Artificial Intelligence in Pharma: FDA and EMA Regulatory Perspectives

PDA Israel

Tel Aviv, February 2025

Iris Shamir

VP Pharma Quality and Medical Device, Gsap

לזכרה של סיגלית:

ד"ר סיגלית אריאלי-פורטנוי נפטרה באופן פתאומי ב-16 ביוני 2024. היא הותירה אחריה צוות מדהים ומסור שממשיך את רוחה ועבודתה. לסיגלית היה ניסיון רב שנים בתעשיית התרופות והיא הייתה בקיאה מאוד בתהליכים פרמצבטיים, תהליכי ניהול שינויים ובניית מפעלי ייצור. תפקידה בתרו היה סמנכ"לית בכירה לתפעול בישראל, ובטבע היא הייתה מנהלת מפעל ה OSD-אחראית על יותר מ-1,000 עובדי ייצור ומכירות שנתיות של 2.4 מיליארד דולר.

ד"ר סיגלית אריאלי-פורטנוי כיהנה כנשיאת הסניף הישראלי של ה PDA משנת 2003 עד 2006.

בשנת 2009, ד"ר סיגלית אריאלי-פורטנוי ייסדה את Gsap המספקת שירותי רגולציה, קליניקה, איכות וולידציה לחברות תרופות, ביוטכנולוגיה, תרפיה תאית ומכשור רפואי וכן לבתי חולים. בתפקיד זה, היא הובילה בהצלחה מאות ביקורות רגולטוריות על ידי משרד הבריאות הישראלי, ה FDA-ה EMA-וגופי הסמכה שונים. תחת ניהולה Gsap ביצעה עשרות הגשות רגולטוריות לתרופות ומכשירים חדשניים.

אנחנו גאים להמשיך את פעילות Gsap ברוחה.

הגדרת המשימה

- ❑ להכין הרצאה בנושא שאני לא מומחית בו
- ❑ הקהל לפחות בחלקו עוד פחות מומחה ממני
- ❑ שתישארו בחדר עד הפסקת הקפה

הלם מצעדי טראמפ בתחום הבריאות: דוחות לא מתפרסמים, נעצרו מענקי מחקר

שיבושים במערכת הבריאות האמריקנית: ממשל טראמפ הוביל להפסקת הפרסומים לציבור של סוכנויות הבריאות החשובות בעולם, לעיכוב במענקי מחקר ולפגיעה פוטנציאלית בתגובה לאיומים בריאותיים גלובליים. בנוסף, עדיין אין מנהל למרכזים לבקרת מחלות ומניעתן (CDC), בעיצומו של גל שפעת העופות. דוח מקרי המוות השבועי של ה-CDC לא פורסם לראשונה מאז 1960

Oracle Corp. ▼ ORCL -1.37% Get Free Report co-founder **Larry Ellison** unveiled plans for an artificial intelligence-driven cancer vaccine system that could deliver personalized treatments within 48 hours, speaking at a White House briefing alongside tech leaders and President **Donald Trump** on Tuesday.

What Happened: The announcement came as part of a broader $500 billion AI infrastructure initiative called Stargate, a joint venture between Oracle, **OpenAI**, and **SoftBank Group**. The project will establish massive data centers across the United States, starting with a facility in Abilene, Texas.

"We can diagnose cancer using AI through a simple blood test," Ellison explained during the briefing. "Once we sequence the genes of that cancer tumor, we can design an mRNA vaccine for each individual robotically using AI in about 48 hours."

The initiative sparked a rally in AI-related stocks, with Oracle shares climbing 7.17% to close at $172.57. Other tech companies also saw significant gains, with **NVIDIA Corp.** ▼ NVDA -4.35% Get Free Report rising 3.95%, **Arm Holdings plc** ▲ ARM +3.80% Get Free Report up 8.94%, and **Dell Technologies Inc.** ▼ DELL -1.85% Get Free Report advancing 4.20%.

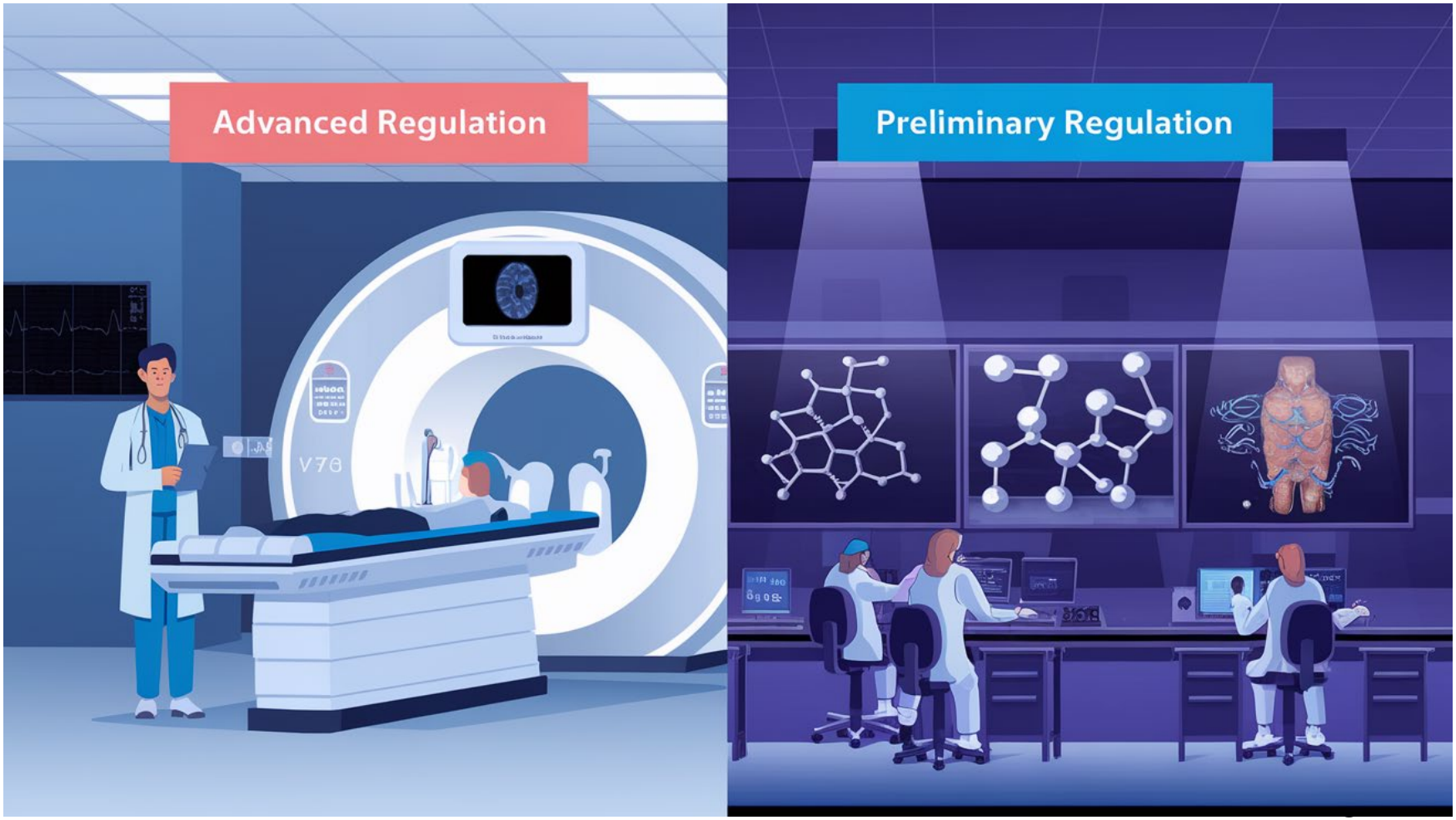
Medicines & Healthcare products Regulatory Agency

Draft guideline on individualised mRNA cancer immunotherapies

Press release

MHRA asks for views on proposed guidance to support the safe regulation of new personalised cancer therapies

Published
3 February 2025


Advanced Regulation
Preliminary Regulation

FDA Experience with AI/ML

FDA has accumulated substantial experience with artificial intelligence (AI) and machine learning (ML) technologies, particularly in the realm of medical devices.

As of September 27, 2024, the U.S. Food and Drug Administration (FDA) has **authorized 1018** AI/ML-enabled medical devices.

In contrast, the FDA's experience with AI applications in pharmaceuticals and biological products is comparatively limited.
Since 2016, the FDA has received over **500 submissions** for drugs and biological products incorporating AI components.

Contains Nonbinding Recommendations

Draft – Not for Implementation

Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on January 7, 2025.

You should submit comments and suggestions regarding this draft document 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, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the Digital Health Center of Excellence at digitalhealth@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov. For questions about this document regarding CDER-regulated products, contact druginfo@fda.hhs.gov. For questions about this document regarding combination products, contact the Office of Combination Products at combination@fda.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Office of Combination Products in the Office of the Commissioner

Contains Nonbinding Recommendations

Draft – Not for Implementation

Table of Contents

Tala Fakhouri -

Associate Director for Data Science and AI Policy at FDA

How Does FDA develop the guidance on AI in Pharma

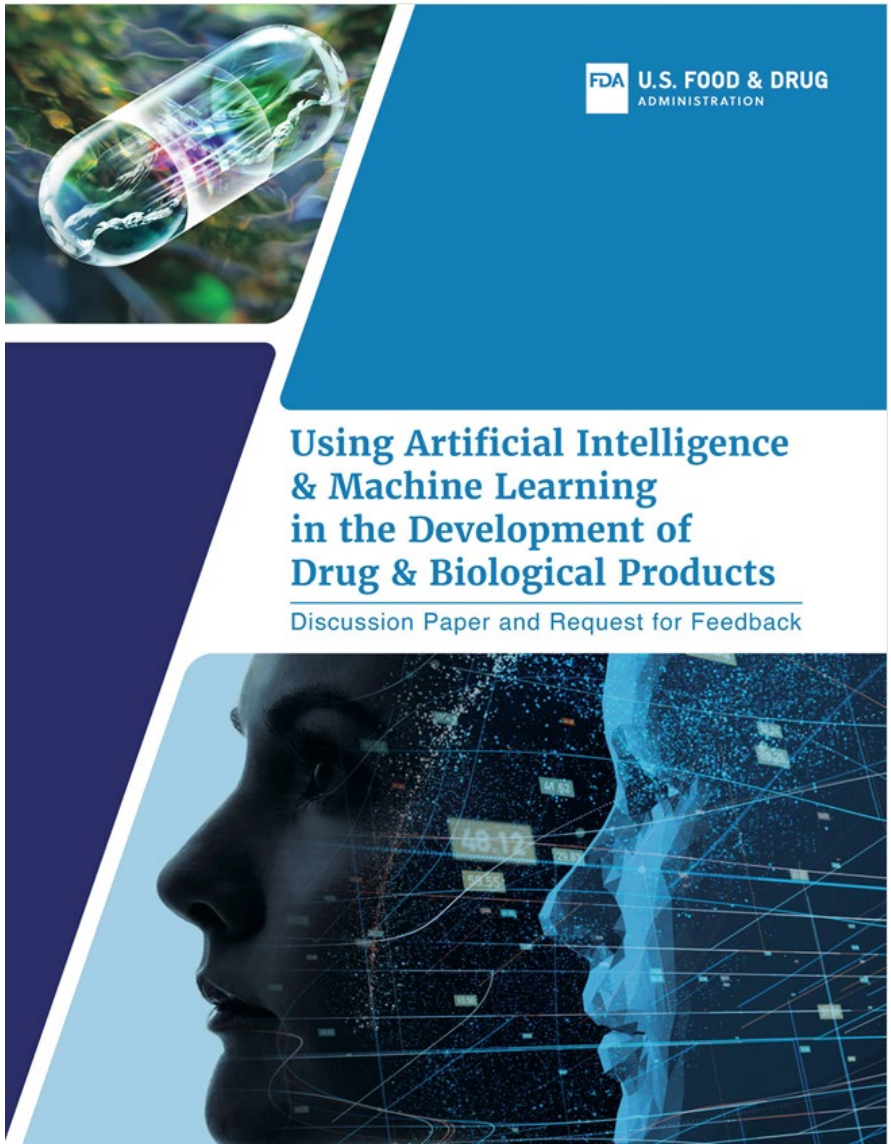
- FDA-sponsored expert workshop convened by the Duke Margolis Institute for Health Policy in Dec. 2022.

  (Israeli Participants: **Dr. Catherine Ela** & **Anat Boehm-Cagan** Ministry of Health, Israel)

- In 2023, **CBER** has joined **CDER** in the effort to provide regulatory guidelines for the use of AI technologies in drug manufacturing. **Two discussion papers were published and FDA received more than 800 comments from interested parties**

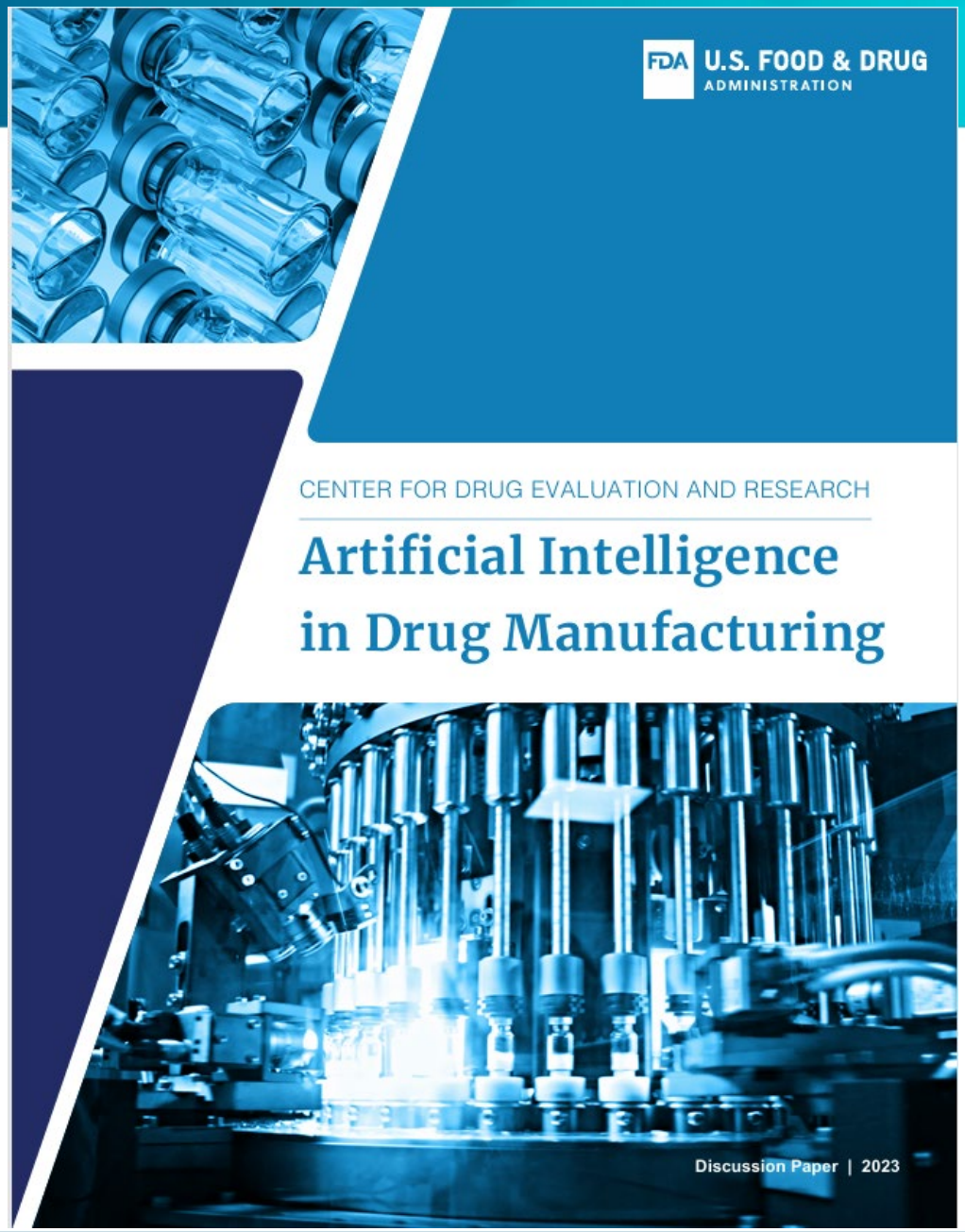
- In March 2024, FDA issued "Artificial Intelligence & Medical Products: How **CBER**, **CDER**, **CDRH**, and **OCP** are Working Together"

- On 06th January 2025 a draft guidance was issued: "**Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products"**


FDA U.S. FOOD & DRUG ADMINISTRATION
Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products
Discussion Paper and Request for Feedback

Current and Potential Uses of AI/ML in Drug Development

- Drug Discovery
- Nonclinical Research
- Clinical Research
- Postmarket Safety Surveillance
- Advanced Pharmaceutical Manufacturing


FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Artificial Intelligence in Drug Manufacturing
Discussion Paper | 2023

Process Design and Scale-up:

- AI models such as machine learning—generated using process development data—could be leveraged to more quickly identify optimal processing parameters or scale-up processes, reducing development time and waste

Advanced Process Control (APC):

- AI methods can develop dynamic control systems that adjust process parameters in real-time based on sensor data.
- Example: In a fermentation process, AI can continuously monitor variables like pH, temperature, and nutrient levels, making real-time adjustments to maintain optimal conditions for microbial growth.
- **APC approaches that combine an understanding of the underlying chemical, physical, and biological transformations occurring in the manufacturing process with AI techniques are expected to see increasing adoption and have already been reported by several pharmaceutical manufacturers.**

Process Monitoring and Fault Detection:

- AI methods can be used to monitor equipment and detect changes from normal performance that trigger maintenance activities, reducing process downtime.
- AI methods can also be used to monitor product quality, including quality of packaging (e.g., vision-based quality control that uses images of packaging, labels, or glass vials that are analyzed by AI-based software to detect deviations from the requirements of a product's given quality attribute)

Trend Monitoring:

- **AI can be used to examine consumer complaints and deviation reports** containing large volumes of text to identify cluster problem areas and prioritize areas for continual improvement.
- **AI methods integrated with process performance and process capability metrics can be used to proactively monitor manufacturing operations for trends**. These methods can also predict thresholds for triggering corrective and preventive action effectiveness evaluations

Areas of Consideration and potentially Associated Requirements

Cloud applications may affect oversight of pharmaceutical manufacturing data and records

- **Data integrity and data quality must be ensured in these environments**.
- Existing **quality agreements between the manufacturer and a third party** (e.g., for cloud data management) may have gaps with respect to **managing the risks of AI** in the context of manufacturing monitoring and control.
- **During inspections, this may lead to challenges in ensuring that the third-party creates and updates AI software with appropriate safeguards for data safety and security**.
- **Further, FDA inspection approaches for evidence gathering of records management may need to expand due to the complexity of managing third-party cloud data and models**

Areas of Consideration and potentially Associated Requirements

Regulations:

21 CFR 11, 211.180, 211.184, 211.194, 600.12

- **Draft Guidance for Industry:**

Data Integrity and Compliance with CGMP (April 2016)

- **Guidance for Industry:**
  - **Contract Manufacturing Arrangements for Drugs: Quality Agreements (November 2016)**
  - **ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)**

Areas of Consideration and potentially Associated Requirements

Digitizing manufacturing controls – increase in data recorded and analyzed–
which data needs to be stored and/or reviewed and how loss of these data would impact future quality decisions such as product recalls?

How about retrieval ability?

Privacy requirements?

A need for clarity regarding regulatory compliance for the generated data.

Areas of Consideration and potentially Associated Requirements

Applicants may need clarity about whether and how the application of AI in pharmaceutical manufacturing is subject to regulatory oversight.

- AI could be used in various manufacturing operations such as monitoring and maintaining equipment, identifying areas for continuous improvement, scheduling and supply chain logistics, and characterizing raw materials.
- Applicants will need to understand the applications of AI in manufacturing operations that are subject to regulatory oversight (e.g., CGMP compliance, new drug or biologics license applications)

Areas of Consideration and potentially Associated Requirements

How to validate AI models –

Biases? As AI methods become more complex, it becomes more challenging to explain how changes in model inputs impact model outputs. In these cases, applicants may be challenged to define standards that validate the model and sustain the explainability of the model's output and impact on product quality.

Areas of Consideration and potentially Associated Requirements

Continuously learning AI systems that adapt to real-time data may challenge regulatory assessment and oversight

Applicants may need clarity on:

(a) the expectations for verification of **model lifecycle strategy** and the approach for FDA's examination of continuously updated AI control models during a site inspection, and

(b) (b) expectations for **establishing product comparability** after changes to manufacturing conditions introduced by the AI model, **especially for biological products**

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

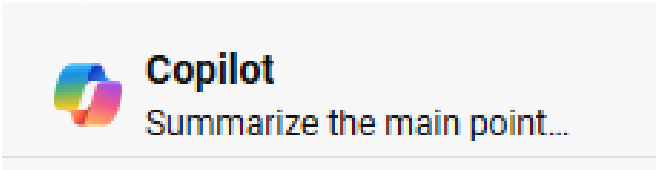
This guidance document is being distributed for comment purposes only.

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



Scope

- **Focuses** on AI models used to produce information or data **for regulatory decision-making.**
- **Excludes** AI use in **drug discovery and operational efficiencies** that do not impact patient safety, drug quality, or study reliability.

Example 1 Summary

Question of Interest:

- **Clinical Development**: Drug A is associated with a life-threatening adverse reaction. The question is: "Which participants can be considered low risk and do not need inpatient monitoring after dosing?"

Context of Use (COU):

- **Clinical Development**: An AI model will predict a participant's risk for the adverse reaction based on baseline characteristics and lab values. The AI model will stratify participants into low- and high-risk groups, determining their need for inpatient or outpatient monitoring.

Example 1 Summary

Model Risk Assessment:

•**Clinical Development**:

- **Model Influence**: High, as the AI model is the sole determinant for patient monitoring.
- **Decision Consequence**: High, due to the potential life-threatening nature of the adverse reaction if misclassified.

Example 2 Summary

Question of Interest:

- **Commercial Manufacturing**: Drug B is a parenteral injectable dispensed in a multidose vial. The question is: “Do vials of Drug B meet established fill volume specifications?”

Context of Use (COU):

- **Commercial Manufacturing**: An AI-based visual analysis system will perform 100% automated assessment of the fill level in the vials to determine if a deviation in volume has occurred. Independent verification of the fill volume is performed on a representative sample for each batch, so the AI model is not the sole determinant for product release.

Example 2 Summary

Model Risk Assessment:

•Commercial Manufacturing:

- **Model Influence**: Low, because the AI model is not the sole determinant for product release.
- **Decision Consequence**: High, due to the critical nature of fill volume for product quality and potential medication errors.

Determination of Model Risk:

•Given that the decision consequence is high and the model influence is low due to the independent verification process, **the overall model risk for this COU is determined to be medium**. This medium risk level indicates that while the AI model plays a significant role in assessing fill volume, the additional verification steps help mitigate the potential impact of any errors made by the AI model.

Early Engagement

"**FDA strongly encourages sponsors and other interested parties** to engage early with FDA to

(1) set expectations regarding the appropriate credibility assessment activities for the proposed model based on model risk and COU and

(2) help identify potential challenges and how such challenges may be addressed".

Table 1. Engagement Options Other Than Formal Meetings

Engagement Option	Intended Use of AI Model	Contact Information
Center for Clinical Trial Innovation (C3TI)	Sponsor is interested in discussing the use of AI in clinical trial designs with CDER before formally submitting them to their investigational new drug (IND) application	Email CDER C3TI program at CDERclinicaltrialinnovation@fda.hhs.gov
Complex Innovative Trial Design Meeting Program (CID)	Sponsor is interested in using AI in novel clinical trial designs	For details about how to apply for the CID program, please see http://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program FDA encourages sponsors to send an email to CID.Meetings@fda.hhs.gov to provide notification that your CID meeting request application has been submitted.
Drug Development Tools (DDTs) and Innovative Science and Technology Approaches for New Drugs (ISTAND)	Sponsor or other interested party is interested in qualifying a drug development tool that uses AI, such as use of AI-based algorithms to evaluate patients, adjudicate endpoints, or analyze clinical trial data	Email CDER Biomarker Qualification Program at CDER-BiomarkerQualificationProgram@fda.hhs.gov Email CDER Clinical Outcome Assessment Qualification Program at COADDTQualification@fda.hhs.gov Email CDER and CBER Animal Model Qualification Program at

EU

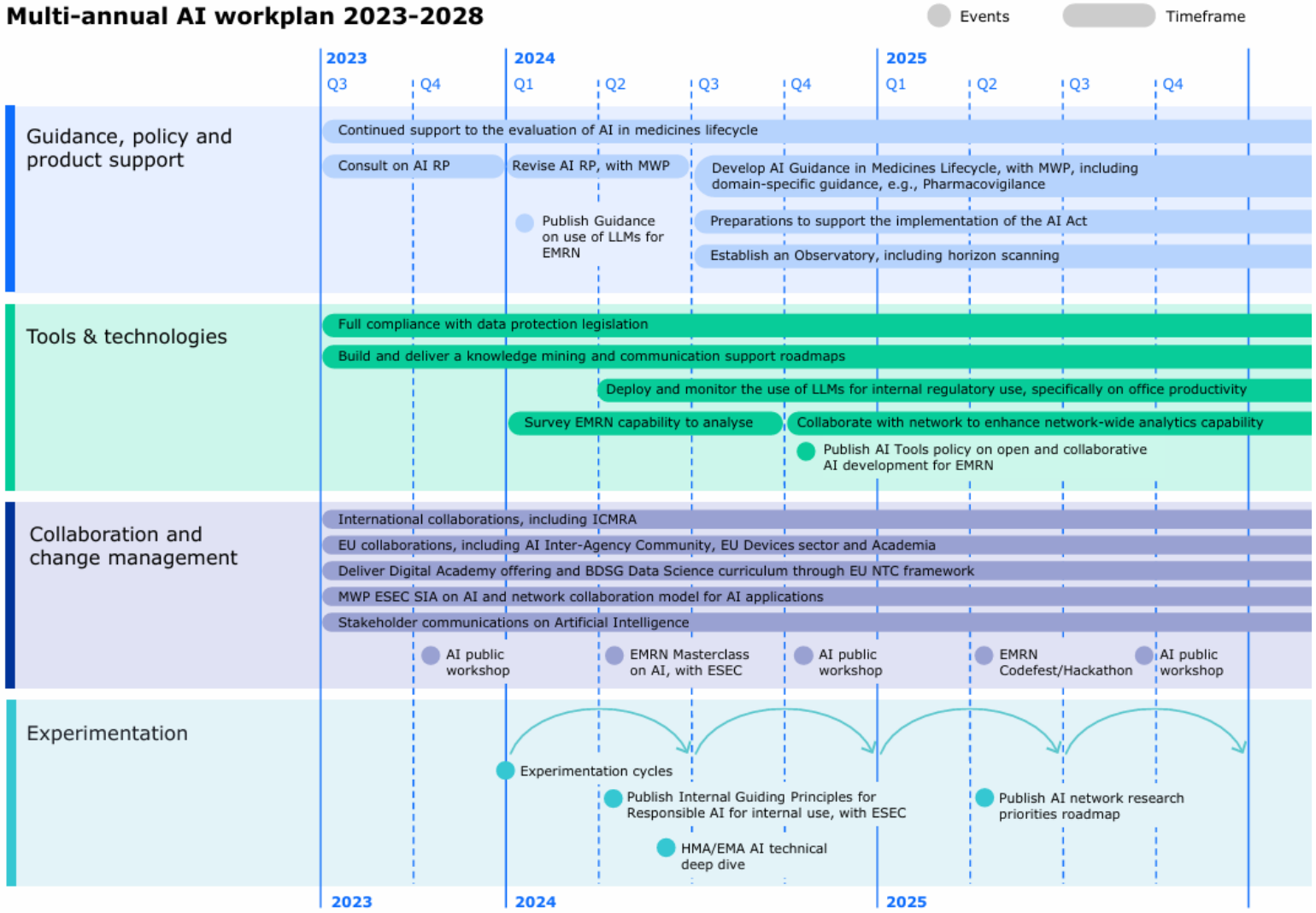
The **EU Artificial Intelligence Act (AI Act)** is a comprehensive legal framework designed to regulate AI systems within the European Union. Here are some key points:

1.Risk-Based Classification: AI systems are classified into four risk categories:

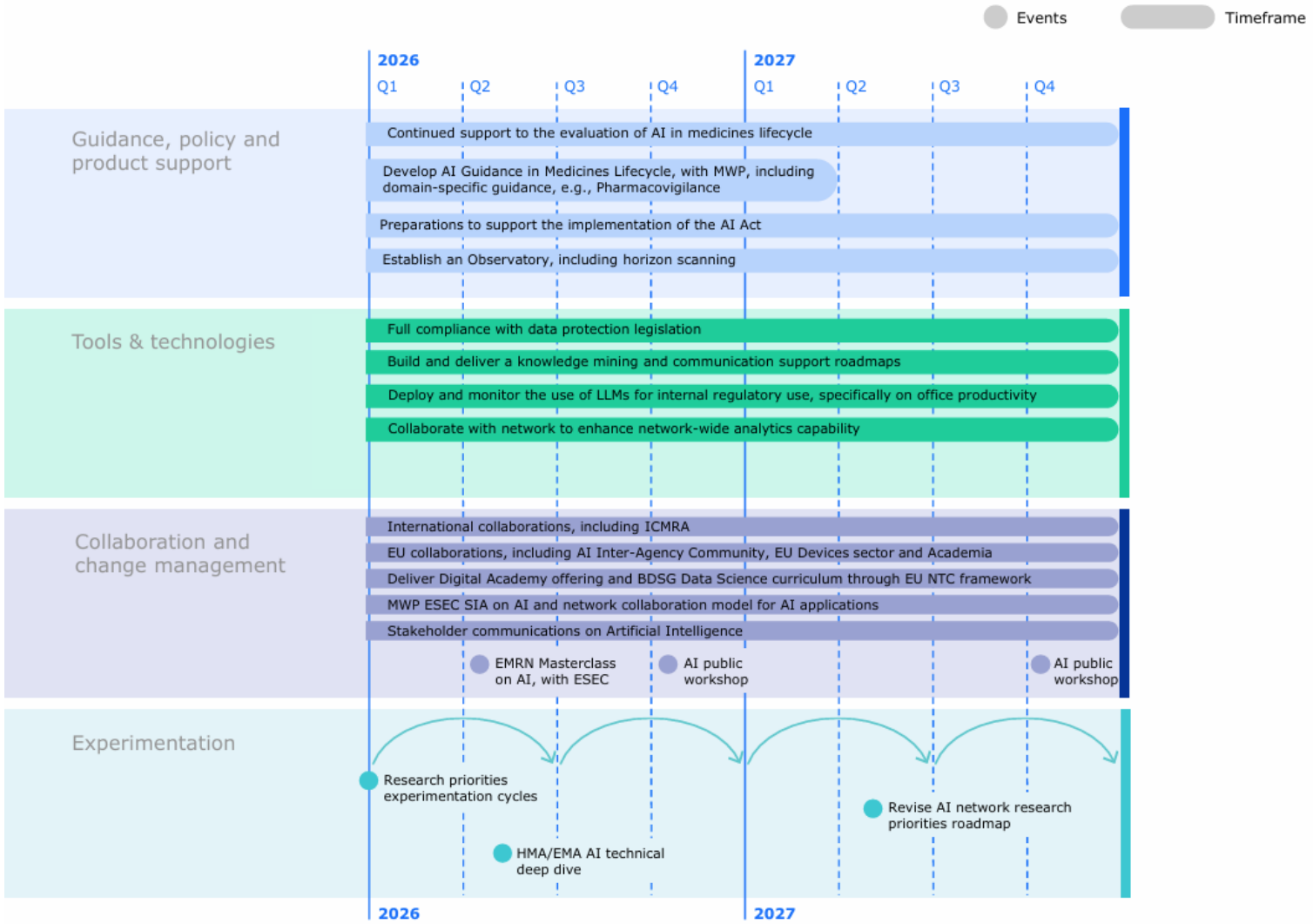
1. **Unacceptable Risk**: Prohibited systems, such as social scoring and manipulative AI.
2. **High Risk**: Systems impacting safety or fundamental rights, like those in healthcare and law enforcement, subject to strict regulations[2].
3. **Limited Risk**: Systems with lighter transparency obligations, such as chatbots[1].
4. **Minimal Risk**: Mostly unregulated systems, like AI in video games

The **EU AI Act** came into force on **August 1, 2024**.
Full enforcement of the Act will begin on **August 2, 2026**.


EMA
EUROPEAN MEDICINES AGENCY
HMA
Heads of Medicines Agencies
Multi-annual AI workplan 2023-2028
HMA-EMA Big Data Steering Group
VERSION 1 – NOVEMBER 2023
Bigdata@ema.europa.eu


Multi-annual AI workplan 2023-2028
Events
Timeframe
2023
Q3
Q4
2024
Q1
Q2
Q3
Q4
2025
Q1
Q2
Q3
Q4
Guidance, policy and product support
Continued support to the evaluation of AI in medicines lifecycle
Consult on AI RP
Revise AI RP, with MWP
Develop AI Guidance in Medicines Lifecycle, with MWP, including domain-specific guidance, e.g., Pharmacovigilance
Publish Guidance on use of LLMs for EMRN
Preparations to support the implementation of the AI Act
Establish an Observatory, including horizon scanning
Tools & technologies
Full compliance with data protection legislation
Build and deliver a knowledge mining and communication support roadmaps
Deploy and monitor the use of LLMs for internal regulatory use, specifically on office productivity
Survey EMRN capability to analyse
Collaborate with network to enhance network-wide analytics capability
Publish AI Tools policy on open and collaborative AI development for EMRN
Collaboration and change management
International collaborations, including ICMRA
EU collaborations, including AI Inter-Agency Community, EU Devices sector and Academia
Deliver Digital Academy offering and BDSG Data Science curriculum through EU NTC framework
MWP ESEC SIA on AI and network collaboration model for AI applications
Stakeholder communications on Artificial Intelligence
AI public workshop
EMRN Masterclass on AI, with ESEC
AI public workshop
EMRN Codefest/Hackathon
AI public workshop
Experimentation
Experimentation cycles
Publish Internal Guiding Principles for Responsible AI for internal use, with ESEC
HMA/EMA AI technical deep dive
Publish AI network research priorities roadmap
2023
2024
2025
Classified as public by the European Medicines Agency

EU



Workplan Overview

•**Guidance and Policy**: Development of AI guidance, including domain-specific areas like pharmacovigilance.

•**Tools and Technologies**: Compliance with data protection, implementation of AI tools, and monitoring their use.

•**Collaboration**: Enhancing network-wide analytics capability and international collaborations.

•**Experimentation**: Conducting experimentation cycles to expedite learning and reduce uncertainty.

Key Dates

•**2023-2024**: Public consultation on AI reflection paper, preparation for AI Act, and initial implementation of AI observatory.

•**2024-2027**: Annual public workshops, technical deep dives, and publication of AI research priorities roadmap.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 September 2024
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023
Final version agreed by MWP	6 September 2024
Final version adopted by CHMP	9 September 2024
Final version adopted by CVMP	11 September 2024

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

- Data protection – appears 11 times in this reflection paper

- "This reflection paper describes the current experience of EMA in a field where scientific knowledge is fast evolving. It should be read in coherence with both legal requirements and overarching EU principles and legislation on AI (**including the AI act and AI liability directive**), data protection (including **GDPR**), cyber security (including the **Cybersecurity act**), and medicines regulation (see references)

- "It is **the responsibility of the applicant or MAH** to ensure that all personal data, including those indirectly held within AI/ML models, are stored and processed in accordance with Union data protection legislation"

General Considerations

- **Risk-Based Approach**: AI/ML tools should be developed and deployed using a risk-based approach, considering potential impacts on patient safety and regulatory decision-making.
- **Early Regulatory Interaction**: Early interaction with regulatory authorities is advised for AI/ML systems impacting the benefit-risk balance of a medicinal product.
- **Responsibility**: Clinical trial sponsors, marketing authorization holders (MAHs), and manufacturers must ensure AI/ML systems comply with legal, ethical, technical, scientific, and regulatory standards.
- **Risk Management**: Relevant risks should be systematically managed throughout the AI system lifecycle, from early development to decommissioning.

AI in the Lifecycle of Medicinal Products

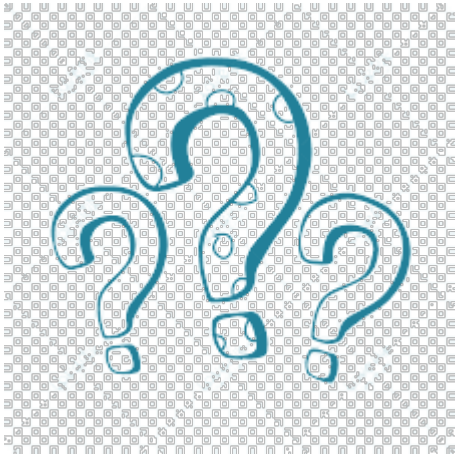
- **Drug Discovery**: AI can enhance drug discovery but must be managed to avoid bias. If results contribute to regulatory review, principles for non-clinical development must be followed.
- **Non-clinical Development**: AI can improve data analysis and reduce animal testing, adhering to Good Laboratory Practice (GLP) guidelines.
- **Clinical Trials**: AI must comply with Good Clinical Practice (GCP) guidelines and be carefully monitored. AI systems used in clinical trials may be considered medical devices and must comply with relevant regulations.

AI in the Lifecycle of Medicinal Products

- **Precision Medicine**: AI can individualize treatment but requires careful regulatory oversight. Applications in precision medicine are considered high patient risk and high regulatory impact.
- **Manufacturing**: AI can optimize manufacturing processes, adhering to quality risk management principles and guidelines like ICH Q8, Q9, and Q10.
- **Post-authorization**: AI can support post-authorization activities like pharmacovigilance but must be validated and monitored.

- **US:**
- At this stage More advanced guidance
- Focus on data integrity
- **EU**
- Holistic approach – Legislation (AI – Act)
- 5 years plans
- Focus on data protection and privacy
- No advanced guidance published

שאלות



תודה על ההקשבה

www.Gsap.co.il

Iris@Gsap.co.il