U.S. FOOD & DRUG ADMINISTRATION

CDER's Perspective on the Continuous Manufacturing Journey

Thomas O'Connor, Ph.D.
Deputy Director Office of Testing and Research
Vice-Chair CDER's Emerging Technology Team
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

2023 NanoDay Symposium: Continuous Manufacturing of Nanomaterials
October 11, 2023

Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

What is Continuous Manufacturing?

- CM is an integrated process that consists of a series of two or more unit operations (“the system”).

Continuous Manufacturing

FDA has identified continuous manufacturing (CM) as a novel technology for the pharmaceutical industry

CM may not be fit for *every* drug manufacturing process, but it can **bring potential advantages** to companies:

- **Better efficiency**
- **Reduced cost/footprint**
- **Improved process control**

Annual sales of drug products made using CM*

*Fisher AC, et al. An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US. *Int J Pharmaceut* (2022)

CM Benefits to Companies

One pharmaceutical company that switched to CM reported:

- **50%** reduction in operating costs
- **33%** reduction in waste
- **80%** reduction in manufacturing and testing cycle time
- **66%** reduction in time from testing to release

*Kuehn S., Janssen embraces continuous manufacturing for Prezista. *Pharmaceutical Manufacturing* (2015)

*MacDonald G., Janssen working on other continuous processes post US FDA OK for Prezista. *inpharmatechnologist.com* (2016)

CM Benefits to Companies

Human elements: one pharmaceutical company adopted CM for a Grignard reaction (spontaneous heat release)

- Safe and well-controlled process
- Little operator involvement
- Less manual material movement between unit operations

*Garguilo L., Safety Led Lilly To Leadership In Continuous Manufacturing *Outsourced Pharma* (2022)

Advanced Manufacturing Benefits

- **Produce better quality medicine**. Facilitates six-sigma operation, no more than 3.4 defects per 1M opportunities.
- **Re-shore drug manufacturing facilities.** Helps domestic drug manufacturers compete in a global market.
- **Develop drugs rapidly.** Speeds the development of novel or patient-focused therapeutics.
- **Prevent drug shortages.** Reduces today's quality-related manufacturing issues causing 62% of drug shortages.
- **Improve emergency preparedness.** Provides more agility and flexibility to help pivot in a public health emergency.

Continuous Manufacturing Journey

2014

- **1st International Symposium on Continuous Manufacturing of Pharmaceuticals**
- **Forming of CDER'S Emerging Technology Program**

2015

- **First CM application approved**
- **Two papers published:**
  - Regulatory and Quality Considerations for Continuous Manufacturing
  - Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

2016

- **First approved switch from a batch to continuous application**

FDA

2017

- One CM application approved
- Finalized Guidance for Industry: Emerging Technology Team

2018

- Two CM applications approved
- ICH Q13 endorsed (Step 1)

2019

- One CM application approved
- Draft Guidance for Industry: Quality Considerations for Continuous Manufacturing

FDA

2020

- First approved continuous drug substance process
- First approved semi-continuous bioprocess
- Two approved semi-continuous processes for sterile drug products

2021

- Graduation of Continuous Direct Compression from the ETP

2022

- First approved CM process at a CMO facility

2023

- First approved continuous synthesis process for complex API
- Guidance for Industry: ICH Q13 Continuous Manufacturing of Drug Substances and Drug products

CDER Advanced Manufacturing Programs

ADVANCED MANUFACTURING

ASSESSMENT AND INSPECTION

Emerging Technology Program (ETP)

SCIENCE

Advanced Manufacturing Science & Research

POLICY

ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products

Emerging Technology Program

What is The Emerging Technology Program?

WHAT	An OPQ program established in late 2014 that promotes and facilitates the **adoption of innovative approaches to pharmaceutical product design and manufacturing**
WHO	A **cross-functional team** (approximately 30 members with additional ad-hoc SME members) with representation from all relevant FDA quality review and inspection programs **Offices include: OPQ, OC, ORA (*One Quality Voice*)**
HOW	The program provides an **opportunity for industry to engage and collaborate early with the FDA** to discuss, identify, and resolve technical and regulatory issues during a novel technology's development and adoptions

Program Objectives

To serve as a **centralized location for external inquiries** on novel technologies

To provide a forum for firms to **engage in early dialogue with FDA** to support innovation

To **ensure consistency, continuity, and predictability** in review and inspection

To **engage international regulatory agencies** to share learnings and approaches

To **identify and evaluate potential roadblocks** relating to existing guidance, policy, or practice

To **facilitate knowledge transfer** to relevant CDER and ORA review and inspection programs

To help **establish scientific standards and policy**, as needed

ETP Collaborative Approach

Over the course of the ETP Technology Lifecycle, the Emerging Technology Team may employ a combination of collaborative approaches to engage with the technology.

The same Emerging Technology Team representative(s) will be involved in the entire process.

The composition of a review team will likely remain the same throughout the entire process.

Control Strategy Considerations

Evaluation of the proposed attributes and specifications of raw materials	• Impact of variations in material properties on the performance of CM and product quality
Characterization of process dynamics for critical steps and integrated system	• Residence time distribution for a proposed mass flow rate • Understanding of the system response to transient disturbances
Process monitoring and control strategy	• Monitor and detect transient disturbances and process deviation • PAT measurements and models • Active process controls
Material collection and diversion	• Start up and shutdown • Strategy to identify, isolate and divert non-conforming materials
Real-time release testing	• PAT tools for assay and content uniformity • Dissolution models

Facility Considerations

FDA

Adjustments to existing facility pharmaceutical quality system (PQS)

- Updates to Quality and production procedures
- Quality oversight of automated controls, process data, RTR, and electronic batch records

Integrated equipment train

- Knowledge gained from equipment qualification to support the proposed batch size or run time
- Cleaning validation, maintenance, and performance monitoring to support commercial lifecycle and multiproduct manufacturing

Process Validation, readiness for commercial manufacturing, and knowledge management

- Demonstration of robustness, process monitoring, and broader control strategy
- Assessment of change controls for total impact

Quality evaluation when material is diverted and quarantined

- Deviations, level of investigation, root cause analysis, corrective and preventive action, understanding diversion event (common vs. unexpected) for continuous improvement, etc.

Additional controls for incoming raw materials

Advanced Manufacturing Research

CDER Research and Emerging Technology Program

- Knowledge gained from the internal and sponsored research inform policy, review, inspection, and surveillance activities
- Ensure that FDA regulatory policies reflect state-of-the-art manufacturing science

Shared Learning and Open Communication to Accelerate Adoption of Emerging Technologies to Advance Product Quality

CDER Product Development Science Capabilities

Research Areas
Novel Manufacturing Unit Operations
Precision Analytics
Advanced Manufacturing of Complex Products
Novel Process Analytical Technologies
Process Modeling and Simulation
Industry 4.0 and Smart Manufacturing

Over 100 published publications and reports

Continuous perfusion bioreactor

3D Printing

High resolution mass spectrometry

The Impact of CM Research

- **Provided recommendations that guide product/technology development under the ETP**
- **Informed assessment of regulatory submissions that included CM**
- **Informed the ICH Q13 guidance and the developing ICH Q5A guideline revision** (Viral Safety Evaluation of Biotechnology Products)
- **CDER's process models have been applied to aid the assessment of CM submissions**
  - CDER researchers recently awarded the AIChE Award for Excellence in Integrated Quality by Design Practice for their use of modeling for quality risk management of CM processes

ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products

Q13 Strategy to Address Challenges

ICH

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Final version

Adopted on 16 November 2022

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

Main Body of the Guideline

- Covers **fundamental aspects of CM** that are not specific to technology, dosage form, or molecule type
  - CM Concepts
  - Scientific Approaches
  - Regulatory Considerations

Annex I	Annex II	Annex III	Annex IV	Annex V

Provide illustrative examples and considerations specific to certain modalities (e.g., chemical entities, therapeutic proteins), technologies, and production methods

CM Concepts

- Batch definition (ICH Q7)
  - Unlike batch manufacturing, CM batch size is **not necessarily constrained by equipment size**
  - **Flexible approaches** (e.g., quantity of output material, quantity of input material, or runtime at a defined mass flow rate) can be used to define a batch size
- Different modes of CM
  - Q13 focuses on integration of **two or more CM unit operations**
    - ➢ Partial integration of CM unit operations
    - ➢ Full integration of CM unit operations for drug substance or drug product manufacture
    - ➢ End-to-end integration of drug substance and drug product CM manufacturing

Lee et al., J Pharm Innov 2015 (DOI 10.1007/s12247-015-9215-8)

Scientific Approaches

- Control Strategy
  - Emphasize a **holistic approach** based on understanding of process dynamics
  - Highlight the possible use of **material diversion** as part of control strategy
- Changes in production output
  - Describe different approaches based on **changes in run time and mass flowrate**, **duplication of equipment** (i.e., scale out), and changes in equipment size.
- Continuous process verification (CPV)
  - Highlight the opportunity to use **CPV as an alternative approach for process validation**

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q13

ICH Consensus Guideline

TABLE OF CONTENTS

PART I: CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS 1
1. INTRODUCTION 1
1.1. Objective 1
1.2. Scope 1
2. CM CONCEPTS 1
2.1. Different Modes of CM 1
2.2. Batch definition 2
3. SCIENTIFIC APPROACHES 2
3.1. Control Strategy 2
3.2. Changes in Production Output 6
3.3. Continuous Process Verification 7
4. REGULATORY CONSIDERATIONS 7
4.1. Description of Manufacturing Process and Process Controls 8
4.2. Control Strategy 8
4.3. Batch Description and Batch Size 10
4.4. Process Models 10
4.5. Drug Substance and Drug Product Stability 10
4.6. Conversion of a Batch Process to CM 11
4.7. Process Validation 11
4.8. Pharmaceutical Quality System 12
4.9. Lifecycle Management 12
4.10. Submission of CM-Specific Information in the CTD 12

i

Regulatory Considerations

- Clarify what and **where CM specific information should be included in the dossier** according to the CTD
- Describe pharmaceutical quality system (PQS) specifically with respect to **management of disturbances and material diversion**
- Highlight options to generate batches for primary stability data
  - **Single manufacturing run vs. multiple shorter manufacturing runs**

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q13

ICH Consensus Guideline

TABLE OF CONTENTS

PART I: CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS 1
1. INTRODUCTION 1
1.1. Objective 1
1.2. Scope 1
2. CM CONCEPTS 1
2.1. Different Modes of CM 1
2.2. Batch definition 2
3. SCIENTIFIC APPROACHES 2
3.1. Control Strategy 2
3.2. Changes in Production Output 6
3.3. Continuous Process Verification 7
4. REGULATORY CONSIDERATIONS 7
4.1. Description of Manufacturing Process and Process Controls 8
4.2. Control Strategy 8
4.3. Batch Description and Batch Size 10
4.4. Process Models 10
4.5. Drug Substance and Drug Product Stability 10
4.6. Conversion of a Batch Process to CM 11
4.7. Process Validation 11
4.8. Pharmaceutical Quality System 12
4.9. Lifecycle Management 12
4.10. Submission of CM-Specific Information in the CTD 12

i

Concluding Statements

Impact of Continuous Manufacturing

International Journal of Pharmaceutics

An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US

- **CM applicants had <u>shorter</u> times to approval and marketing compared to batch applicants**
  - 3 months faster to approval
  - 4 months faster to marketing
  - Translates to <u>~$100-500M</u> in early revenue
- **No substantial regulatory barriers for CM related to:**
  - Manufacturing process changes
  - Pre-approval inspections

Regulatory Hurdles and FDA Actions

Manufacturers were hesitant to adopt CM…	FDA Actions
Without additional engagement from FDA	**2014**: Created the Emerging Technology Program (ETP)
Before FDA approved a product manufactured with CM	**2015**: Approved the first product manufactured with CM (and have since accepted over 50 proposals from industry into the ETP and approved 14 additional submissions)
For existing products before the FDA approved a switch from batch manufacturing to CM	**2016**: Approved the first switch from batch to CM for a drug product.
Without guidance from FDA	**2019**: Draft guidance *Quality Considerations for Continuous Manufacturing* **2022**: Draft revision to the guidance *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* (includes viral safety evaluation for CM)
Because they feared the timelines for FDA approval might be longer	**2022**: Showed that applications using CM were approved faster than similar applications using batch manufacturing
Without internationally harmonized guidance	**2023**: Internationally harmonized guidance *Q13 Continuous Manufacturing of Drug Substances and Drug Products*.

https://ispe.org/pharmaceutical-engineering/july-august-2023/removing-regulatory-hurdles-continuous-pharmaceutical

Lessons Learned

- CM delivers benefits for manufacturers and patients in a number of instances
- Early engagement and collaboration is essential
- Science needs to lead the way
- Importance of international harmonization

Acknowledgements

- Adam Fisher, Ph.D.
- Rapti Madurawe, Ph.D.
- Joel Welch, Ph.D.
- Geng Tian, Ph.D.
- Larry Lee, Ph.D.

FDA U.S. FOOD & DRUG ADMINISTRATION