EPSTEIN BECKER GREEN

AI Regulation in Drug Discovery and Development

Bradley Merrill Thompson

EPSTEIN
BECKER
GREEN

AI Discrimination in Healthcare

Causes of Bias in Clinical Algorithms

Don’t confuse AI bias with human prejudice

Does not depend on the deliberate or the unusual, but only on a connection to patients

- It is:
  - harmful statistical bias, and
  - covers a wide range of human demographics including poverty and rural Americans
- Case study, an algorithm to detect possible sepsis
  - Unpacking Averages: Understanding the Potential for Bias in a Sepsis Prediction Algorithm, a Case Study, Health Law Advisor, June 1, 2023
    - The use of data that differ by race
    - The use of hardware that performs differently for people of different races
    - The use of physician text notes
- Millions of black people affected by racial bias in health-care algorithms: Nature 574, 608-609 (2019)
  - Study reveals rampant racism in decision-making software used by US hospitals

Mission in the Drug Industry

Notice the FDA language

1. Safe and effective in general population
2. Safe and effective in a specific sub-population
    a. Consider a diagnostic that is 99% accurate in white males and 70% accurate in black females

EPSTEIN
BECKER
GREEN

Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence

President's October 30 Executive Order

Section 8 covers healthcare

(v) Within 365 days of the date of this order, the Secretary of HHS shall develop a strategy for regulating the use of AI or AI-enabled tools in drug-development processes. The strategy shall, at a minimum:

(A) define the objectives, goals, and high-level principles required for appropriate regulation throughout each phase of drug development;

(B) identify areas where future rulemaking, guidance, or additional statutory authority may be necessary to implement such a regulatory system;

(C) identify the existing budget, resources, personnel, and potential for new public/private partnerships necessary for such a regulatory system; and

(D) consider risks identified by the actions undertaken to implement section 4 of this order.

“Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products” May 2023

A. Drug Discovery
   1. Drug Target Identification, Selection, and Prioritization
   2. Compound Screening and Design

B. Nonclinical Research

C. Clinical Research
   1. Recruitment
   2. Selection of Trial Participants
   3. Dose/Dosing Regimen Optimization
   4. Adherence
   5. Retention
   6. Site Selection
   7. Clinical Trial Data Collection, Management, and Analysis
   8. Clinical Endpoint Assessment

D. Postmarket Safety Surveillance
   1. Case Processing
   2. Case Evaluation
   3. Case Submission

E. Advanced Pharmaceutical Manufacturing
   1. Optimization of Process Design
   2. Advanced Process Control
   3. Smart Monitoring and Maintenance
   4. Trend Monitoring

Areas to Expect Regulatory Developments

Authorities FDA can use

- **Good Laboratory Practice** regulations (21 CFR 58.1) for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by FDA to assure the quality and integrity of the data.
- **Good Clinical Practice** regulations (e.g. 21 CFR 312) regulate scientific studies that are designed to develop evidence to support the safety and effectiveness of investigational drugs GCPs are intended to ensure the integrity of clinical data on which product approvals are based and to help protect the rights, safety, and welfare of human subjects.

Guidance FDA is considering

1. Human-led governance, accountability, and transparency;
2. Quality, reliability, and representativeness of data;
    a) Including bias, integrity, privacy and security, provenance, relevance, replicability, reproducibility and representativeness
3. Model development, performance, monitoring, and validation.

Comments or Questions

EPSTEIN BECKER GREEN

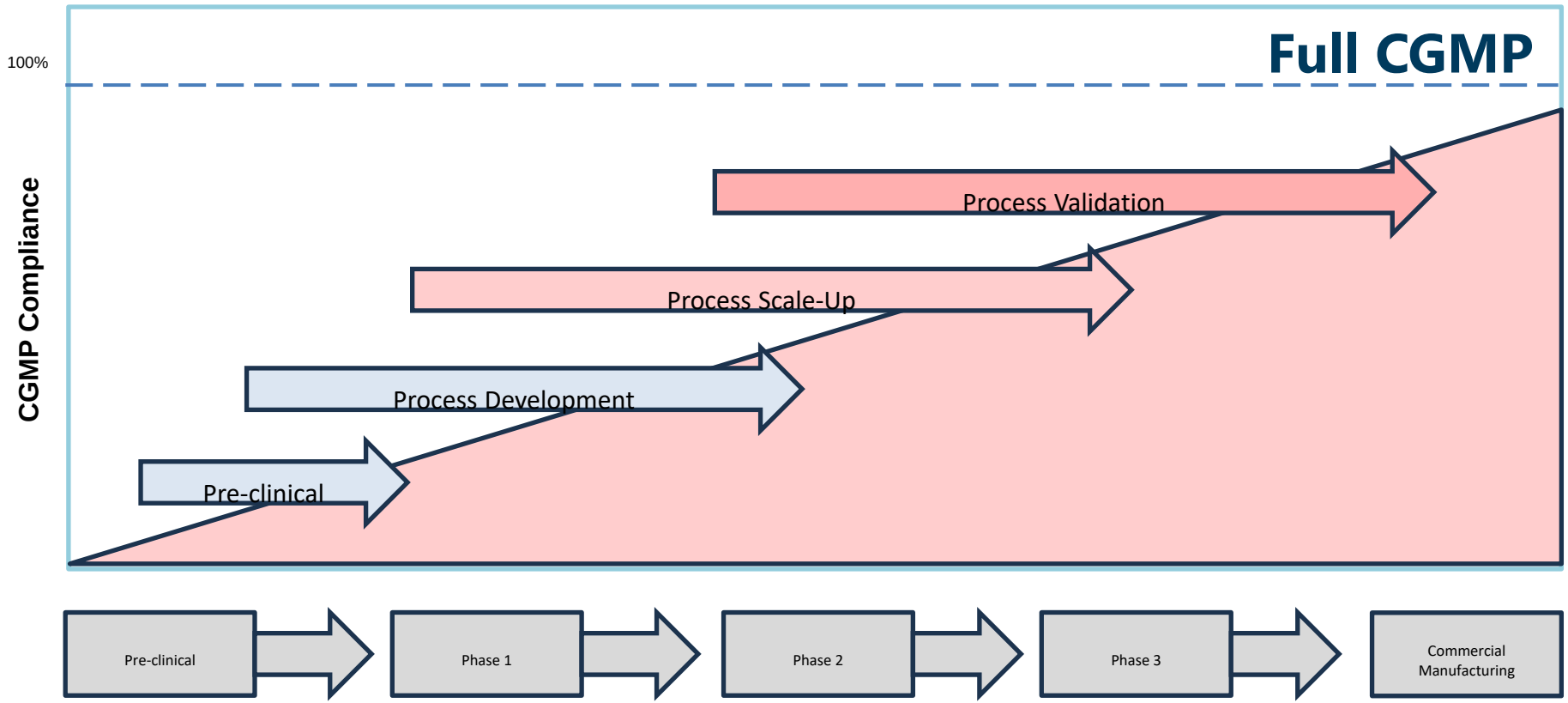
ALSTON & BIRD LLP




Artificial Intelligence in Drug Manufacturing

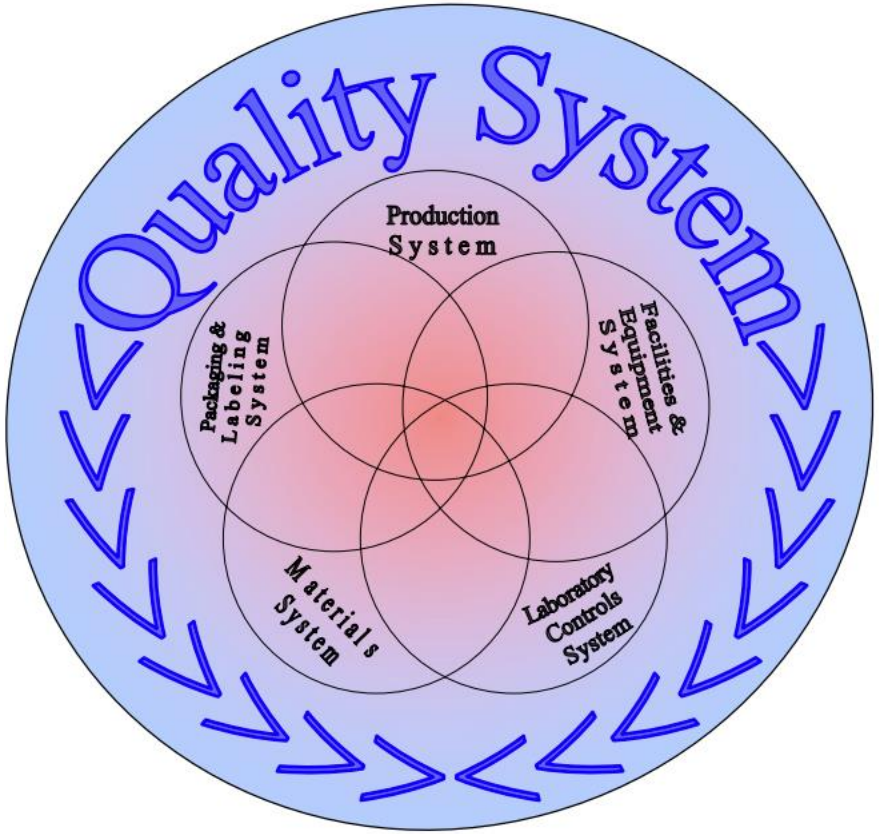
Brendan M. Carroll, Partner
Alston & Bird, LLP
brendan.carroll@alston.com

Regulation of Drug Manufacturing



CGMP Regulations (21 CFR Parts 210 and 211)

- Quality
- Production
- Laboratory
- Materials
- Facilities & Equipment
- Packaging & Labeling



Advanced Manufacturing

Advanced manufacturing is a collective term for new medical product manufacturing technologies that can improve drug quality, address shortages of medicines, and speed time-to-market

- Integrate novel technological approaches
- Use established techniques in a new or innovative way, or
- Apply production methods in a new domain where there are no defined best practices or experience.

Emerging Technology Program

Share | Post | Linkedin | Email | Print

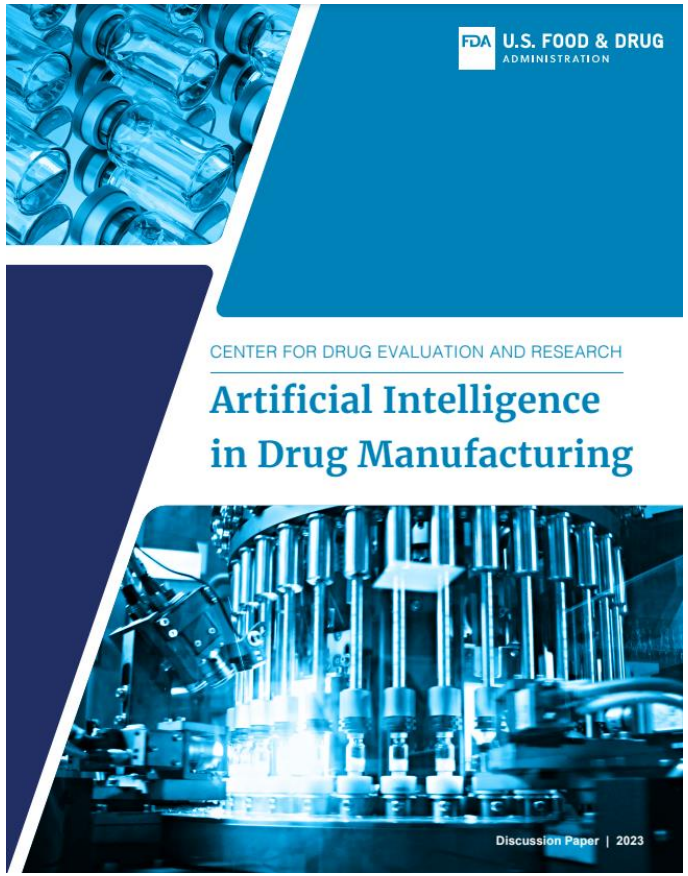
Isolator Technology

3D Printing

***Artificial Intelligence**

The National Academies of Sciences, Engineering, and Medicine issued a 2021 report titled *Innovation in Pharmaceutical Manufacturing on the Horizon: Technical Challenge, Regulatory Issues, and Recommendations*, highlighting innovations in integrated pharmaceutical manufacturing processes. These innovations could have implications for measurement, modeling, and control technologies used in pharmaceutical manufacturing. Artificial intelligence (AI) may play a significant role in monitoring and controlling advanced manufacturing processes.

FDA Discussion Paper (May 2023)



https://www.fda.gov/media/165743/download

AI Meets CGMPs

Scope

As FDA considers the application of its risk-based regulatory framework to the use of AI technologies in drug manufacturing, the Agency has identified in this discussion paper areas for which public feedback would be valuable. CDER scientific and policy experts identified these areas from a comprehensive analysis of existing regulatory requirements applicable to the approval of drugs manufactured using AI technologies.[1] The areas of consideration in this discussion paper are those for which FDA would like public feedback. There are additional areas of consideration not covered within this document; for example, difficulties that could result from potential ambiguity on how to apply existing Current Good Manufacturing Practice (CGMP) regulations to AI or lack of Agency guidance or experience.[2] The areas of consideration presented in this discussion paper focus on the manufacture of drug products that would be marketed under a New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologics License Application (BLA).

[1] This analysis included a review of applicable statutory provisions, regulations, and guidance related to quality assessment and inspections to determine whether an application presenting an advanced manufacturing technology implementing AI can fit within our current regulatory framework. The analysis did not extend to applications of AI in supply chain management of drugs.

Potential Application

- Process Design and Scale Up
- Advanced Process Control
- Process Monitoring and Fault Detection
- Trend Monitoring

Potential Challenges

- Ongoing interaction b/w cloud applications and process controls
- Increased data → strain on data management practices
- Computer system validation presents unique challenges
- Software control and data storage safeguards
- Data integrity!

How will application of AI fit into CGMP framework (applications, inspections, PhV)?

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

In the current paradigm, models deployed in manufacturing (e.g., in-process controls, real-time release testing) are developed, validated, implemented, and updated as needed through the change control process within the pharmaceutical quality system. AI models (e.g., machine learning-based models) can involve continuous learning wherein the model evolves over time as new information becomes available.

CGMP Regulations (Part 211)

- **21 CFR 211 Subpart A** – General Provisions
- **21 CFR 211 Subpart B** – Organization and Personnel
- **21 CFR 211 Subpart C** – Buildings and Facilities
- **21 CFR 211 Subpart D** – Equipment
- **21 CFR 211 Subpart E** – Control of Components and Drug Product Containers and Closures
- **21 CFR 211 Subpart F** – Production and Process Controls
- **21 CFR 211 Subpart G** – Packaging and Labeling Control
- **21 CFR 211 Subpart H –** Holding and Distribution
- **21 CFR 211 Subpart I** – Laboratory Controls
- **21 CFR 211 Subpart J –** Records and Reports

Other Requirements and Guidances

Data Integrity and Compliance With Drug CGMP
Questions and Answers
Guidance for Industry

Q9(R1) Quality Risk Management
Guidance for Industry

Contract Manufacturing Arrangements for Drugs: Quality Agreements
Guidance for Industry

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 Veterinary Medicine (CVM)

November 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Guidance for Industry

Process Validation: General Principles and Practices

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 Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM PROGRAM 7346.832

CHAPTER 46—NEW DRUG EVALUATION

SUBJECT:	IMPLEMENTATION DATE:
Preapproval Inspections Revision: Compliance program revised to add elements of International Council for Harmonisation (ICH) guidances for industry *Q10 Pharmaceutical Quality System* and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*,[1] control of nitrosamine impurities, and alternative tools for evaluating facilities.	10/17/2022

Thank You!

King & Spalding

More than Medical Devices: Development and Use of Companion Apps for Pharmaceutical Products and Beyond

FDA's Draft PDURS Guidance

January 31, 2024

PRESENTED BY

Jessica Greenbaum

Counsel, King & Spalding LLP

Agenda

- Introduction and Background
- End-User Output v. Software Function
- Regulation of PDURS Output as Labeling
- Follow-On Products

Introduction and Background

Prescription Drug Use-Related Software Defined

"Software that (1) is disseminated by or on behalf of a drug sponsor and (2) produces an end-user output that supplements, explains, or is otherwise textually related to one or more of the sponsor's drug products."

Drug product

A drug delivery device (sometimes)

Software application

Examples

Drug Adherence Tracking
The patient ingests a pill that is enabled to communicate with (or that is paired with a patch that communicates with) a mobile app that tracks the timing of each dose.

Dose Tracking Systems
A mobile app pairs with software in a Bluetooth-enabled autoinjector to record drug dosage and/or timing.

Dose Recommending Programs
Software that gives a physician dosing recommendations based on monitoring of patient's symptoms and risk factors.

PDURS History

2018
Federal Register Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–3017]

Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments

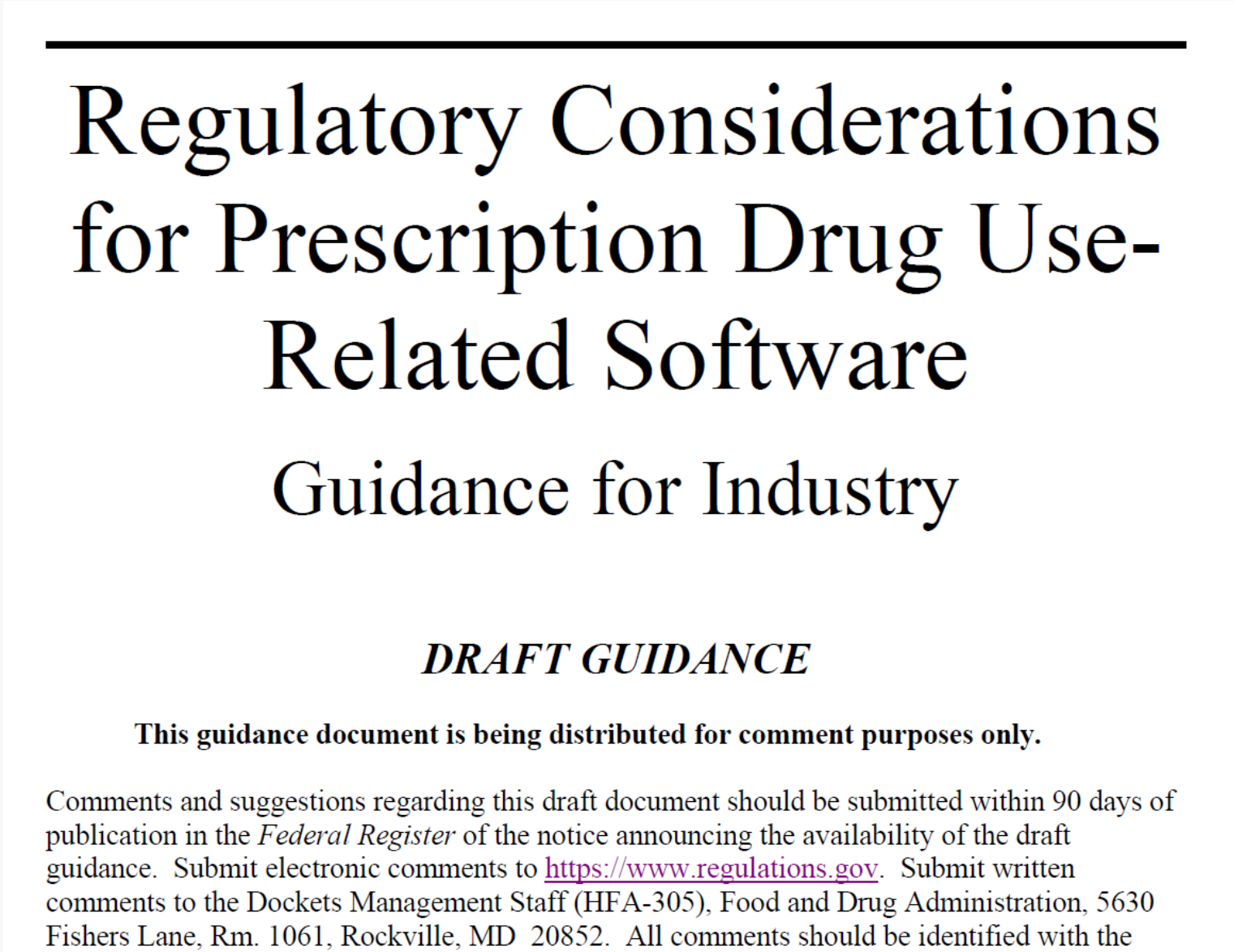
AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for comments.

2022
PDUFA VII Commitment

6. By the end of FY 2023, FDA will publish draft, revised or final guidance on regulatory considerations for Prescription Drug Use-Related Software that includes information about software that is disseminated by a drug applicant for use with a prescription drug or biologic product that may be described in labeling, including prescribing information. This guidance will cover software that is distributed with a drug or integrated as part of a drug- or biologic-led combination product, as well as software that is distributed by an applicant independent of an approved product.

PDURS Draft Guidance



Regulatory Considerations for Prescription Drug Use-Related Software

Guidance for Industry

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

End-User Output and Software Function

Definitions

End-User Output

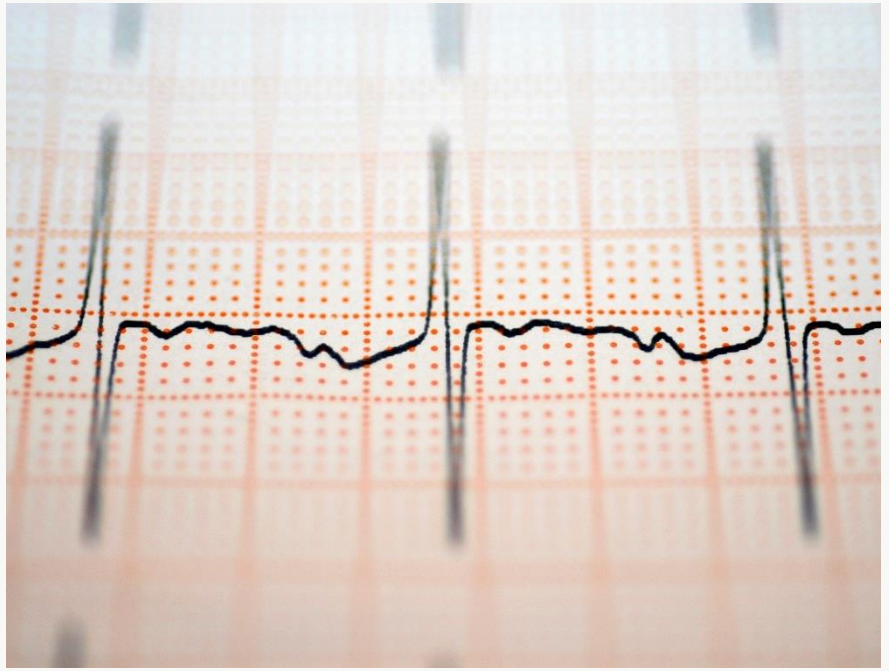
"any material or content presented to a patient, caregiver, or health care practitioner (end user) by the prescription drug use-related software constitutes the end-user output, and such end-user output constitutes drug labeling."

Software Function

"any distinct purpose of the software—in this case, prescription drug use-related software. Prescription drug use-related software can have one or more software functions."

Examples of PDURS “output”

- Material presented to the PDURS end user (e.g., a patient, caregiver, or healthcare professional)
- Screen displays (displays for patient entry of data)
- Sounds (reminders alerts or alarms)
- Audio messages
- Software provided instructions for use and to adjust dosing



Software Function

Software may meet the definition of a device

Products do not meet definition of "device" and therefore are **not regulated by FDA**

Products **meet definition of "device" and are high risk** and therefore are **"actively regulated" by FDA**

Products **meet definition of "device" but are low risk** and therefore are **not "actively regulated" by FDA**

Software Function

FDA Review of PDURS Function

- For “device-connected” PDURS, FDA reviews the software as part of the drug-device combination program
- For “non-device-connected PDURS,” FDA review will depend on whether the PDURS meets the device definition
  - **Open Question**: standalone marketing applications for SAMD constituent parts

PDURS Output as Labeling

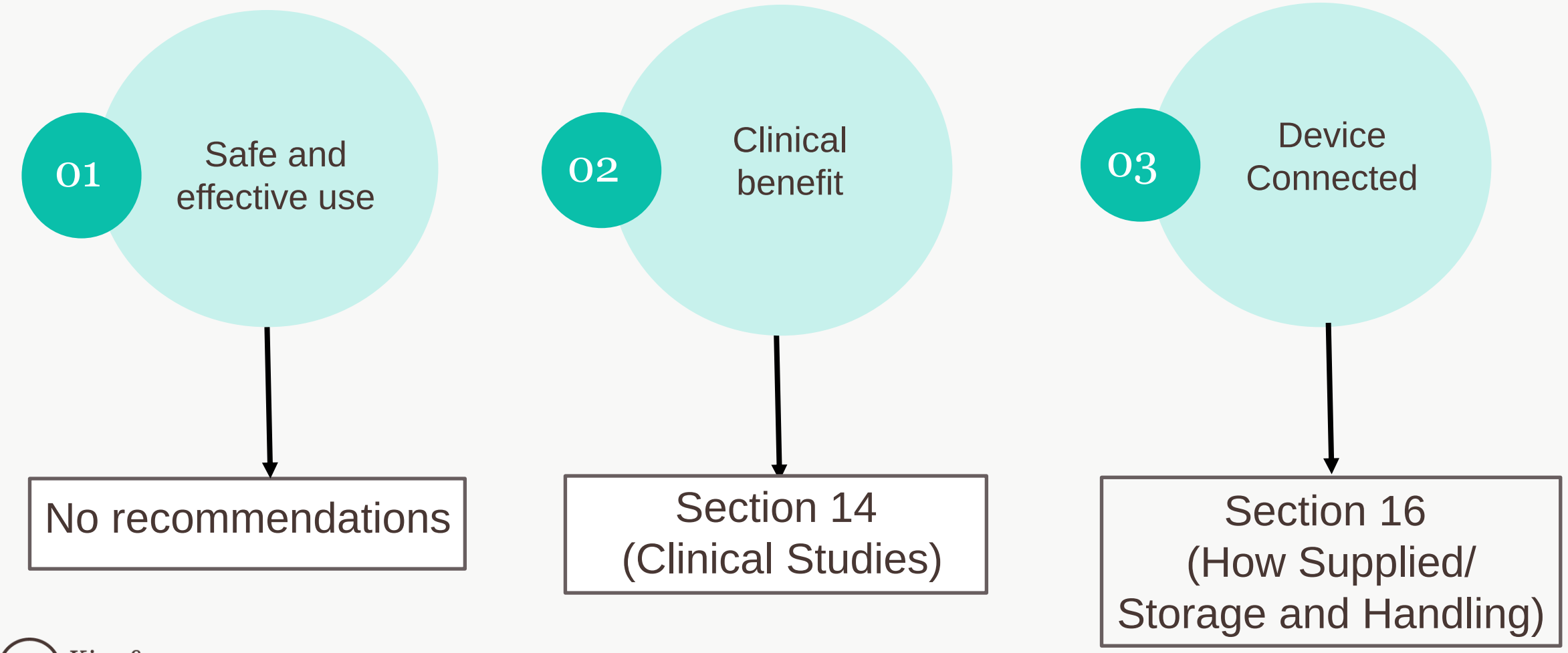
FDA-Required or Promotional Labeling

01 Whether PDURS provides a function that is essential to the safe and effective use of the product

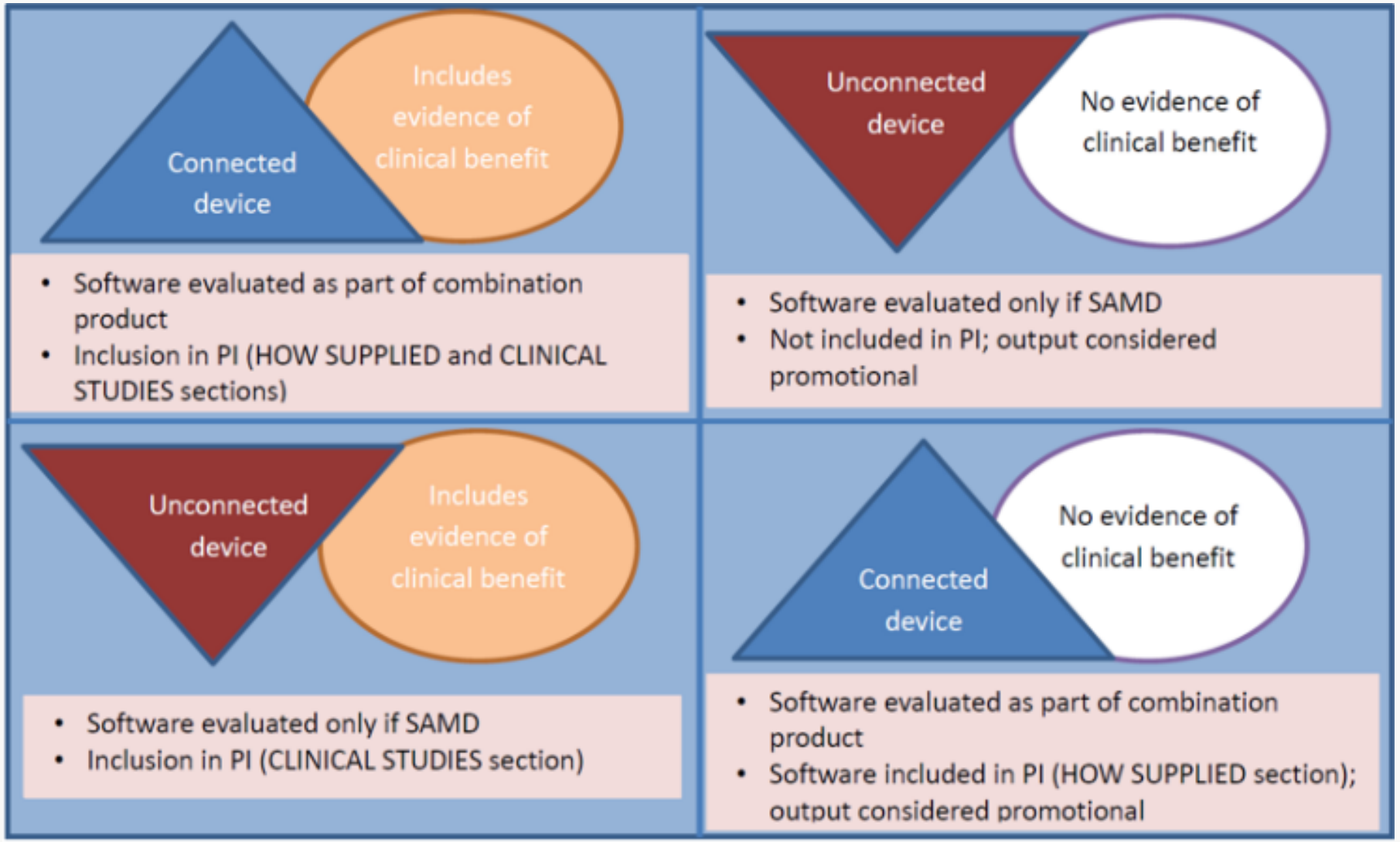
02 Whether evidence is provided to support a clinical benefit from use of PDURS

03 Whether the PDURS is device-connected

FDA-Required Labeling: Recommendations for PI



Overview of the PDURS Scheme



PDURS and Follow-On Products

Follow-On Products

- Requirements for approval include:
  - ANDAs: expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling
  - Biosimilars: no clinically meaningful differences
- Both ANDAs and biosimilars cannot have “conditions of use” that differ from their respective reference listed drug (“RLD”) or reference product (“RP”)
- ANDAs must have “same labeling” as the RLD (exception for different manufacturers), and biosimilars should incorporate “relevant” data and information from the RP labeling

Follow-On Products and PDURS

When, and under what circumstances, may a generic or biosimilar differ from its RLD or RP in the context of PDURS?

- If a PDURS provides a clinically meaningful benefit, could the PDURS be carved out while still meeting the approval standard?
- How similar must the PDURS be?
- Increasingly complicated questions in the context of drug-device and biologic-device combination products

- Any Questions