U.S. FOOD & DRUG ADMINISTRATION

Integrating Artificial Intelligence into Pharmaceutical Manufacturing

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WCBP Symposium

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Agenda

- Uses for AI across the Drug Product Life Cycle
- Thinking about AI use in pharmaceutical manufacturing
- CDER AI Guidance
- Manufacturing example from AI guidance
- Key takeaways

Potential Use of AI Across the Drug Product Life Cycle

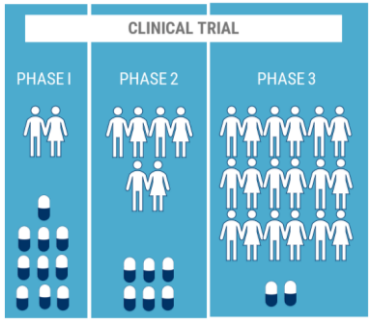
Discovery

- Drug Target Identification, Selection, and Prioritization
- Compound Screening and Design

Nonclinical Research

- PK/PD and toxicologic studies
- Dose range finding

Clinical Research



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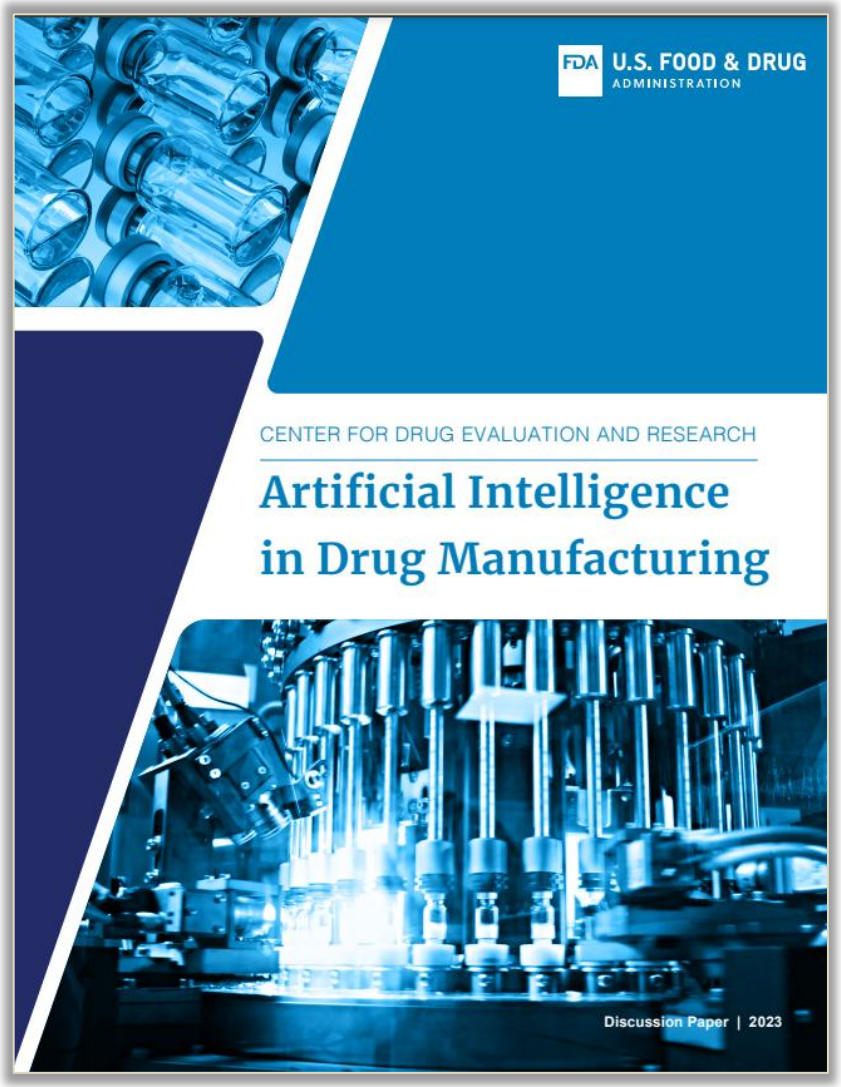
- Dose range finding
- Site selection
- Recruitment and Retention
- Adherence
- Data collection, management, and analysis
- RWD analyses
- Clinical endpoint assessment

Manufacturing and Postmarket Safety Monitoring

- Advanced pharmaceutical manufacturing
- Postmarket safety surveillance or pharmacovigilance (PV)

Discussion Paper for AI in Drug Manufacturing – Key Topics (2023)

- Cloud applications might affect oversight of pharmaceutical manufacturing data and records
- The amount of data generated 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



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Process Models Paper* (2024)

- Process models as tools used in pharmaceutical manufacturing process design and control
- Discussion of risk-based frameworks for model validation and lifecycle maintenance
- Hypothetical case studies (including an AI example) to illustrate the implications of applying model risk framework

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An examination of process models and model risk frameworks for pharmaceutical manufacturing

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ABSTRACT

Process models are a growing tool for pharmaceutical manufacturing process design and control. The Industry 4.0 paradigm promises to increase the amount of data available to understand manufacturing processes. Tools such as Artificial Intelligence (AI) might accelerate process development and allow better predictions of process trajectories. Several examples of process improvements realized through the application of process models have been shown in lyophilization, chromatography, fluid bed drying, bioreactor control, continuous direct compression, and wet granulation. An important consideration of implementing a process model is determining the impact of the model on the quality of the product and the risks associated with model maintenance over the product lifecycle. Several regulatory documents address risk-based considerations for process models. This work discusses existing risk-based frameworks for model validation and lifecycle maintenance that could aid the adoption of process models in pharmaceutical manufacturing. Hypothetical case studies illustrate the implications of applying a model risk framework to facilitate model validation and lifecycle maintenance in the manufacture of pharmaceuticals and biological products.

1. Introduction

In 2002, FDA laid the foundation for implementation of a modern, risk-based pharmaceutical quality assessment (U.S. Food and Drug Administration, 2004). Part of FDA's initiative encouraged manufacturers to use the latest scientific advances in pharmaceutical manufacturing technology throughout the lifecycle of a product to improve the efficiency of developing and manufacturing drugs. This has also been encouraged by EU as part of the EU directive 2001/83 and various CHMP (Committee for Medicinal Products for Human Use) guidelines e.g., CHMP guideline on manufacture of the finished dosage form (EU CHMP, 2015). As scientific and engineering knowledge about pharmaceutical manufacturing has grown, the use of models to aid process development, enhance process control and forecast future process and product quality outcomes has increased. The types of models being developed have also evolved. Models can be broadly categorized into three main types (Kourti et al., 2014).

- Mechanistic models (also known as first principles models or theoretical models) are mathematical representations of physical, chemical, or biological phenomena which drive processes.
- Empirical models build on available data which may be collected with intent (causal) or available as historical process data. Artificial Intelligence (AI) based models that are mainly based on heuristics are categorized as empirical models.
- Hybrid models bridge theoretical knowledge with available data sets to generate a working representation of a process. An AI model (Executive Order 14110 of October 30, 2023) coupled with a mechanistic model is an example of a hybrid model. (See Fig. 1.)

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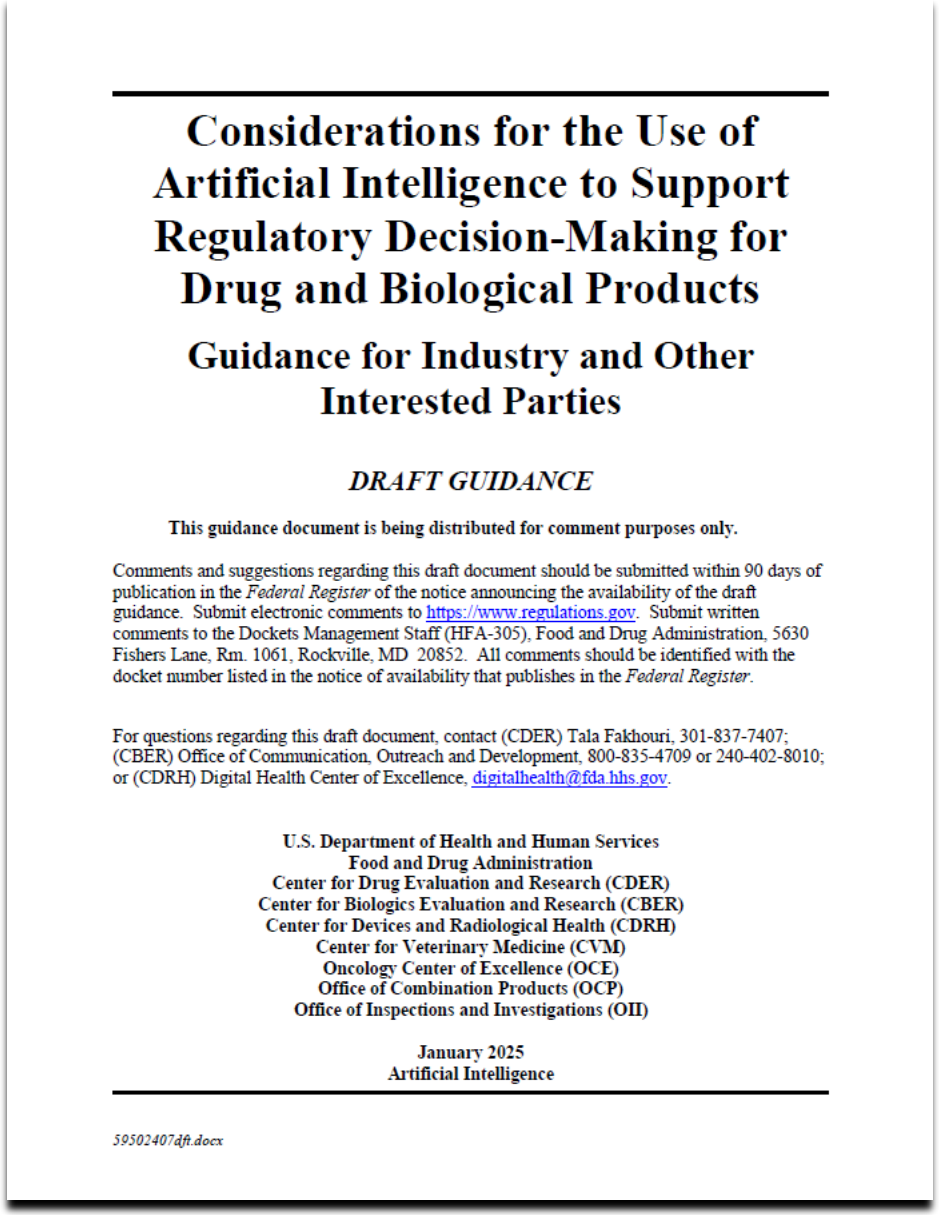
AI Guidance (2025)

- Published January 2025
- Recommendation on the use of AI to produce information or data intended to support regulatory decision making
- Outlines risk-based credibility assessment framework
  - Establishing and evaluating AI model for particular context of use (COU)
- Examples: Clinical and manufacturing
- Lifecycle maintenance



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.

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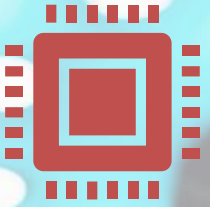
AI Use in Pharmaceutical Manufacturing



AI can be used in a variety of different contexts, for example:

Advanced manufacturing

Process control

Surveillance

Records retrieval

Remember that AI is a TOOL – an AI model provides OUTPUT

Decisions are made by PEOPLE

The Absolute Basics

- Implementation of AI must be in accordance with CGMP (sec. 501(a)(2)(B) of FD&C Act and 21 CFR 210 and 211)
  - e.g., AI models should be appropriately validated for the context of use and records kept

- Quality control unit is ultimately responsible for ensuring the overall quality of the final drug product (21 CFR 210.3)
  - e.g., the quality control unit responsibilities are described in 21 CFR 211.22 and 211.68 for finished drug product

Manufacturing Example – Question of interest and Context of use (COU)

Drug B is a parenteral injectable dispensed in a multidose vial. The volume is a critical quality attribute (CQA) for the release of vials of Drug B. A manufacturer is proposing to implement an AI-based visual analysis system to perform 100% automated assessment of the fill level in the vials, to enhance the performance of the visual analysis system and identify deviations.

However, as part of release testing, independent verification of the fill volume is performed on a representative sample for each batch. Therefore, the AI-based model will not be the sole determinant for the release of product.

- What is the question of interest?
  - *Do vials of Drug B meet established fill volume specifications?*

- What is the context of use for this AI Model?
  - *The AI model will be used to visually identify deviations in fill volume, but there will be independent verification of this CQA on a representative sample for each batch.*

Manufacturing Example - Assessing Model Risk

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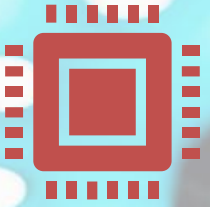
- Model risk considerations
  - Volume is a CQA; incorrect volume measurements would have a high impact on product quality (e.g., patient will not be able to get the labeled number of doses) – **decision consequence is *HIGH***
  - As part of release testing, independent verification of fill volume on a representative sample for each batch – this reduces the model influence – **model influence is *LOW***
  - Overall model risk for this COU - ***MEDIUM***

- Credibility assessment activities would be commensurate with the model risk for this specific COU

Key Takeaways

- Use of AI in pharmaceutical manufacturing must comply with CGMP regulations (21 CFR 210 and 211)
- AI can be integrated into many parts of the manufacturing process
  - Think about how AI will be used in the process
  - AI model will only be as useful based on the ***quality of the data*** used to train the model – remember GIGO
- Think about risk
  - AI model risk for credibility assessment
  - Overall quality risk management (e.g., ICH Q9 principles)
- Think about human-in-the-loop
- Ultimate responsibility belongs to the ***quality unit***

AI Use in Pharmaceutical Manufacturing



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Questions?


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