen Coordination and Alignment Between Medical Product Centers, with Particular Focus on CDER and CBER

- Rare Disease Policy and Portfolio Council (RDPPC)
- Rare Disease Evidence Principles (RDEP)
- CDER and CBER promotion of cross-center knowledge sharing and joint educational opportunities, particularly with reviewers of related diseases and conditions

RDIH 2025 Strategic Agenda – Goal Three

Create a Centralized Point of Contact for External Partners

- Program Roadmap
- Rare Disease Day – February 23, 2026
- Educational Materials Review – Building on LEADER 3D
  - FDA Materials – CDER and CBER
  - External Stakeholder Materials
  - Multi-year Process

RDIH 2026 Strategic Agenda

Strategic Agenda 2026

- Planning FDA Rare Disease Day – February 2027
- Engagement with industry and patient community on innovative methods and designs
- Three RISE Workshops
- Community point of contact (non-product specific)
- Patient voice in drug development process

U.S. FOOD & DRUG ADMINISTRATION

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Nicole Scobie

Chair of the Board, Patient Advocate

ANDREW McDONOUGH B+ FOUNDATION

Why ACCELERATE Matters

- **Key Challenge:** Although paediatric cancer survival has improved over the past decades, it remains the leading disease-related cause of death in children. For survivors, long term toxicities are still too frequent and severe
- **Critical Gap:** Therapies approved for adults often take **years** before being available to children.
- **How to move forward:** Bring all stakeholders together to identify problems, research and develop recommendations and solutions in an international, neutral and inclusive platform

ACCELERATE

Bringing together all stakeholders as equal partners: parents, survivors, patient advocates with academic researchers and clinicians, industry representatives and regulators from Europe and North America.

MISSION

Mobilize the global stakeholder **community** to collectively **identify challenges** in paediatric cancer drug development and **work collaboratively** to **drive** accountable, effective, and sustainable **solutions**.

ANDREW McDONOUGH B+ FOUNDATION®

OUR NAME IS OUR **MISSION**

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

STRATEGIC PRIORITIES

1 Community

A GLOBAL MULTI-STAKEHOLDER CONVENER

2 Action

STRATEGIC PLANNING IN INNOVATIVE DRUG DEVELOPMENT

3 Impact

EVIDENCE-BASED RECOMMENDATIONS, MULTI-STAKEHOLDER ENGAGEMENT AND IMPACT

IMPACT: A connected ecosystem

- **Amplified Stakeholder Engagement:** ACCELERATE has successfully brought together all relevant parties—academia, advocacy, industry, and regulators—to co-develop solutions
- **Evidence of Results**: Multiple peer-reviewed publications, regulatory impact, delivery of clinical trials and practice changing recommendations
- **Global:** Born in Europe, ACCELERATE is now an international organization with FDA, EMA, Health Canada and Swissmedic, COG, ITCC, SIOPE, ANZCHOG, Japan…

Patient Partnership In

FDA Rare Disease Day 2026

Moving Forward.
Looking Ahead.

Maeve Smart & Ann Graham
MIB Agents Osteosarcoma

THE BEGINNING: MIB Agents Osteosarcoma

- Wife & Mom of three girls and three Dogs
- Director of Sales & Marketing at Luxury Hotel Group
-Training for a Marathon
-Leg hurt
-Doctor visits over nine months
- Nine misdiagnoses

- Unable to walk, requested (again) an MRI
- Discovered bone tumor proximal left tibia
- Biopsy & Pathology revealed diagnosis of osteosarcoma
-Treated on pediatric cancer floor at age 43

- Three months of chemotherapy, including Cisplatin, Doxorubicin, & Ifosfamide.
- Surgery to remove tumor and replace tibia, knee, and femur with titanium parts
- Six more months of chemotherapy with added high dose Methotrexate

THE REALIZATION: MIB Agents Osteosarcoma

46 Years Since a New Treatment

- Osteosarcoma has had the same treatment protocol since 1980.
- If I was treated in 1980 when I was 13, it would be the same as my treatment in 2010 and the same as it would be today.

WE Must Make It Better Together

-The chemotherapy wasn't working, kids I knew with my same cancer were dying. I asked my doctor what's next.
- Neither I, nor my fellow patients, had then or now have a 2nd line treatment option.

-Desperate, alone in my room, my prayer was "Use Me to Make it Better."
- Make It Better became MIB Agents Osteosarcoma in 2012 with our first MISSION for a fellow osteosarcoma patient.

TODAY: How We Make It Better

Programs

Ambassador Agents

Family Funds

Gamer Agents

Healing Hearts

Junior Advisory Board/NextGen

osTEAo AYA podcast

Prayer Agents

Warrior Mail

Education

Connective Issue

FACTOR Conference

Newly Diagnosed Resources

OS Handbook

OsteoBites

TURBO

Research

CURE-OS

FACTOR Conference

OutSmarting Grants

Research Bees

A journey toward the fulfillment of any worthy goal, desires the hearts of M A N Y.

The goal to Make It Better can only be built on a foundation of L O V E & B E L O N G I N G with and to each other.

MOVING FORWARD: Collaborative Impact

FACTOR OSTEOSARCOMA CONFERENCE

Funding, Awareness, Collaboration, Trials, Osteosarcoma Research

Since 2017, MIB Agents annual FACTOR Osteosarcoma Conference has brought together leading researchers, clinicians, industry, and patient families with the goal of improving osteosarcoma treatments and Collaborating for a Cure.

- 269 ATENDEES
- 30 KIDS IN HQ
- 7 COUNTRIES
- 37 STATES
- 50 SCIENTIFIC SPEAKERS
- 111 FAMILIES
- 45 INSTITUTIONS
- 15 SCIENTIFIC POSTER PRESENTERS

What Happens at FACTOR?

- **Improve osteosarcoma awareness and patient outcomes** through a collaborative disease management approach.
- Brainstorm challenges and **develop collaborative solutions** to fast-track improvements for osteosarcoma.
- Create a synergistic bridge between the **osteosarcoma scientific and patient communities.**

MOVING FORWARD: Collaborative Impact

RESEARCH FUNDING

OutSmarting Osteosarcoma

Launched in 2017, the OutSmarting Osteosarcoma Research Grant has driven progress in the field by **awarding $2.5 million to 32 dedicated investigators advancing osteosarcoma research**. Our rigorous scientific review process emphasizes collaboration and uniquely incorporates patient and family perspectives. Grant administration includes regular reporting and investigator updates, ensuring transparency and accountability for our funders.

Family Funds Supporting Science

Collaboration among the scientific and patient community is a key hallmark of MIB Agents. OutSmarting Osteosarcoma grants are supported by MIB Agents Family Funds™, whose dedication to Making It Better and fostering collaboration and education in the scientific community makes every MIB Agents award incredibly meaningful.

MOVING FORWARD: Collaborative Impact

SCIENTIFIC EDUCATION

MiB AGENTS RESEARCH BEE

By leveraging lived experience, we help provide the patient experience data necessary to inform research and clinical trials.

Defying Osteosarcoma is described as the largest and most unified effort in pediatric osteosarcoma research in North America, involving more than 20 researchers across eight leading cancer centers.

15MM

TURBO Virtual Tumor Board

TURBO brings together multidisciplinary osteosarcoma experts worldwide to review complex cases and share experience and knowledge.

CURE-OS

(Collaborative Understanding of the Range and Evolution of Osteosarcoma Single-cells)

CURE-OS is a working group uniting researchers to fund and coordinate efforts that translate single-cell discoveries into clinically meaningful outcomes in osteosarcoma. The group's shared goals are to aggregate and centralize existing single-cell data, establish a gold-standard dataset for future studies, and develop a framework that connects experimental models to therapeutic translation.

MOVING FORWARD: Collaborative Impact

SCIENTIFIC EDUCATION

OsteoBites

A weekly webinar and podcast featuring the leaders in osteosarcoma research and other topics of interest to the osteosarcoma community. 6 seasons, 162 episodes, and over **43K lifetime views**

Annual Thought Leader & Young Investigator Networking Event at CTOS

Each year we gather osteosarcoma thought leaders and young investigators at CTOS to network, exchange ideas, and ignite colalboration to advance and accelerate research and clinical care.

Canine Trials

Our Canine Clinical Trials Resource connects scientists and resourcesto Make It Better for both canine and human patients. It features educational materials, a directory of veterinary oncology programs, and listings of open canine osteosarcoma trials across North America.

MOVING FORWARD: Collaborative Impact

PATIENT PROGRAMS

Warrior Mail

We deliver 12,000 letters annually to an average of 45 OsteoWarriors each month from Writer Agents around the world, sharing messages of humor, support, and cheer.

Prayer Agents

Prayer Agents lift OsteoWarriors, OsteoAngels, and their families with prayers and intentions on the first Sunday of each month. MIB Agents posts a prayer from a different cleric or spiritual practice each month.

Gamer Agents

Our private online gaming network of OsteoWarriors and OsteoSiblings. The moderators are trained Lead Gamer Agents, playing around the world and around the clock.

Ambassador Agents

Connecting current OsteoWarriors and their families to trained osteosarcoma survivors and their families. There are three training sessions and **40+ Matches annually.** A tote bag with in-patient essentials is included for the matched OsteoFamily.

MOVING FORWARD: Collaborative Impact

PATIENT PROGRAMS

Osteosarcoma Handbook

Written by osteosarcoma families and edited by leading physicians, *Osteosarcoma: From our Families to Yours*, and *Osteosarcoma: De Nuestras Familias a la Suya* are comprehensive guides to OS. MIB Agents **distributes more than 900 copies of the handbook a year** in English and Spanish, with over 300 free downloads in English, Spanish, and Mandarin.

OS Navigation Packets

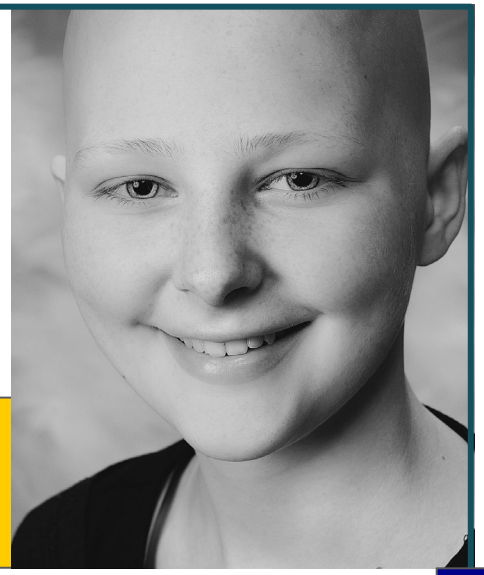
Healing Hearts for Parents Group

Offering a safe haven of love & comfort for grieving osteosarcoma families. Annually there are **48 weekly virtual Healing Hearts sessions** and workshops, as well as in-person sessions at the annual MIB FACTOR conference.

Connective Issue

Connective Issue is a monthly newsletter sent to over 10,000 patients, caregivers, advocates, medical professionals, and industry stakeholders in our community.

THE REALIZATION: MIB Agents Osteosarcoma



2011-2015

- MAP chemotherapy and LSS
- 3 years on crutches
- Localized recurrence → above knee amputation and more chemotherapy
- 4 years and 18 surgeries later… returned to school in-person in 11th grade

2017-2022

- Moved to Boston to attend Northeastern University
- MIB Ambassador Agents training
- MIB Junior Advisory Board President
- Co-op in Dr. Katie Janeway's lab at DFCI

2024-2026

- Moved to New Hampshire to begin medical school
- M2 at Geisel School of Medicine (Dartmouth)
- MIB Agents NextGen

LOOKING FORWARD: Junior Advisory Board

Junior Advisory Board

The JAB are active participants and advisors within MIB, and remarkable advocates in the greater community.

10	23	8	2020	10
New Members	Total Members	Medical Conferences Attended	Origin Year of JAB	Number of First JAB Members


Allisen


Alejandro


Anne


Camille


Daniel


Elise


Evan


Gillian


Inaaya


Jacob


Keely


Lincoln


Luke

Mackenzie


Michaela


Mikaela


Molly

Sammy


Sebastian


Sloane


Te'von

LOOKING FORWARD: NextGen

NextGen

NextGen is the vital link between the Junior Advisory Board (JAB) and the wider MIB community. Its members are advocates and mentors with a lived experience of osteosarcoma who both guide younger JAB members and learn from experienced community leaders.


Andrew Bisaga


Kara Skrubis


Maeve Smart


Matthew Ceelen

Matthew Allen


Max Penzer


Sammy Ulloa


Sona Kocinsky

Walker Smallwood

osteao

SPILLING THE TEA ON OSTEOSARCOMA & AYA CANCER

COLLABORATIVE IMPACT: The FDA and Advocacy

October 2024

October 2025

February 2026

ADVOCACY: The foundation of love and belonging that sustains the journey toward a CURE

CURE ID

FDA U.S. FOOD & DRUG ADMINISTRATION

NIH National Center for Advancing Translational Sciences

Rare Disease

Patients, Care Partners, or Healthcare Providers

Learn how your experience may help to inform future research, identify promising treatments, or treatments that are ineffective or harmful. These treatment experiences may also inform the drugs studied in clinical trials.

About CURE ID

Working with patient and clinician advocacy groups, the FDA and NIH established CURE ID, an online treatment registry that allows Patients, Care Partners, or Healthcare Providers to share their real-world experiences using existing drugs in new ways.

Visit the link to learn more

https://cure.ncats.io

Study partners

Clear Cell Sarcoma Foundation · Anticancer Fund · Rogel Cancer Center, Michigan Medicine · Memorial Sloan Kettering Cancer Center · National Leiomyosarcoma Foundation · MIB Agents · Sarcoma Foundation of America (SFA) · xCures · Noonan Syndrome Foundation · RASopathies Network (connect · collaborate · accelerate) · CFC International (Cardio-Facio-Cutaneous Syndrome) · CURE SYNGAP1 · EveryCure · The Menkes Foundation

GET IT ON Google Play

Download on the App Store

U.S. FOOD & DRUG ADMINISTRATION

AI Tools at FDA

William Liu, Ph.D.
Director, AI Governance and Implementation
FDA AI Internal Council (AIIC)

What is Artificial Intelligence (AI)?

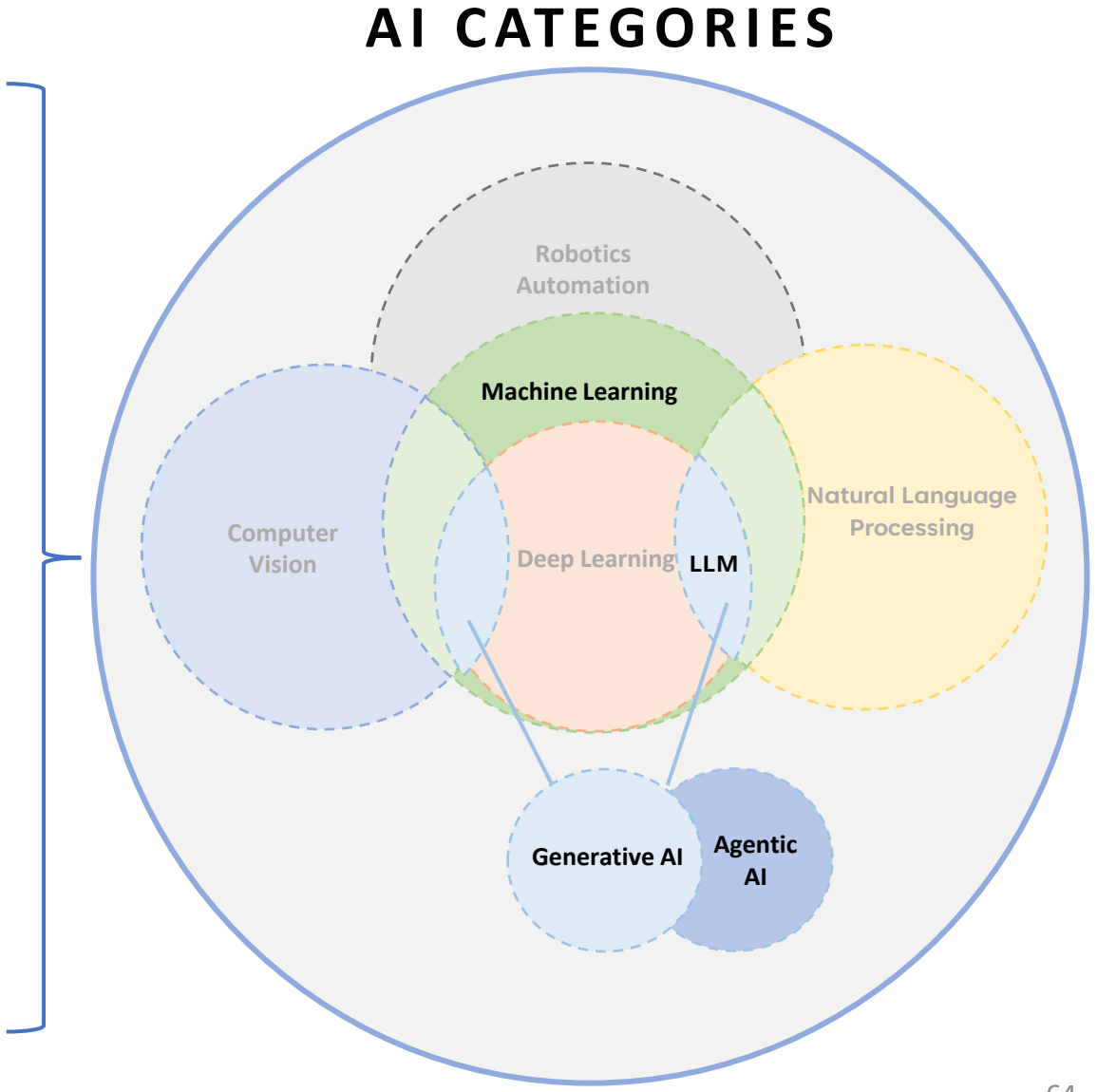
Artificial Intelligence: A machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments. AI systems use machine- and human-based inputs to perceive real and virtual environments; abstract such perceptions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

Machine Learning Model (ML): A mathematical construct that generates an inference or prediction for input data. This model is the result of an ML algorithm learning from data. Models are trained by algorithms, which are step-by-step procedures used to process data and derive results. AI systems (e.g., AI-enabled medical devices) employ one or more models to achieve their intended purpose.

Generative AI (Gen AI): The class of AI models that emulate the structure and characteristics of input data to generate derived synthetic content. This can include images, videos, audio, text, and other digital content.

Large Language Model (LLM): The class of AI model trained on large text datasets to learn relationships between words in natural language. LLM models can apply these learned patterns to predict and generate natural language responses to a wide range of inputs or prompts they receive, to conduct tasks like translation, summarization, and question answering. These models are characterized by a vast number of model parameters (i.e., internal learned variables within a trained model).

Agentic AI: AI tools and systems that autonomously or semi-autonomously perceive, reason, act, and learn to achieve goals through adaptive interaction with data, tools, and their environment. Agentic AI can: (1) autonomously and semi-autonomously break down tasks into sub-tasks, iteratively execute them, and refine outputs; (2) allow persistent memory across steps, including retrieval from external knowledge bases or user history; (3) integrate with external tools, Application Programming Interfaces (APIs), databases, or other systems to perform actions beyond standard text generation.



Why AI Matters to FDA

"There has never been a better moment in agency history to modernize with tools that can radically improve our ability to accelerate more cures and meaningful treatments."[1]
FDA Commissioner Marty Makary, M.D., M.P.H.

AI strengthens FDA's ability to protect public health by enabling:

- More efficient workflows / accelerated processes
- Improved consistency and accuracy of work products
- Faster analysis of large, complex datasets
- Better decision support
- Stronger regulatory readiness and experience

"…the FDA will be focused on delivering faster cures and meaningful treatments for patients, especially those with neglected and rare diseases"[2]

1) https://www.fda.gov/news-events/press-announcements/fda-expands-artificial-intelligence-capabilities-agentic-ai-deployment
2) https://jamanetwork.com/journals/jama/fullarticle/2835314

FDA's AI Journey

FDA has been leveraging AI/ML tools and capabilities for decades; FDA currently has **67** use cases listed publicly at HHS[6]

Artificial Intelligence (AI) / Machine Learning (ML)

- Data mining of adverse event reports (*1990s*)[1]
- Predictive toxicology, computational toxicology, quantitative structure activity relationship (QSAR) modeling (*2000s – present*)[2]

Generative AI

- Extraction of adverse event data from FDA drug labels (2025)[3]
- Elsa Enterprise: FDA's generative AI tool/platform (2025)[4]

Agentic AI

- Agentic AI @ FDA (Gemini Enterprise @ FDA): Exploratory sandbox for agentic AI, deep research (2025)[5]
- Elsa Enterprise (2026)

1) https://www.fda.gov/science-research/data-mining/data-mining-fda-white-paper
2) https://www.fda.gov/media/109634/download
3) https://pmc.ncbi.nlm.nih.gov/articles/PMC12098182/
4) https://www.fda.gov/news-events/press-announcements/fda-launches-agency-wide-ai-tool-optimize-performance-american-people
5) https://www.fda.gov/news-events/press-announcements/fda-expands-artificial-intelligence-capabilities-agentic-ai-deployment
6) https://www.hhs.gov/programs/topic-sites/ai/use-cases/index.html

AI Tools at FDA - AI Supports. Humans Decide

- AI tools and capabilities serve in an assistive capacity that can **help** enhance and support **human-led** decision making
- All AI outputs must be **validated** by staff with relevant expertise and domain knowledge
- **All regulatory decisions or actions must be made by human experts** – AI outputs may only be used to assist in informing decisions or supporting human expertise

This image was generated by Gemini for Government @ HHS

AI Governance at FDA - Implementation and Policy

AI Internal Council (AIIC)

- The AIIC oversee and governs the **responsible** implementation and adoption of **innovative**, **trustworthy**, and **effective** AI applications that **enhance** and **accelerate** FDA's **internal operations to protect and promote public health,** in alignment with **federal** and **department-wide** AI guidelines
- **Creates** and **promotes FDA-wide AI best practices**, maintains an FDA-wide AI inventory, promotes the **development**, **implementation**, **scaling**, and **oversight** of enterprise AI tools and capabilities

AI Policy Coordination and Planning Council (AIPC)

- The AIPC serves as the Agency's AI **policy coordinating** body to promote the use of AI across the product lifecycle – including the use of AI in the development of FDA-regulated products and AI-based, regulated products.
- Supports **cross-cutting AI policy development** across product Centers and Offices, supporting regulatory science initiatives such as technology harmonization and guidance development

Comprised of representatives from every Center and Center-level Office, selected by the Chief AI Officer, Center Directors, and Office Leadership

Works in coordination with Center and Office-specific AI governing bodies (e.g., CDER AI Council), and with broader HHS and Federal AI organizations

Enterprise GenAI Tools Available to FDA Staff

FDA has deployed multiple generative AI tools for FDA staff

Elsa Enterprise@ FDA

- Deployed June 2nd, 2025
- Platform containing multiple foundational LLMs (including Claude Sonnet 4.5, Gemini Pro 2.5), to assist staff with their work
- Built specifically for FDA staff; includes FDA-specific document libraries and data
- In compliance with the Federal Risk and Authorization Management Program (FedRAMP) High

Gemini Enterprise @ FDA

- Deployed on December 1st, 2025
- Exploratory tool that enables the creation of complex AI workflows to assist with multi-step tasks (Agentic AI)
- In compliance with the Federal Risk and Authorization Management Program (FedRAMP) High

HHS-wide AI Tools

- ChatGPT @ HHS: Deployed Sept 9th, 2025
- Claude @ HHS: Deployed December 3rd, 2025
- Gemini for Government @ HHS: Deployed February 2nd, 2025

Other AI Use Cases at FDA

Classical AI/ML

- **Drug Shortage Predictive Modeling**: Pilot program leveraging a classical/traditional AI/ML approach to predicting drug shortages; intended to help with prevention and mitigation of drug shortages by signaling early risks to a supply chain, potentially ensuring patients maintain access to essential medications.
- **Warp Intelligent Learning Engine (WILEE):** AI Tool that that identifies emerging chemical signals and violative food substances, enabling post-market surveillance, signal detection, and knowledge discovery.

Generative AI

- **HIVE AI Pilot:** CBER AI tool that assists in the review process of IND submissions - provides recommendations for the most appropriate review disciplines for each submission; assists in identifying grossly deficient submissions
- **Real World Data/Evidence:** AI tool that assists in identifying and cataloging submissions containing real-world data through text extraction from unstructured documents

Additional FDA use cases can be found in the 2025 HHS AI Use Case Inventory: https://www.hhs.gov/programs/topic-sites/ai/use-cases/index.html

FDA's Agentic AI Innovation Challenge

This image was generated by Gemini for Government @ HHS

- As part of the FDA's agentic AI deployment, the agency launched a two-month Agentic AI Challenge for staff to build agentic AI solutions; finalists presented their exploratory use-cases at the FDA Scientific Computing Day in January 2026.
- Three finalists and one winner were selected from over **180** submissions
- FDA will continue to explore agentic AI solutions to enhance the Agency's regulatory and operational work

What's next?

- *"…the FDA will be focused on delivering faster cures and meaningful treatments for patients, especially those with neglected and rare diseases"*

FDA will continue to responsibly adopt new AI tools and technologies that can advance and accelerate FDA's regulatory and operational functions, with the ultimate goal of protecting and promoting the public health

U.S. FOOD & DRUG ADMINISTRATION

Exploring the use of artificial intelligence to support FDA regulatory review in oncology

Gautam Mehta, M.D.

Associate Director for Oncology Clinical Policy, OCE

Objectives

- Discuss how use of AI can support FDA's mission
- Review approaches to using AI in regulatory settings
  - Ensure safety
  - Build trust and credibility
  - Encourage uptake

FDA's Mission

The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

High Quality Regulatory Review

- Has wide-ranging public health implications
- Expectations are similar to clinical care
  - Must be complete
  - Must be confidential
  - Errors not acceptable
  - Based on knowledge of condition and regulations/law
  - Strengthened by experience

Regulatory Review is Sequential

Primary Clinical Reviewer

- Individual safety reports
- Other clinical information

Team Leader

- Research studies
- Protocol amendments

Division Director

- Commercial studies
- Meetings/Advice
- Marketing applications

Using AI for Regulatory Review

FDA Review Teams

- Disease experts
- Have decades of regulatory experience
- Understand how to apply laws/regulations
- Regulatory memory
- Sequential review limits errors

Artificial Intelligence

- Processes information faster
- Access to large data sources (i.e., internet)
- Can ensure completeness of review
- Complete menial tasks so focus can be on complex review work
- Basic clinical and regulatory understanding
- *Can hallucinate/make errors*

Adding AI to Sequential Regulatory Review

- Collects data
- Makes an initial recommendation

- Verifies data
- Makes complex regulatory decision based on experience and understanding of the clinical and regulatory context

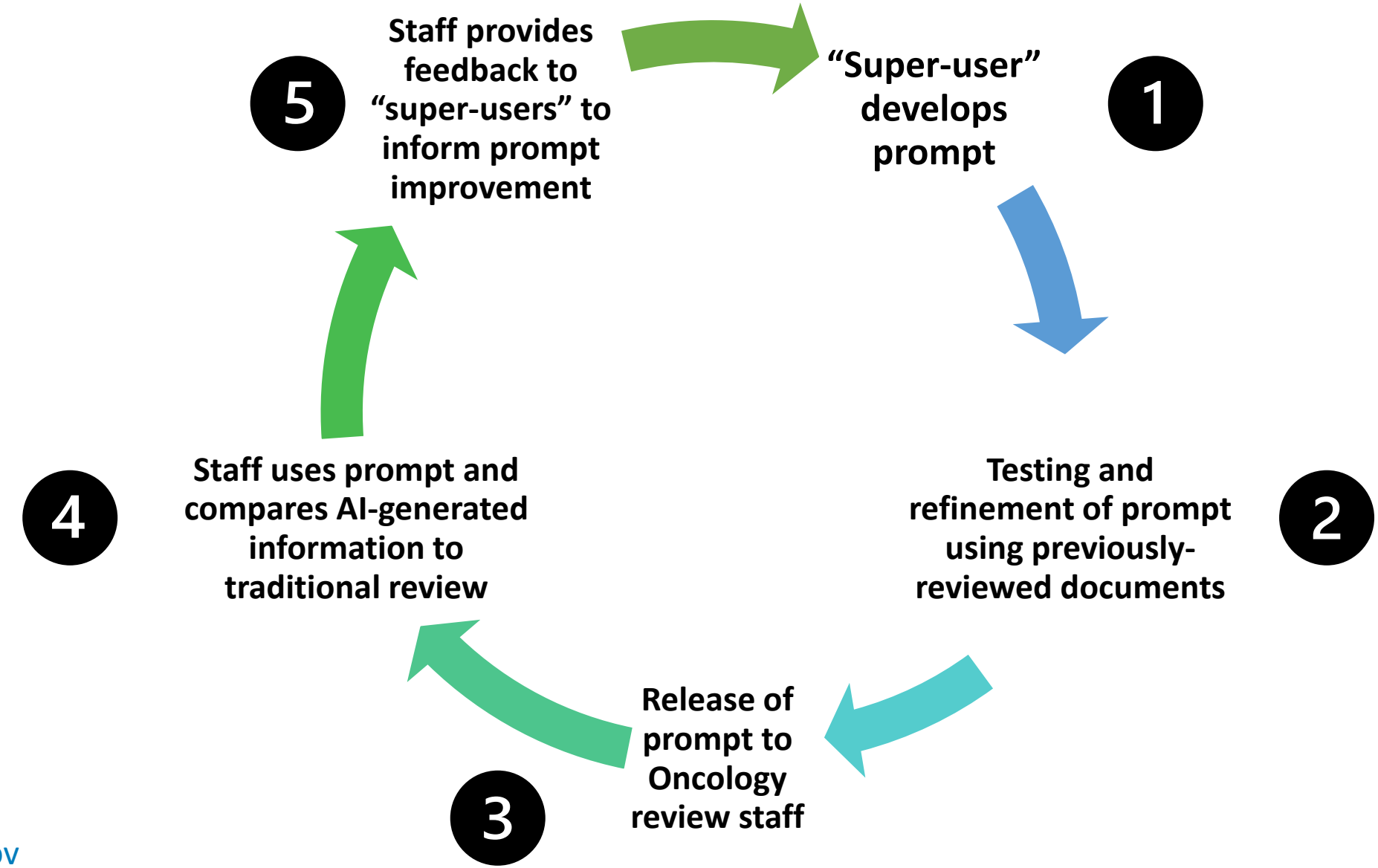
AI for Regulatory Review in Oncology v1.0

- Individual reviewers developed their own prompts
- Output depended on the human user
  - Prompt Quality: Different levels of experience
  - Application: Need to know how to apply AI generated information

AI for Regulatory Review in Oncology v2.0

- “Super-user” reviewers developed prompts for others to use
- Better prompt quality
- Implemented safeguards
  - Model flagged page numbers for verification of information
- Issues:
  - Prompt may work best for the individual who developed it
  - Still need to know how to apply AI-generated information
  - Passive approach: Still need to build trust among review staff/encourage uptake

AI for Regulatory Review in Oncology v3.0



Integrated Approach for Regulatory AI Improvement

- Allows for continual improvement to produce the best product
  - Based on increasing experience with AI
  - Can keep up with technology changes

- Engages all users
  - Encourages uptake of AI for this purpose
  - Allows users to see how AI can help them improve regulatory review
  - Helps users build trust in AI

Prompt Pilot for Pediatric Study Plan Reviews

- Regulatory process with some common elements across reviews

1. Development: Two expert pediatric clinical reviewers developed an initial prompt
2. Testing/Refinement: Prompt tested and refined using 10 previously-reviewed pediatric study plans and multiple AI models
3. Wider testing (current phase): Oncology review staff using prompt in parallel with standard review process and submitting feedback for prompt improvement

Conclusions

- AI can improve oncology regulatory review
- Safe and appropriate use requires an understanding of the benefits and limitations of this technology
- Safeguards are in place to ensure AI supports high quality regulatory review
- An integrated approach that engages all users may lead to a better product, increased uptake, and greater trust
- Optimal approach will evolve as technology changes (e.g., agents)

Acknowledgements

Oncology Center of Excellence

- Tamy Kim
- Martha Donoghue
- Alex Akalu
- Esther Park
- Deborah Elliot
- Angelo DeClaro

Office of Oncologic Diseases

- Michael Barbato
- Justin Ferrell
- Jeevan Puthiamadathil

U.S. FOOD & DRUG ADMINISTRATION

The Application of Artificial Intelligence in Drug Development and Regulation

Qi Liu, Ph.D., M.Stat.

Associate Director for Innovation & Partnership,
Office of Clinical Pharmacology, Office of Translational Sciences, CDER,
Co-chair, CDER AI Council Lead,
CDER AI Review Rapid Response (R3) Team, CDER

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

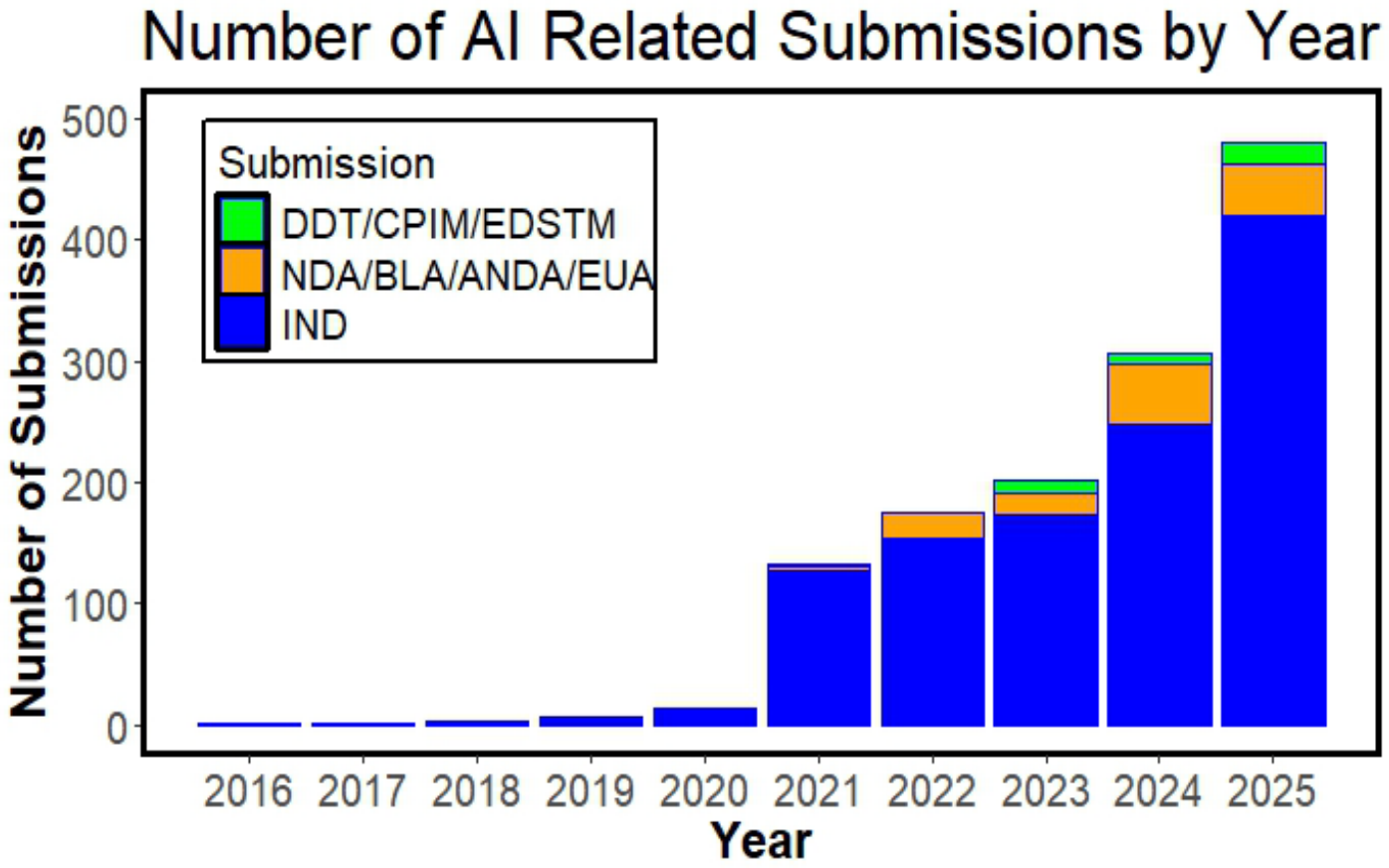
This analysis was performed by searching for submissions with key terms "machine learning" or "artificial intelligence" in Center for Drug Evaluation and Research (CDER) internal databases for Investigational New Drug applications, New Drug Applications, Abbreviated New Drug Applications, and Biologic 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.

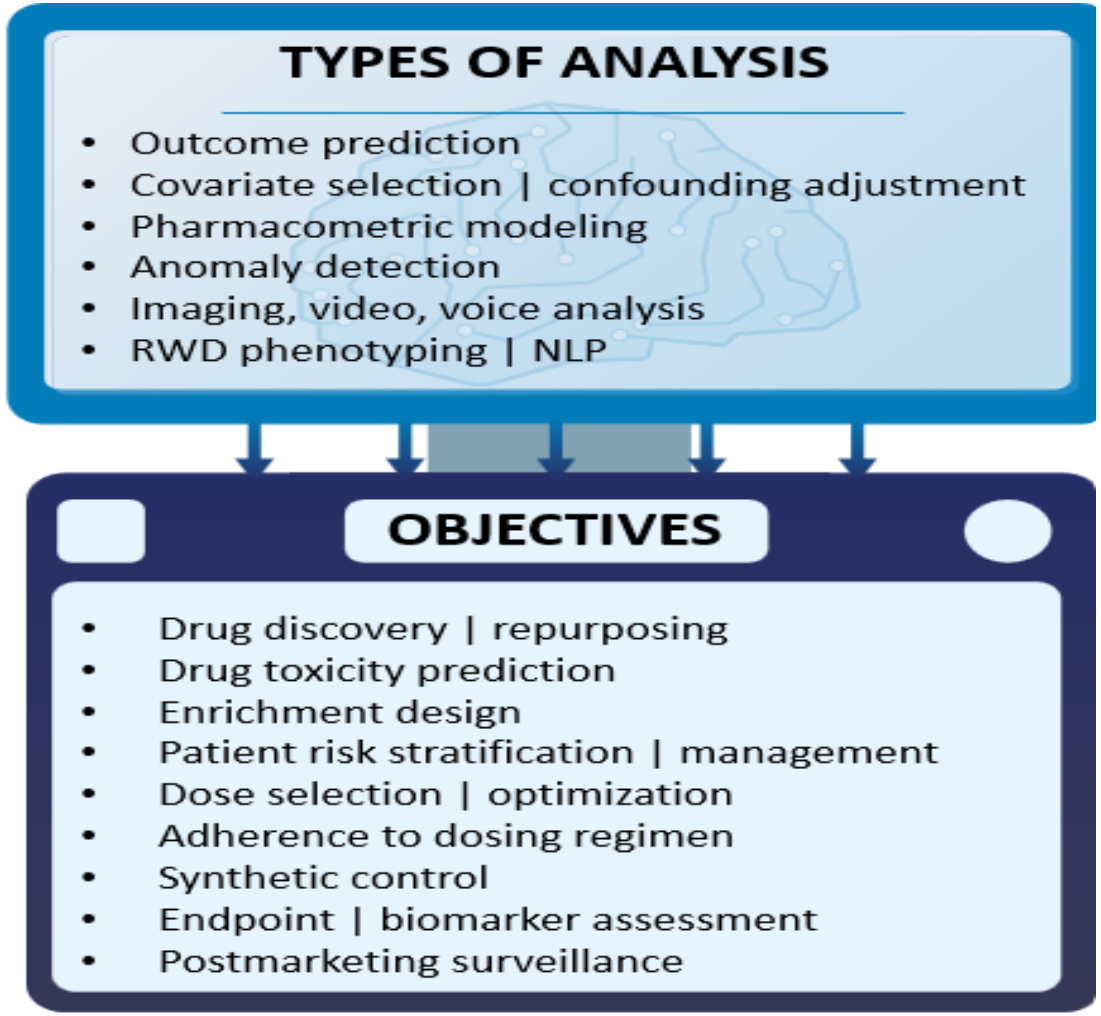
Received March 16, 2022; accepted May 19, 2022. doi:10.1002/cpt.2668

Updated analysis with submissions in 2022-2025



(Figure credit: Dr. Menglun Wang)

Types of AI Related Analyses & Objectives



Liu Q, 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 ®

AI-Based Drug Development Tool

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.

Examples of AI Application in Rare Disease Regulatory Submissions

- Medical imaging-based endpoints in clinical trials
- In combination with wearable devices for clinical endpoints in clinical trials
- Biomarker identification and enrichment trial designs
- Medication adherence monitoring
- Prediction of patient's risk for certain adverse events
- Mechanistic assessment of adverse events

Biomarker Identification for Idiopathic Multicentric Castleman Disease (iMCD) Using Proteomics Data

Perelman School of Medicine, University of Pennsylvania

David Fajgenbaum
Michael Gonzalez
Joseph Zinski
Melanie Mumau

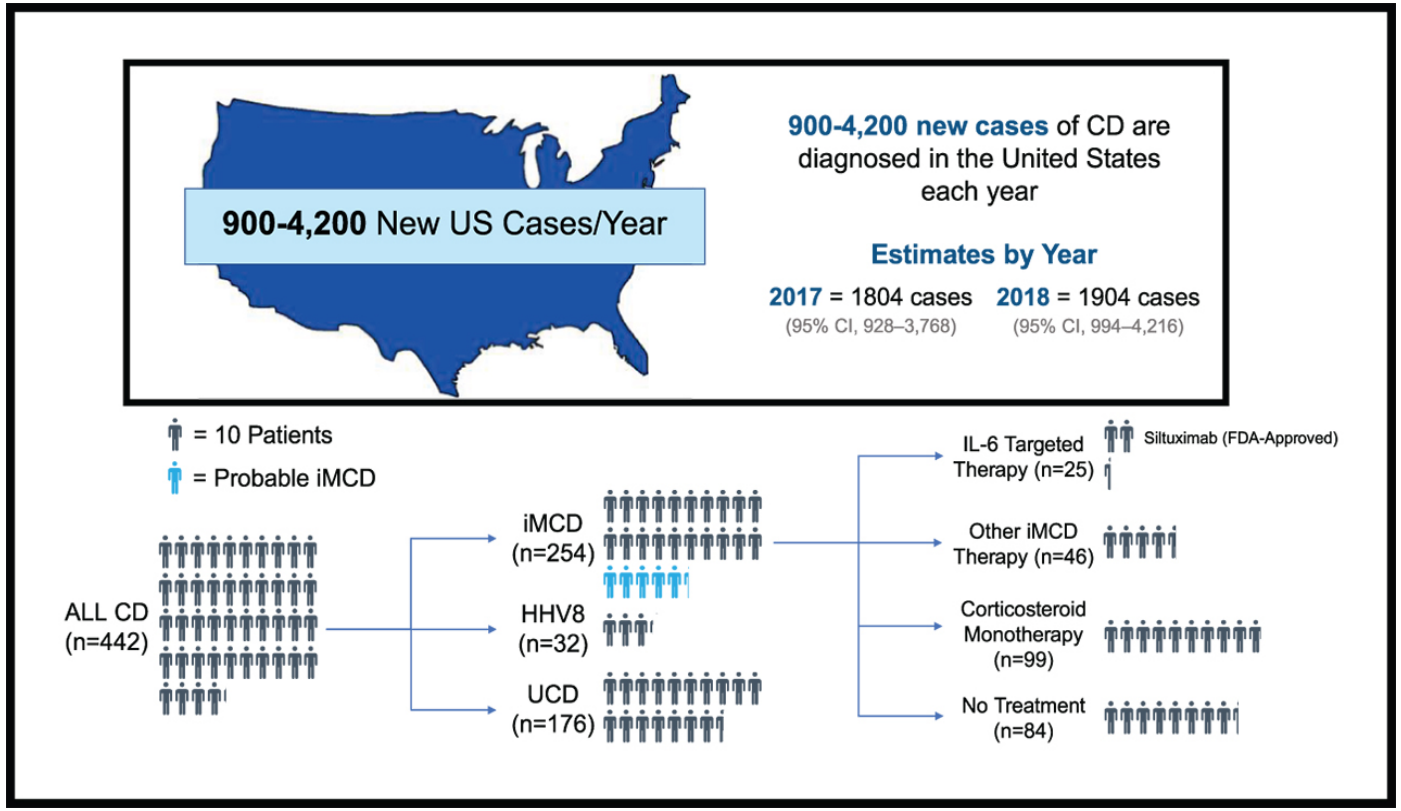
U.S. Food & Drug Administration

Qi Liu
Lixia Zhang
Ruihao Huang
Hanrui Zhang
Menglun Wang
Robert Schuck
Michael Pacanowski
Shirley Seo
Sudharshan Hariharan
Margatet Thompson
Ann Farrell
Hao Zhu
Maryanne Dingman
Santiago Carrasquilla
Caroline Atyeo
Kaiwen Deng
Yiheng Pan
Zhuxuan Xu
Boguang Sun
Guodong Chen
Mitra Ahadpour

Biomarker Identification for Idiopathic Multicentric Castleman Disease (iMCD) Using Proteomics Data

- University of Pennsylvania - proteomics data collection
  - clinical trial
  - real-world clinical practices

- FDA - data analyses using AI for the following questions:
  - Are there iMCD-specific protein biomarkers compared to healthy controls and related disorders?
  - Are there protein signatures in iMCD that can predict treatment response?



Mukherjee, S. · Martin, R. · Sande, B. · et al. Epidemiology and treatment patterns of idiopathic multicentric Castleman disease in the era of IL-6-directed therapy. Blood Adv. 2022; 6:359-367

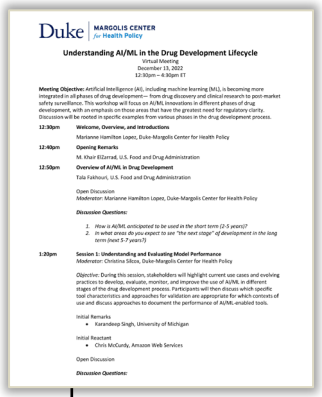
CDER AI Initiatives

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 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. Discussions 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.

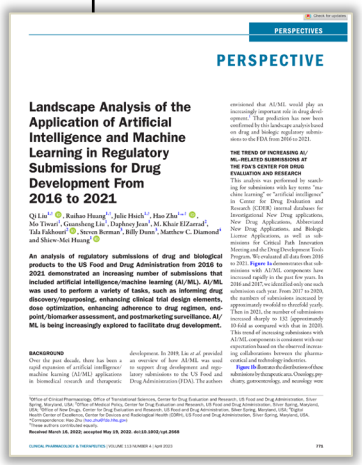
Initial Remarks
- Karandeep Singh, University of Michigan

Initial Reactant
- Chris McCurdy, Amazon Web Services

Open Discussion

Discussion Questions:

2022


PERSPECTIVES

PERSPECTIVE

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

Liu et al Landscape Analysis

2023

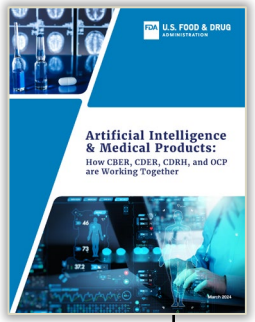
Discussion Papers


CERSI
Home About People
AGENDA
SPEAKER BIOS
Application of Artificial Intelligence & Machine Learning for Precision Medicine

CERSI Workshop

2024

Areas of Focus



CDER AI Council


Artificial Intelligence (AI) in Drug & Biological Product Development Hybrid Public Workshop

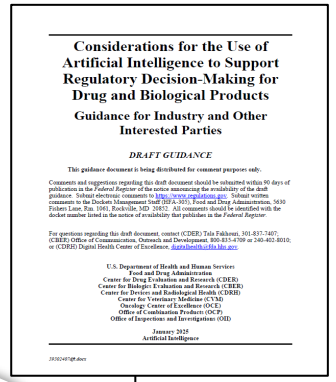
Save the Date: Tuesday, August 6, 2024
Registration opens in early May.

U.S. FOOD & DRUG ADMINISTRATION
CLINICAL TRIALS TRANSFORMATION INITIATIVE

CTTI Workshop

2025

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.

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


Artificial Intelligence in Drug & Biological Product Development Hybrid Public Workshop 2025

Tuesday, October 7, 2025
National Press Club, Washington, D.C.
529 14th Street NW, 13th Floor
Washington, DC 20045

U.S. FOOD & DRUG ADMINISTRATION
CLINICAL TRIALS TRANSFORMATION INITIATIVE

CTTI Workshop

Considerations for AI Use in Regulatory Decision-Making

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

59502407dft.docx

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

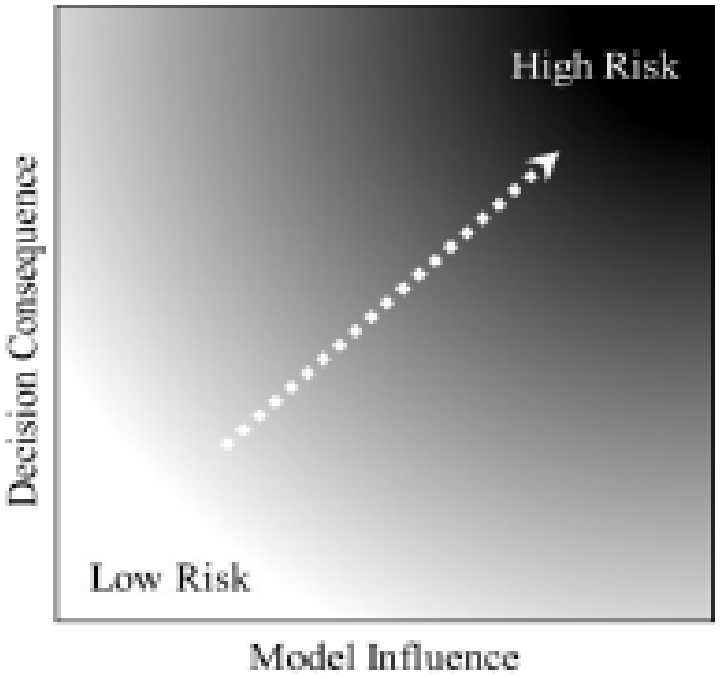


Figure 1. Model risk matrix. The model risk moves from low to high as decision consequence or model influence increases. The ratings for decision consequence and mode influence are independently determined.

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

Use of Artificial Intelligence (AI) in Drug and Biological Product Development

Johnny Lam, Ph.D.

Associate Director for Policy Office of Therapeutic Products, CBER

Outline

- Brief 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

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**

www.fda.gov

[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 & 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

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

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

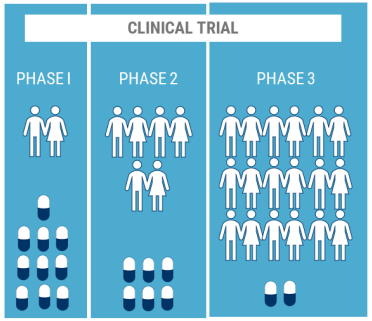
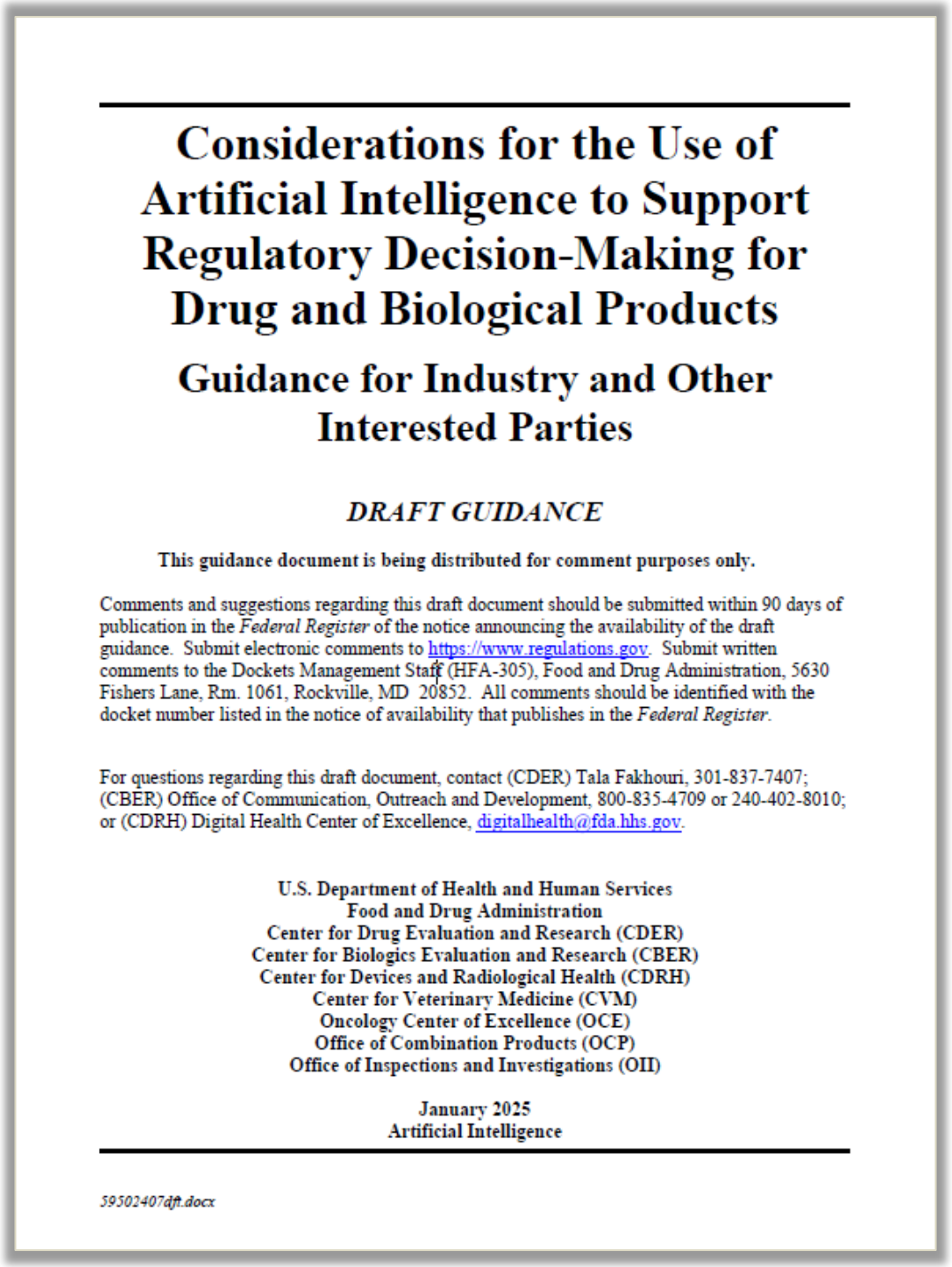


Image source: cbinsights.com

- 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)



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)

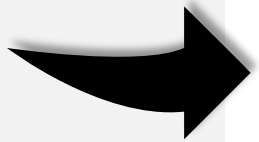
January 2025
Artificial Intelligence

59502407dft.docx

- 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

Table of Contents



- 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

Table of Contents

- 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 produce information/data to support regulatory decision-making

Table of Contents

- 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

Table of Contents

Table of Contents

- 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

Step 1: Define the Question of Interest

Step 2: Define the Context of Use for the AI Model

Step 3: Assess the AI Model Risk

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

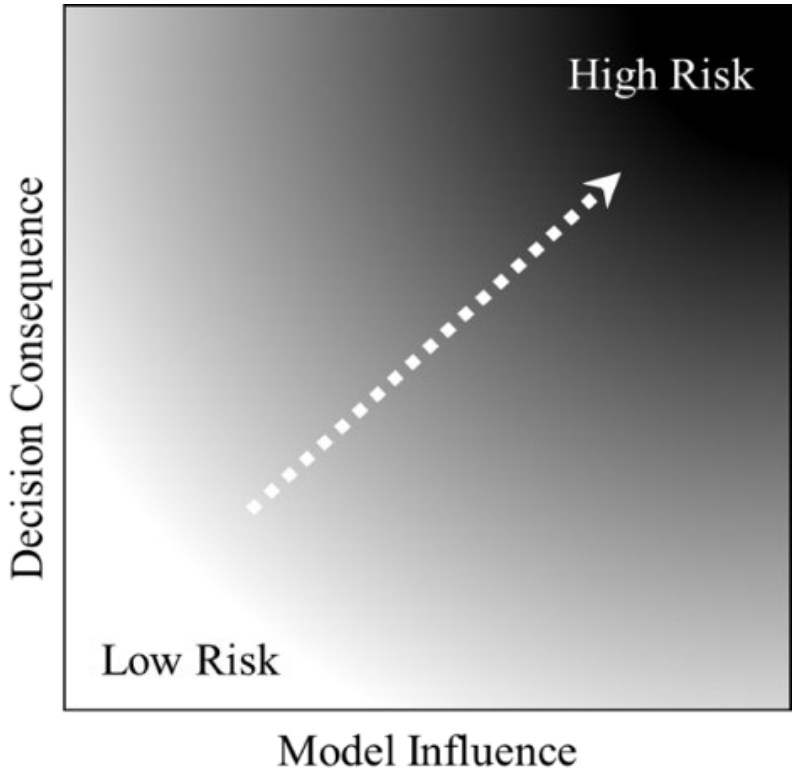
b. Describe the model evaluation process

Step 5: Execute the Plan

Step 6: Document the Results of the Credibility Assessment Plan and Discuss Deviations From the Plan

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

We Encourage Early Engagement with FDA

- 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

Closing Thoughts

- Whenever appropriate, all centers are coordinating and collaborating on AI efforts, leveraging expertise across multiple disciplines
- 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

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

U.S. FOOD & DRUG ADMINISTRATION

AI/ML-enabled Medical Devices: Opportunities & Challenges in Rare Diseases

Shawn Forrest, MS

Digital Health Specialist

CDRH AI Standards Committee Lead

Digital Health Center of Excellence

Moving Forward: Why AI/ML is an Advancement

Traditional Challenges:

- 10,000+ rare diseases affecting 30M Americans
- Many lack FDA-authorized treatments
- Small patient populations - trials often infeasible
- Patients face 5-7 year “diagnostic odyssey”
- Limited data for traditional development approaches

AI/ML as Transformative Advancement:

- Potential to overcome data scarcity through:
  - Multi-site data aggregation
  - Real-world evidence integration
  - Synthetic data augmentation
- Enable novel approaches impossible with traditional methods
- Accelerate diagnosis and treatment development

Opportunities for AI/ML to Advance Medical Devices for Rare Diseases

1. Enhanced Diagnosis:

- Shorten diagnostic odyssey

2. Novel Data Utilization:

- Extract insights from small datasets

3. Accelerated Development:

- Optimize trial design for small populations

4. Continuous Improvement:

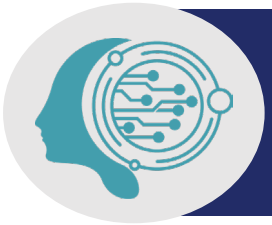
- Adaptive algorithms learn over time

FDA's Digital Health Center of Excellence provides leadership and strategic direction in these areas:

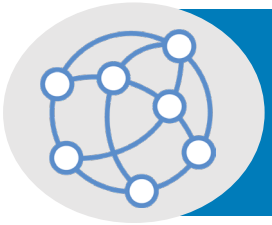
Digital Health Technology

Digital Health Policy and Guidance

Digital Health Innovation

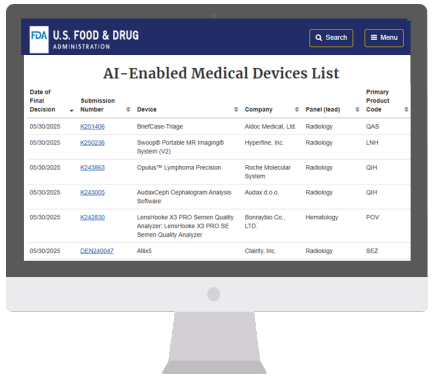


Digital Health Literacy

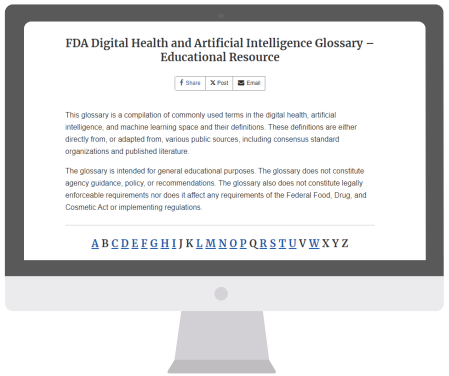


Digital Health Collaborations

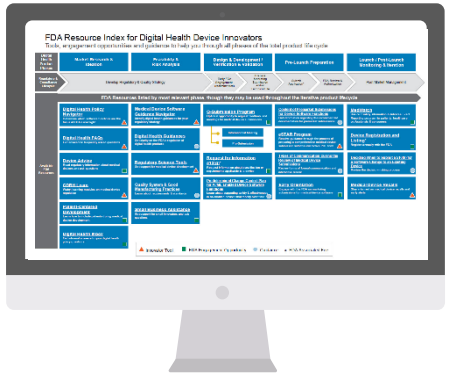
Digital Health AI Resources



AI-enabled Medical Device List



Digital Health & AI Glossary



Regulatory Accelerator

On our website: Artificial Intelligence in Software as a Medical Device (accessed at www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-software-medical-device).

A focused strategy for AI regulation

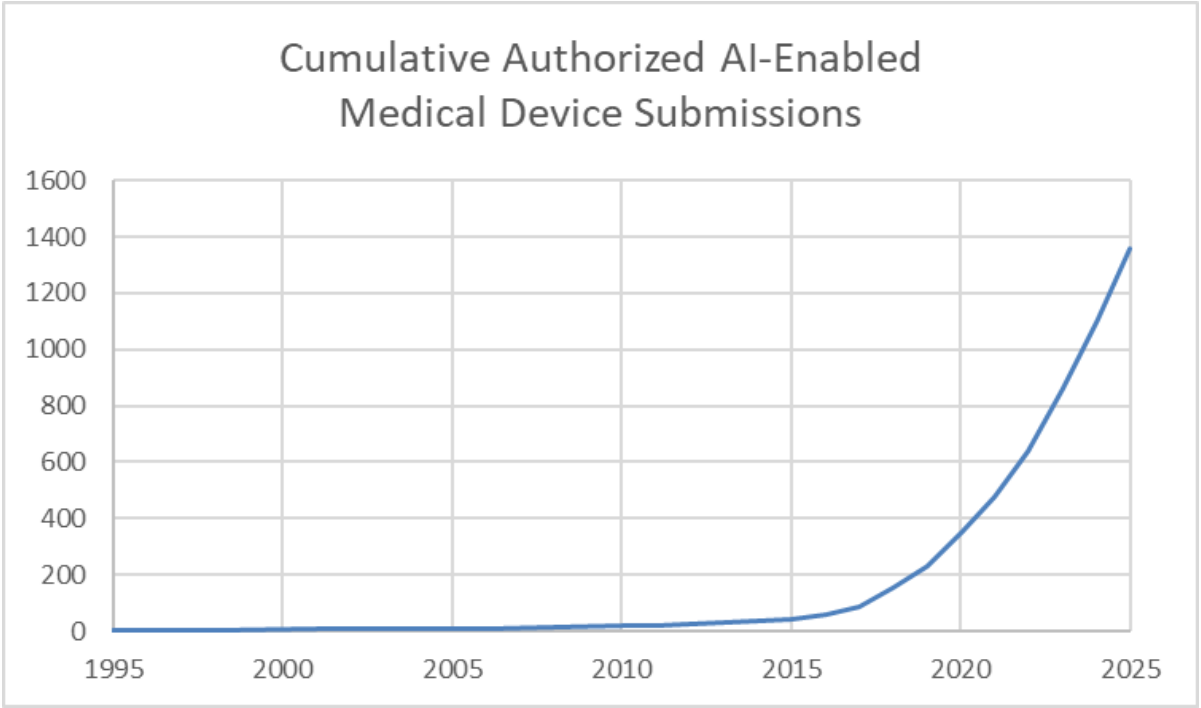
The CDRH AI Action Plan led to an approach to regulating AI from device concept to retirement

The approach to reviewing AI-enabled devices includes focusing on:

- How data for the product is managed
- How the algorithm used to generate information works
- Data to demonstrate the algorithm works as intended
- Monitoring the product as it is being used by patients

Moving Forward: CDRH's Draft AI Guidance (Jan 2025)

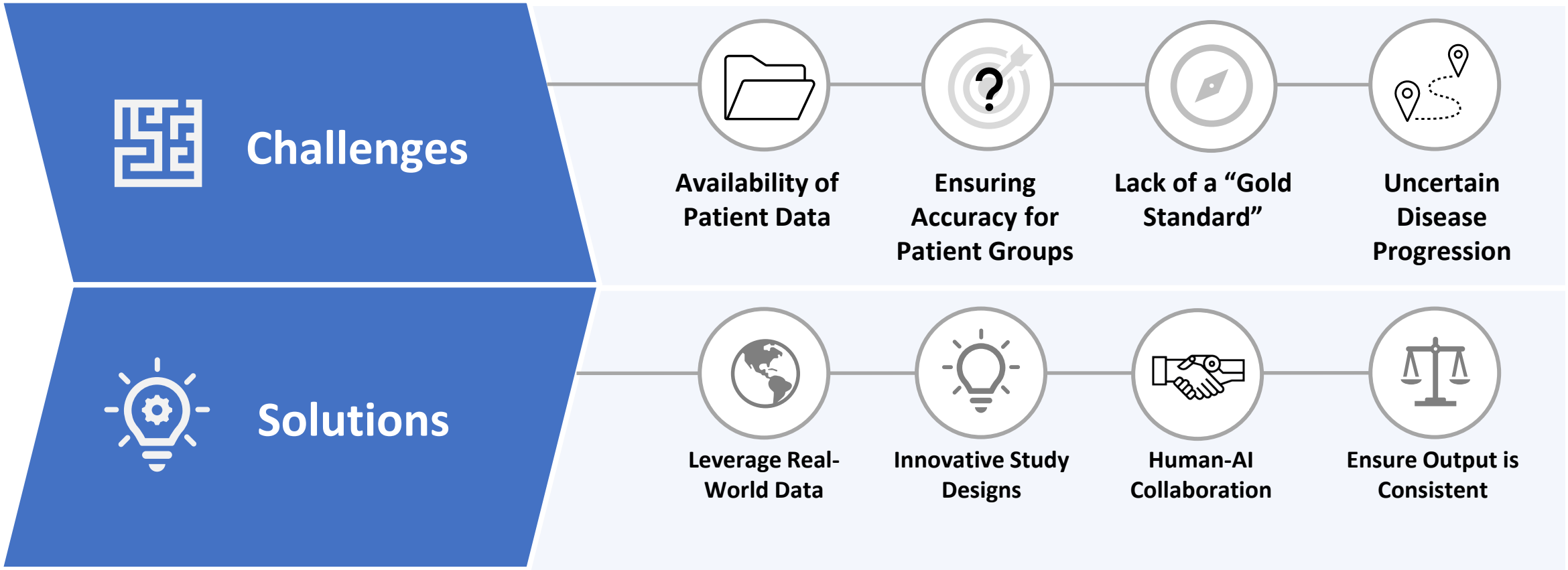
- We have many years of experience reviewing and authorizing over 1,300 AI-enabled devices.
- That depth of review experience informed our publication of guidance for innovators in 2025.



- This guidance helps medical device innovators understand what FDA is looking for and provides information on a clear and predictable path for these devices.

Source: Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations (Jan 2025) (accessed at https://www.fda.gov/media/184856/download).

Challenges: Making Sure that AI Works for Everyone



Challenges: Making Sure that AI Works for Everyone

Understanding How AI Makes Decisions:

Why This Matters:

- AI can be like a “black box” - hard to see how it works
- Patients and doctors need to trust AI recommendations
- Important to understand what AI can and cannot do

Goal is to provide enough information to make informed decisions without being overwhelming

FDA Expects Clear Information:

- Plain language about what the AI does
- Easy-to-understand instructions
- Information about how well AI works for different patient groups
- When possible, visual explanations of AI decisions

Challenge: Making Sure AI Works for All Patients

Recommendations:

Collect data from many places:

- Multiple, different types of hospitals across the U.S.

Include diverse patients:

- Patients from different groups
- Patients at different stages of disease
- Patients with other health conditions

Bottom Line:
FDA wants to make sure AI works safely and effectively for YOU.

Test AI separately from training:

- Use completely different patients to test the AI
- Ideally from different hospitals than where AI was developed

Opportunity: Learning from Real Patient Experiences

AI can help us learn from everyday patient care:

- Read and understand doctor's notes

- Combine information from many sources:
  - Electronic medical records
  - Patient registries (databases of patients with the same disease)
  - Wearable devices (like fitness trackers)
  - Medical images (X-rays, MRIs)
  - Genetic information

- Allow hospitals to share data while protecting patient privacy

Opportunity: Learning from Real Patient Experiences

FDA makes sure this data is trustworthy:

- Check that data is appropriate for the intended use
  - Does it represent the right patients?
  - Was it collected reliably?
- There is a clear plan before collecting data
- Watch out for biases in the data
- Encourage early conversations with FDA
- Track where data comes from and how it's used
- Monitor how AI performs in real-world use

Request For Public Comment: Measuring and Evaluating Artificial Intelligence-enabled Medical Device Performance in the Real-World

This Request for Public Comment is intended for discussion purposes only and does not represent draft or final guidance. It is not intended to propose or implement policy changes regarding the evaluation of devices which integrate artificial intelligence (AI), including generative AI (GenAI)-enabled technology. This document is not intended to communicate the FDA's proposed (or final) regulatory expectations but is instead meant to seek early feedback from groups and individuals outside the Agency and advance a broader discussion among the AI healthcare ecosystem on this topic.

The objective of this 'Request for Public Comment' is to obtain comment and feedback from interested parties and the public on a series of questions related to the current, practical approaches to measuring and evaluating the performance of AI-enabled medical devices in the real-world, including strategies for identifying and managing performance drift, such as detecting changes in input and output. Please submit your comments to https://www.regulations.gov, Docket No. FDA-2025-N-4203 for 'Measuring and Evaluating Artificial Intelligence-enabled Medical Device Performance in the Real World: Request for Public Comment.' FDA intends to consider all comments timely submitted to this docket (FDA-2025-N-4203) by December 1, 2025, related to this topic.

FDA asked the public for input
We asked how to assess how well AI devices perform in real-world use - including from patients and caregivers

Looking Ahead: Adaptive AI Systems with PCCP

Predetermined Change Control Plans (PCCP) - Opportunity for devices for rare diseases

AI/ML's key advantage:
Learns from real-world use and continuously improves performance

FDA Goal:
Enhance healthcare through safe, effective innovation that matches rapid software development cycles

Solution:
PCCPs allow manufacturers to make pre-authorized changes to AI-enabled devices without delay of a new submission

Benefits:
Manufacturers can optimize marketed devices faster

Source: Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence-Enabled Device Software Functions (Aug 2025)(accessed at www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial-intelligence).

Looking Ahead: GenAI considerations

	2024 Digital Health Advisory Committee Docket Responses: Overarching Points
1	Broad Participation and Interest
2	Focus on Regulatory Frameworks
3	Specific Use Case Examples
4	Emphasis on Transparency and Safety
5	Emphasized Need for Human Oversight

Source: Digital Health Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments—Total Product Lifecycle Considerations for Generative Artificial Intelligence-Enabled Medical Devices, 2024 (www.regulations.gov/document/FDA-2024-N-3924-0001)

Questions?

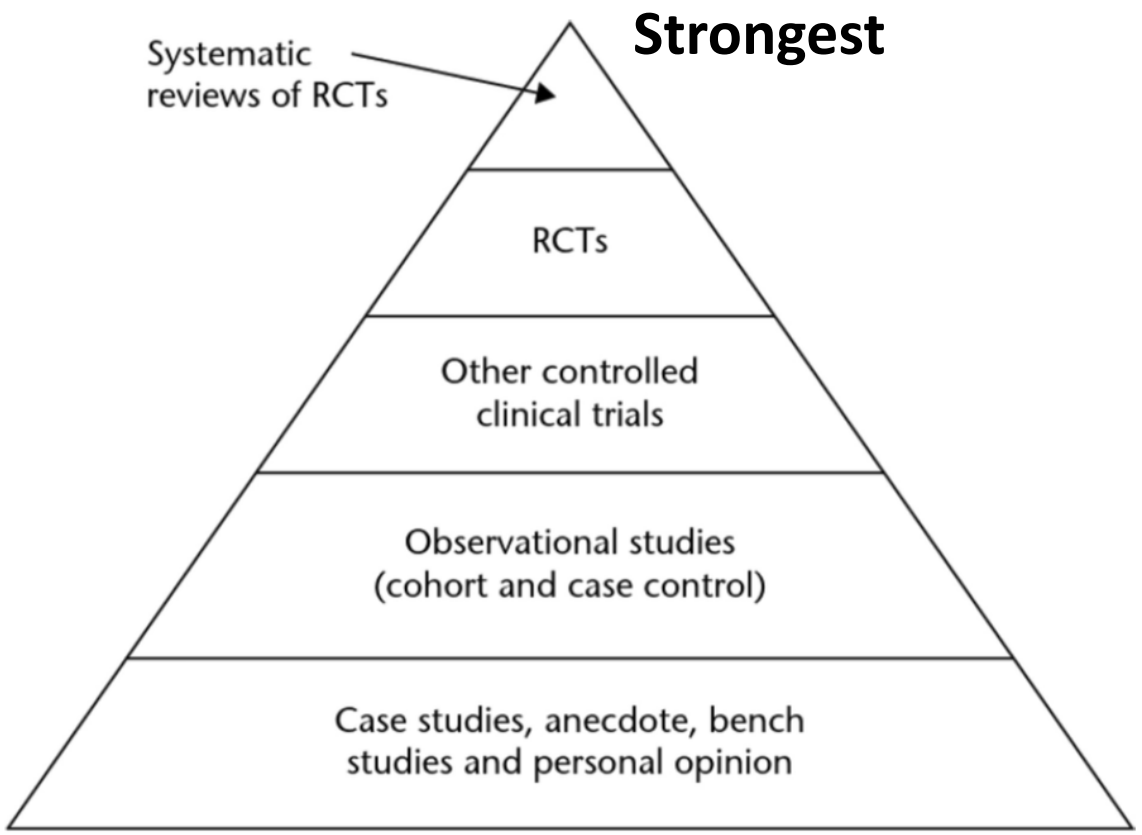
Contact Information:
Shawn.Forrest@fda.hhs.gov

Digital Health Center of Excellence
digitalhealth@fda.hhs.gov

Resources:
www.fda.gov/medical-devices/digital-health-center-excellence

Hierarchies of Study Design – Circa 1990

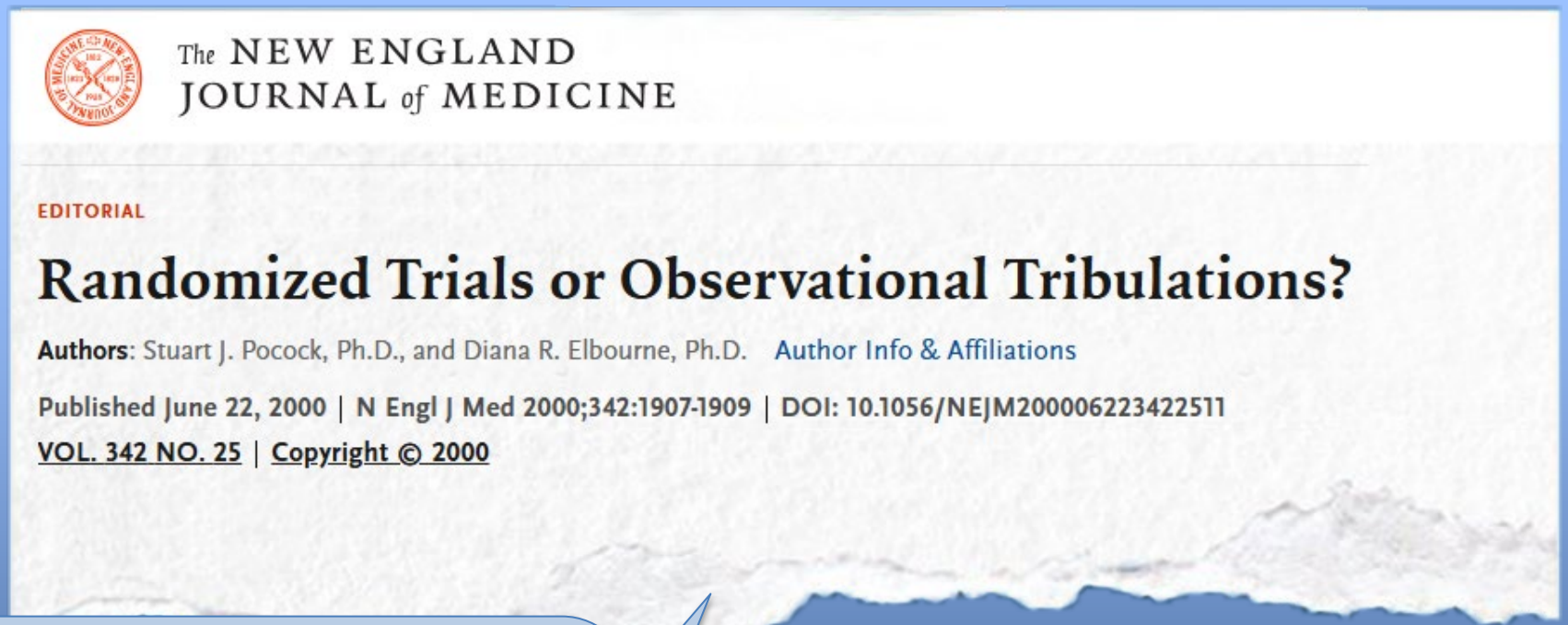
Strength of Evidence



Simplistic hierarchies of research design evolved in the 1990s, designating randomized controlled trials (RCTs) as "gold standard" and suggesting non-randomized study designs are not trustworthy

Adapted from Greenhalgh, Wiley-Blackwell (2010)

Debate– Early 2000s



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Randomized Trials or Observational Tribulations?

Authors: Stuart J. Pocock, Ph.D., and Diana R. Elbourne, Ph.D. Author Info & Affiliations

Published June 22, 2000 | N Engl J Med 2000;342:1907-1909 | DOI: 10.1056/NEJM200006223422511

VOL. 342 NO. 25 | Copyright © 2000

Editorial:
"Only randomized treatment assignment can provide a reliably unbiased estimate of treatment effects."

Debate– Early 2000s

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs

Authors: John Concato, M.D., M.P.H., Nirav Shah, M.D., M.P.H., and Ralph I. Horwitz, M.D. Author Info & Affiliations

Published June 22, 2000 | N Engl J Med 2000;342:1887-1892 | DOI: 10.1056/NEJM200006223422507

VOL. 342 NO. 25 |

"The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic."

‘Contemporary Debate’

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

The Magic of Randomization versus the Myth of Real-World Evidence

Authors: Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P. , and Richard Peto, F.R.S. Author Info & Affiliations

Published February 12, 2020 | N Engl J Med 2020;382:674-678 | DOI: 10.1056/NEJMsb1901642 | VOL. 382 NO. 7

Journal source: Clinical Pharmacology & Therapeutics

REVIEW

Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth

Hans-Georg Eichler[1,2,*], Francesco Pignatti[1], Brigitte Schwarzer-Daum[2,3], Ana Hidalgo-Simon[1], Irmgard Eichler[1], Peter Arlett[1,4], Anthony Humphreys[1], Spiros Vamvakas[1], Nikolai Brun[5] and Guido Rasi[1,6]

2020 Nov 12;109(5):1212–1218. doi: 10.1002/cpt.2083

Emergence of Real-World Evidence

Interest in RWE can be attributed to:

- **Improved access to, and rapid analysis of, information in the era of big data**
- **Research showing observational studies can generate results similar to those of randomized controlled trials (RCTs)**
- **21st Century Cures Act (2016) mandating that FDA evaluate the potential use of RWE for medical product approvals**

Note: With or without invoking the terms "RWD" and "RWE," types of data sources and study designs aren't entirely new and the standard for substantial evidence to approve drug and biologics remains unchanged.

Definitions

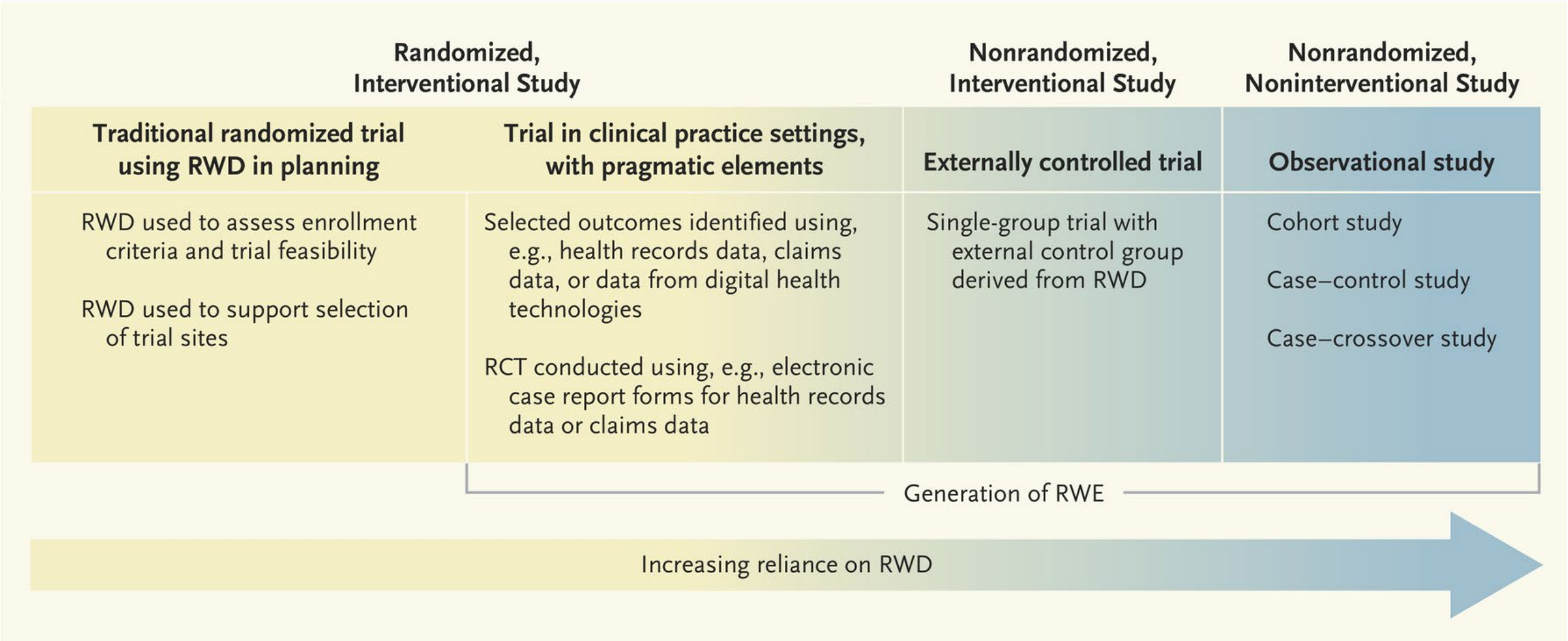
Real-World Data (RWD) are data relating to patient health status and/or delivery of health care **routinely collected from a variety of sources**

- **electronic health records (EHRs)**
- **medical claims data**
- **product and disease registries**
- **data from digital health technologies in non-research setting**
- **other data sources that can inform on health status, such as questionnaires**

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits/risks of a medical product **derived from analysis of RWD**

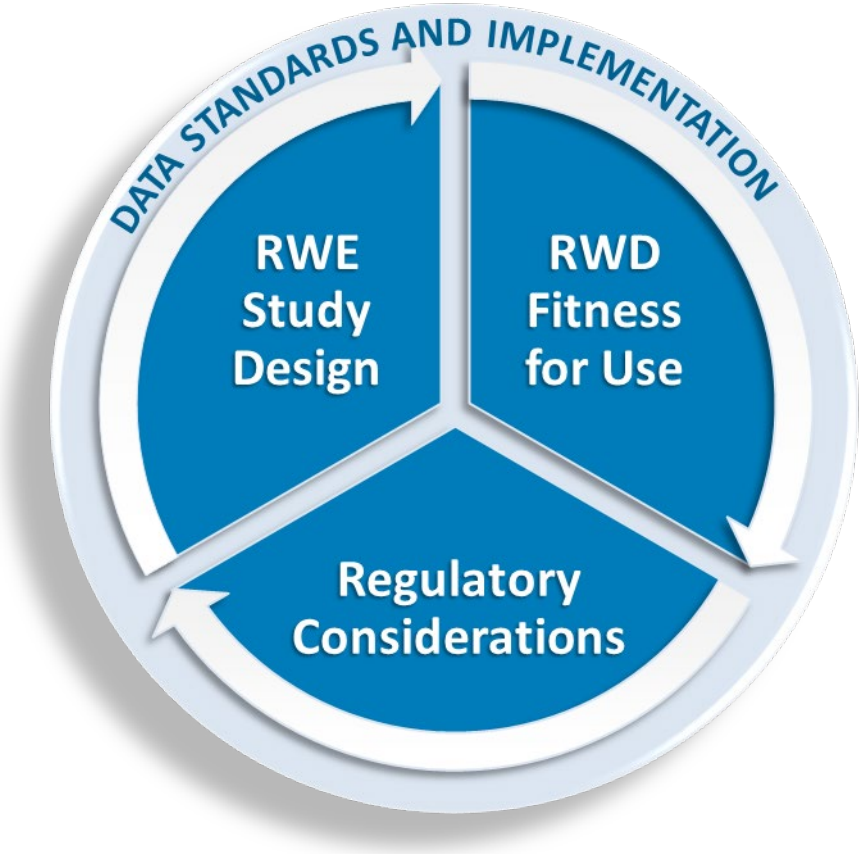
Generated using various study designs—including but not limited to randomized trials (e.g., pragmatic clinical trials), externally controlled trials, and observational studies

Reliance on RWD across study designs



N ENGL J MED 386;18 NEJM.ORG MAY 5, 2022

FDA Approach to Evaluating RWE



Key considerations:

- **Whether the RWD are fit for use (relevant and reliable)**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

Strengths of Real-World Evidence

- **Ability to capture unique, richer outcomes**
  - **For example, capturing data over a longer period of time**
- **Ability to study rare diseases**
  - **Disease-specific RWD sources may be useful for tracking progression or outcomes of diseases**
- **Address ethical issues regarding treatment assignment in a clinical trial**
  - **For example, can provide historic information where it may not be ethical to assign a trial participant to a control or sham**

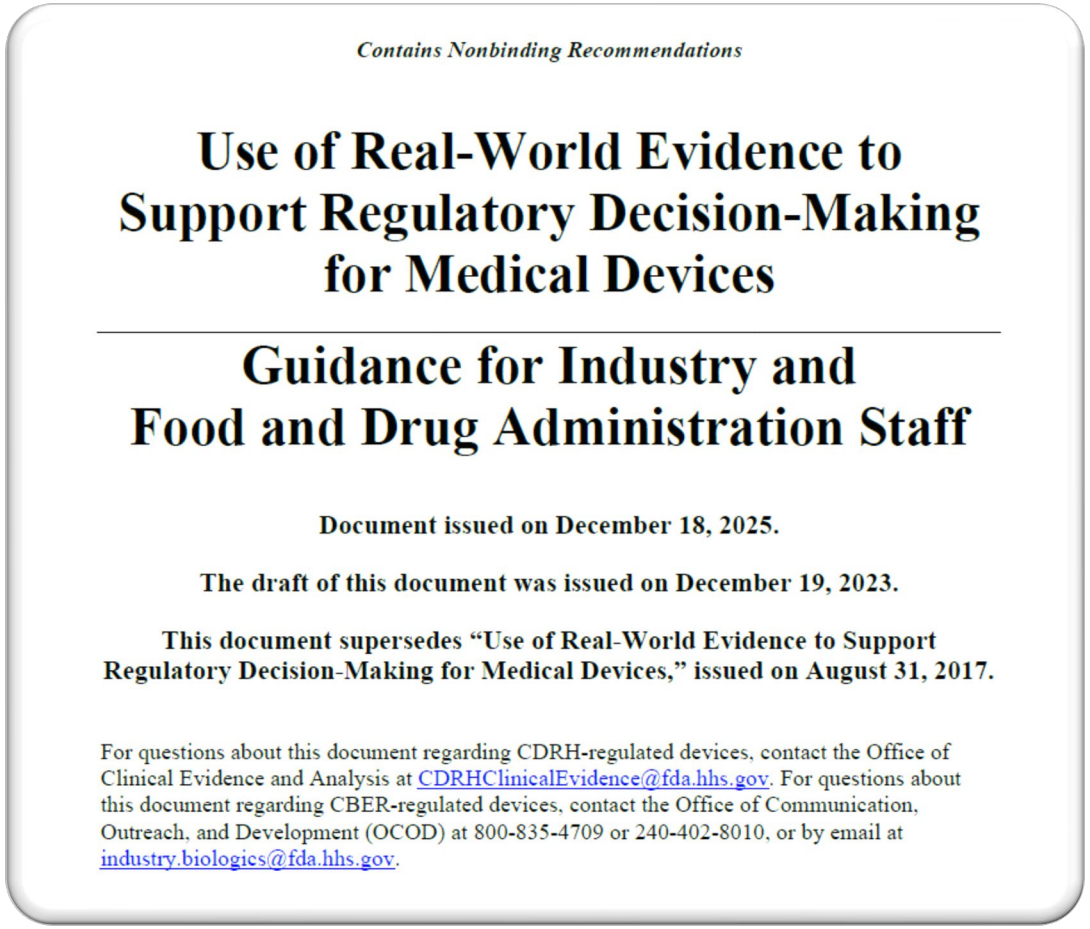
Considerations for data acceptability

- Rationale for choice of data source, if more than one available
- Quality of the data
  - Reliability
    - Accuracy
    - Completeness of key data elements
    - Traceability, including how data were originally collected & coded into variables
  - Relevance
    - Availability of key data elements, such as outcomes of interest & other clinical variables
    - Timing of assessments for key data elements
    - Generalizability

CDRH Real-World Evidence Guidance

2025 Revised RWE Guidance:

- Clarifies how CDRH evaluates real world data (RWD) to determine if it is of sufficient quality to generate RWE.
- Includes factors CDRH considers to assess whether RWD are relevant and reliable.
  - Accurate, complete, of sufficient quality, with appropriate patient protections



Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 18, 2025.

The draft of this document was issued on December 19, 2023.

This document supersedes "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," issued on August 31, 2017.

For questions about this document regarding CDRH-regulated devices, contact the Office of Clinical Evidence and Analysis at CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 800-835-4709 or 240-402-8010, or by email at industry.biologics@fda.hhs.gov.

Real-World Evidence at CDRH

Generalizability

- The study sample should represent the intended use population.

Representative Challenges with Use of RWE

Real-world data sources:

- data reliability and clinical relevance
- missing or "mistimed" data
- suitable capture of outcome data
- need for linkage with other data sources

Design and interpretation of non-randomized studies:

- residual confounding
- problems with index date ("zero time")
- use of inappropriate comparator

Conduct of non-randomized studies:

- protocol and analysis plan not *pre-specified*
- access to patient-level data and ability to inspect RWD sources

Real-World Evidence and Rare Diseases—Devices

Device Identification

- Unique Device Identifiers
- Hospital ordering information
- Procedure –unique devices

Patient Identification

- Diagnostic codes
- Procedure codes
- Unstructured data fields

Benefits to patients with rare diseases

- Generate better data that would otherwise not be available
- Identify patients for potential clinical trials

Approval of alpelisib (Vijoice®) - CDER

- **Indicated for treatment of adult and pediatric patients two years of age and older with severe manifestations of PIK3CA-related overgrowth spectrum (PROS) who require systemic therapy. CDER approved in 2022.**
- **RWD single arm study, EPIK-P1, in 37 patients with severe or life-threatening PROS treated with alpelisib collected from medical charts of patients in an expanded use program.**
- **RWD study was acceptable because:**
  - **Before abstracting data, there was a prospectively defined protocol for data collection and statistical analysis plan**
  - **Outcomes assessed by a blinded independent central review (BICR)**
  - **Broad eligibility criteria for the patients participating in the EAP, reducing concerns for selection bias.**
- **Regulatory programs used:**
  - **Orphan Drug Designation and Breakthrough Therapy Designation (2019)**
  - **Real-Time Oncology Review (RTOR) pilot program-streamlined data submission prior to the filing of the entire clinical application**
  - **Assessment Aid, a voluntary submission from the applicant to facilitate the FDA's assessment.**

Approval of onasemnogene abeparvovec-xioi (Zolgensma)- CBER

- **Indicated for treatment pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene. CBER approved in 2019.**
- **Fatal disease with unmet medical need**
- **Disease course: well-characterized and relatively homogeneous disease**
- **Historical controls from RWD were suitably comparable**
- **Two open-label trials:**
  - **Phase 1: Dose-escalation (low-dose n=3; high-dose n=12) compared with external control (n=23)**
  - **Phase 3: single- arm (n=21) compared with natural-history external controls (n=23)**
- **One adequate and well-controlled trial + confirmatory evidence**
- **Large treatment effect on survival**

Eonis™ SCID-SMA kit

Device: The Eonis™ SCID-SMA kit is intended as an aid in screening newborns for Severe Combined Immunodeficiency (SCID) and as an aid in screening newborns for X-linked agammaglobulinemia (XLA). The test is intended for DNA from blood specimens dried on a filter paper.

early diagnosis and treatment significantly alter outcomes

RWE included to support marketing authorization:

Hospital registry data were used to confirm control status

- age-matched controls;
- archived controls with matched storage time to positives;
- age of newborn specimen collection to mimic intended use population
- specimens with long enough follow up time (years) to confirm clinical status