U.S. FOOD & DRUG ADMINISTRATION

FRAME: Supporting Advanced Manufacturing Technologies

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Pharmaceutical Quality Symposium

November 1, 2023

CDER Advanced Manufacturing Programs

ADVANCED MANUFACTURING

ASSESSMENT AND INSPECTION

Emerging Technology Program (ETP)

SCIENCE

Advanced Manufacturing Science & Research

POLICY

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

U.S. FOOD & DRUG ADMINISTRATION

Framework for Regulatory Advanced Manufacturing Evaluation (**FRAME**)

FRAME Priorities

Seek and Analyze Input	Address Risks	Clarify Expectations	Harmonize Internationally
Ensure CDER's understanding of advanced manufacturing technologies is thorough and its analysis of the regulatory framework is science- and risk-based.	Ensure regulations and policy are compatible with future advanced manufacturing technologies.	Explain the current thinking on a regulatory issue via new or updated guidance as needed.	Ensure global regulatory practice is clear to stakeholders implementing advanced manufacturing.

Cohesive regulatory framework for drugs

Since 2021 PQS

1 Guidance – Q13 Continuous Manufacturing

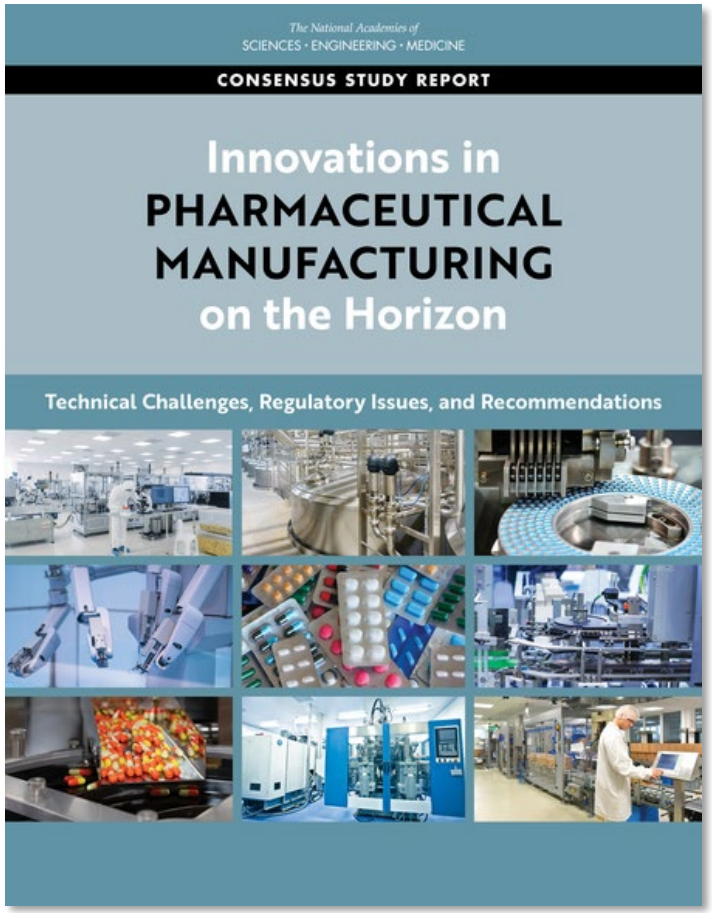
2 Discussion Papers

3 Public Workshops

60+ Comments

400+ Stakeholders

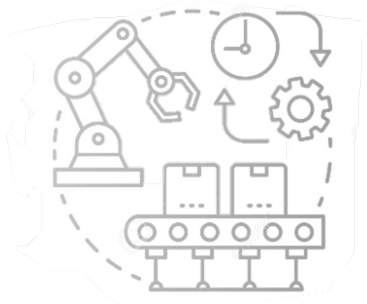
FRAME: Framework for **R**egulatory **A**dvanced **M**anufacturing **E**valuation



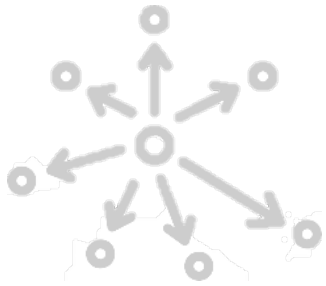
NASEM *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations* (2021)

FRAME Priority Technologies

End to End Continuous Manufacturing (E2E CM)



Distributed Manufacturing (DM)



Artificial Intelligence (AI)

Self-Contained DM (e.g., at point of care)

FRAME Priority Technologies

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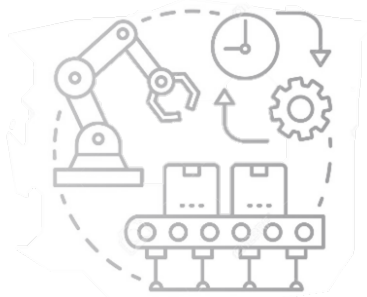

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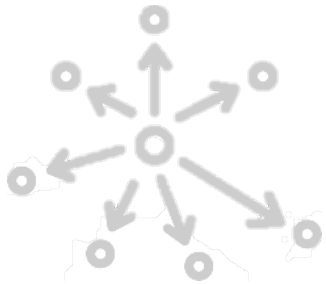

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Q13 Continuous Manufacturing of Drug Substances and Drug Products

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)

March 2023
ICH

ANNEX IV: INTEGRATED DRUG SUBSTANCE AND DRUG PRODUCT CONTINUOUS MANUFACTURING

I. INTRODUCTION (1)

Annex IV supplements the main body of this guidance by providing additional regulatory and scientific considerations that are relevant for the development and implementation of integrated drug substance and drug product CM processes (referred to as integrated process(es) hereafter).

This annex also provides an example of an integrated process for a small molecule tablet dosage form. The example and approaches described in this annex are not exhaustive. Alternative approaches can be used.

II. INTEGRATED SMALL MOLECULE DRUG SUBSTANCE/DRUG PRODUCT PROCESSES (2)

A. Characteristics of Drug Substance and Drug Product Process Steps (2.1)

Considering the differences between the drug substance and drug product process steps enables appropriate design of an integrated process. For example, process steps for drug substance and drug product manufacturing can have different RTDs, and a prevalence for liquid or solid input material addition can lead to a different frequency of in-process measurements. These differences are expected to influence the selection of equipment, equipment connections, surge lines or tanks, and the locations of in-process measurements and material diversion.

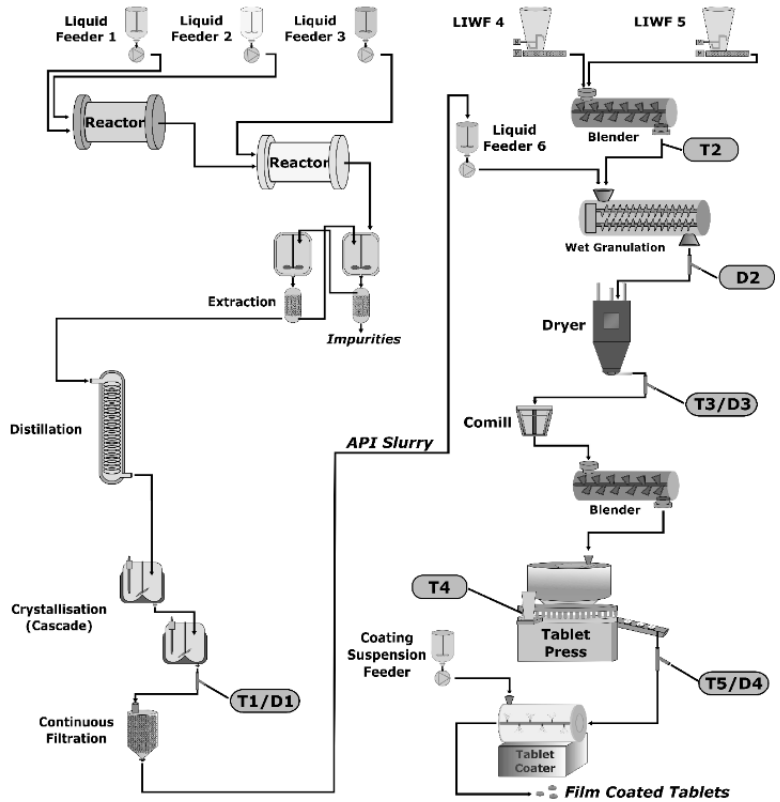
B. Example of an Integrated Process (2.2)

Figure 4, which is not intended to represent a regulatory flow diagram, illustrates a fully continuous integrated drug substance and drug product process. It shows the following elements:

- Material addition points for liquids and solids
- Each process step used for drug substance and drug product manufacturing
- Process design for the interface between the drug substance and drug product
- Sampling locations for all in-line/at-line/offline measurements, including PAT (shown by T1–T5)
- All diversion points (shown by D1–D4)

In this example, chemical reaction using flow reactors, continuous crystallization, and crossflow filtration are used to obtain the drug substance as a highly concentrated crystal slurry. A wet granulation process consisting of blending, granulation, drying, milling, compression and coating unit operations is used to obtain a tablet drug product. The selection of a wet granulation process for the manufacture of the drug product permits the drug substance and drug product processes to

Figure 4: Example of an Integrated Drug Substance and Drug Product CM System



FRAME Priority Technologies

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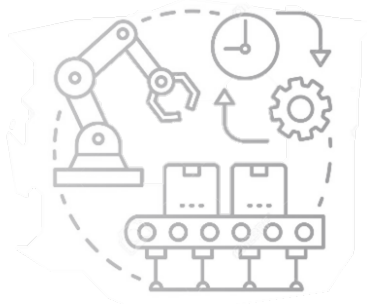

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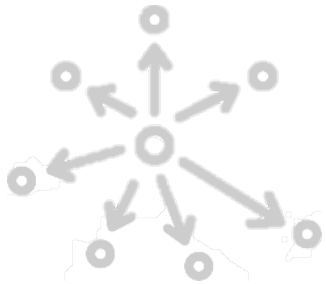

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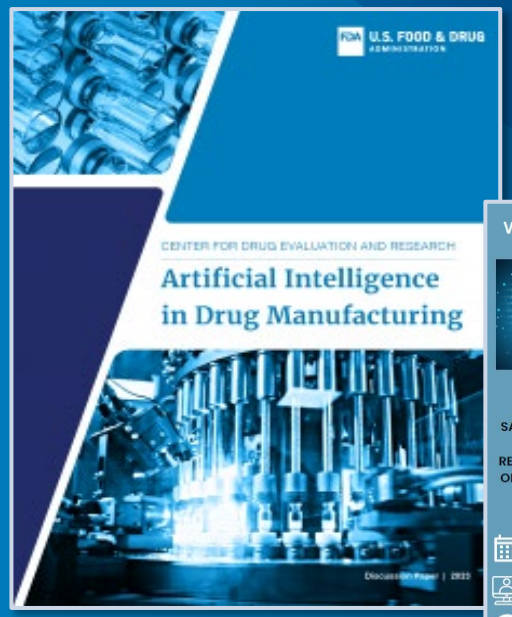
Self-Contained DM (e.g., at point of care)

Public Engagements Inform Regulatory Considerations



Artificial Intelligence in Manufacturing Discussion Paper
March 3, 2023

FDA/PQRI AI in Manufacturing
Public Workshop
September 26-27, 2023

- **Cloud applications may affect oversight of pharmaceutical manufacturing data and records**
- **The amount of data generated could affect existing data management practices**
- **Clarity on regulatory oversight of AI's application in pharmaceutical manufacturing**
- **Standards for AI models used for process control and release testing**
- **Challenges to regulatory assessment and oversight**

Re-opened Federal Register comment period **until Nov 27th**.
Docket ID: FDA-2023-N-0487

FRAME Priority Technologies

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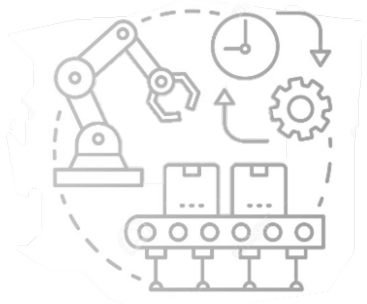

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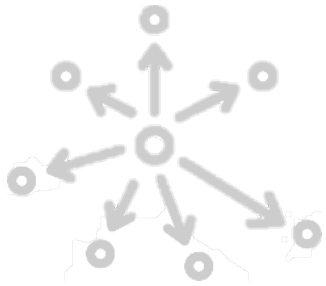

Self-Contained DM (e.g., at point of care)

Public Engagements Inform Regulatory Considerations

Distributed & Point-of-Care Manufacturing Discussion Paper
October 13, 2022

FDA/PQRI Distributed & Point-of-Care Manufacturing Public Workshop
November 14-16, 2022

Distributed Manufacturing of Drugs: Stakeholder Feedback & Action Plan

HOT OFF THE PRESS!

Stakeholder Feedback Areas

- Terminology
- DM PQSs
- DM Applicants
- Operators
- Establishments
- Changing and Adding Locations of DM units
- Inspections
- Considerations for Meeting Established Specifications
- Other Regulated Products and Harmonization

Disclaimer: This paper is for discussion purposes only of stakeholder feedback and is not a draft or final guidance. As such, this document is not intended to convey any current or future requirements, recommendations, or policy related to distributed manufacturing.

Terminology

Stakeholders:

- *Point-of-care* = a location ≠ a manufacturing technology
- POC manufacturing ≠ always a subset of DM
- 'POC' term used differently in medical product areas

Pharmaceutical Quality System (PQS)

Stakeholders:

- A **centralized PQS model** = essential to DM for CDER-regulated products
- Oversees the fleet of units (number and distance)
- PQS info could be provided in regulatory submission and/or facility evaluation

Applicants

Stakeholders:

- DM applicants might be different between CBER and CDER
- Healthcare facility might be responsible for compliance with CGMPs for CBER products
- Model less suited for CDER products made by DM

Operators

Stakeholders:

- CDER products: end users might be responsible for using equipment within validated operating conditions
- CBER products: end users might be expected to perform extensive operations (testing, manipulating raw materials and/or equipment)

Establishments

Stakeholders:

- Current regulations might accommodate registration and listing of stationary DM units
- Proposed various mechanisms for reporting DM unit location changes (application supplements, annual reports)

Changing and Adding Locations of DM Units

Stakeholders:

- Performance at a new locations should be evaluated
  - Existing framework may need comparability, validation, and stability data for each new location
  - “Cloned” or “like-for-like” DM units may reduce risk to drug product quality and may need less evaluation data

Inspections

Stakeholders:

- Proposed inspection model of centralized PQS site on risk-based frequency
- Proposed various models for inspections of units at host sites (preapproval inspection, evaluation during central PQS site inspection)

Considerations for Meeting Established Specifications

Stakeholders:

Rapid, non-traditional approaches to release testing might be needed

- PAT to enable RTRT
- Modeling and Digital Twins
- Parametric Release
- Conditional Release

Considerations for Meeting Established Specifications

Stakeholders:

Destructive end-product testing of each batch may not be feasible for small batch sizes

- Pre- and/or post-patient material runs (i.e., sub-batches) could generate testing samples
- Test samples should be representative and predictive of the administered batch

Procedures for handling rejected material

- Technologies might include the capability to physically detain and/or destroy non-conforming product to prevent use

Other Regulated Products & Harmonization

Stakeholders:
Some approaches used in the regulation of PET drugs could inform the regulation of DM

Stakeholders:
Clear desire for international harmonization on DM to facilitate adoption of these technologies

Summary of Stakeholder Feedback

- Stakeholders identified areas in which they seek regulatory clarity.
- Stakeholders seek assurance that regulations and policies are compatible with DM strategies.
- Stakeholders seek clarified regulatory expectations to facilitate the implementation of DM.
- Stakeholders seek international harmonization on the regulation of DM technologies to facilitate the adoption of DM.

Action Plan

Stakeholders identified areas in which they seek regulatory clarity.

- **Engage participants** in the CDER's ETP and the Center for Biologics and Research's (CBER) Advanced Technologies Team Program (CATT) and visit development sites
- **Incorporate feedback** into compatible regulations and policy

Stakeholders seek international harmonization on the regulation of DM technologies to facilitate the adoption of DM.

Action Plan

Stakeholders identified areas in which they seek regulatory clarity.

Stakeholders seek assurance that regulations and policies are compatible with DM strategies.

- **Conduct a comprehensive analysis** of regulatory requirements applicable to DM strategies for drugs and biological products
- **Assess the ability of FDA's IT systems** to receive and store location information and inform inspections

Action Plan

Stakeholde

Stakeholde
compatible

- **Develop guidance**, as appropriate, to clarify areas of regulatory uncertainty
- **Evaluate existing policy** incorporating stakeholder feedback and develop guidance, as needed, to enable adoption of suitable SCDM technologies

Stakeholders seek clarified regulatory expectations to facilitate the implementation of DM.

Stakeholders seek international harmonization on the regulation of DM technologies to facilitate the adoption of DM.

Action Plan

Stakeholders identified areas in which they seek r

Stakeholders seek assurance that regulations and

ation

- **Coordinate with international regulatory partners** to promote the global adoption of DM technologies

Stakeholders seek international harmonization on the regulation of DM technologies to facilitate the adoption of DM.

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

Continuing to seek public input is a key component to the implementation of a **cohesive regulatory framework advanced manufacturing**.


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