CDER's Perspective on the Continuous Manufacturing Journey

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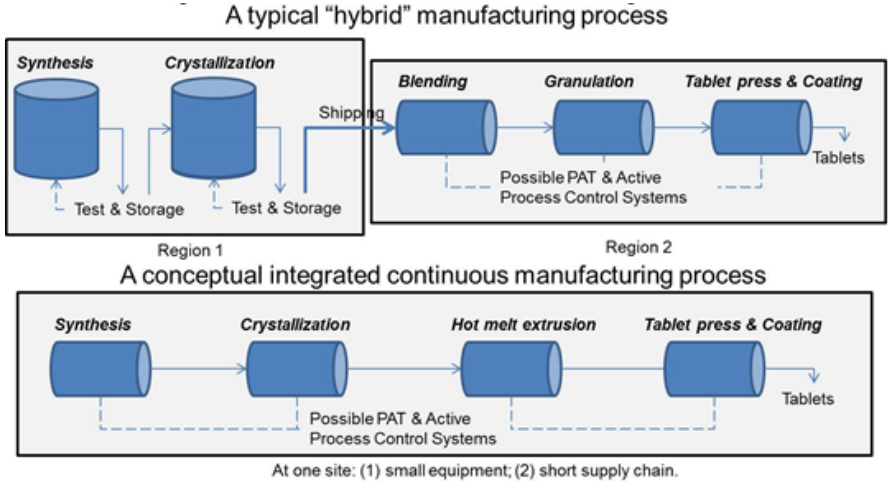
Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

What is Continuous Manufacturing?

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



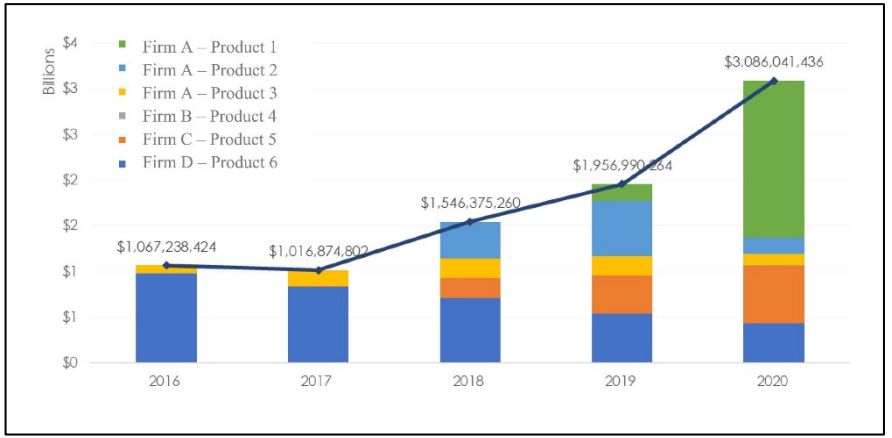
Continuous Manufacturing

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

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Janssen working on other continuous processes post US FDA OK for Prezista

By Gareth Macdonald
12-Apr-2016 - Last updated on 19-Apr-2016 at 13:55 GMT

RELATED TAGS Continuous Manufacturing | Pharmacology | Food And Drug Administration | Pharmaceutical Drug

Janssen is already working on continuous manufacturing methods for other drugs says Rutgers University which helped develop the new Prezista production process approved by the US FDA.

Janssen facility in Gurabo, Puerto Rico

On April 8 the US Food and Drug Administration (FDA) announced it cleared Janssen to change the production method for the 600mg version of the HIV drug Prezista (darunavir) from "batch" to continuous manufacturing.

In an accompanying blog post Lawrence Yu, deputy director of the FDA's office of pharmaceutical quality, said while the switch had not be easy, Janssen stands to gain "*significant rewards*" from doing so.

Craig Stoltz, Janssen manufacturing and technical operations spokesman, told us "*the benefits of Continuous Manufacturing include reduced testing-to-release time from 30 days to a target of 10 days by integrating technology-enabled real-time release testing throughout the control process for critical quality attributes.*

"*It also has the potential to increase yield by reducing waste by 33% and reduce manufacturing and testing cycle time by 80%*" he continued.

Stoltz added that the first Prezista produced in this way "*will likely make its way to the marketplace and patients by early Fall.*"

Continuation

The Johnson and Johnson unit has been developing continuous manufacturing process for some of its solid dose drugs for the last five years in partnership with researchers as Rutgers University.

Project leader Doug Hausner told us "*Janssen is our strongest supporter and we work quite closely with them on both research as well as development projects.*

"*On the development side, we aided with their first CM solid dose product which has been filed for approval, we are working on a second, and there are placeholders for two more.*"

Stoltz confirmed Janssen is working on other batch to continuous conversions.

"*Looking to the future, JSC is investigating continuous manufacturing in drug development on the R&D side and applications in different solids manufacturing processes, which could lead to reduced scale-up time and, eventually, shorter time-to-market.*"

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*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**

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

2017

2018

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

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

2019

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

2020

2021

- Graduation of Continuous Direct Compression from the ETP

2022

- First approved CM process at a CMO facility

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

2023

CDER Advanced Manufacturing Programs

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

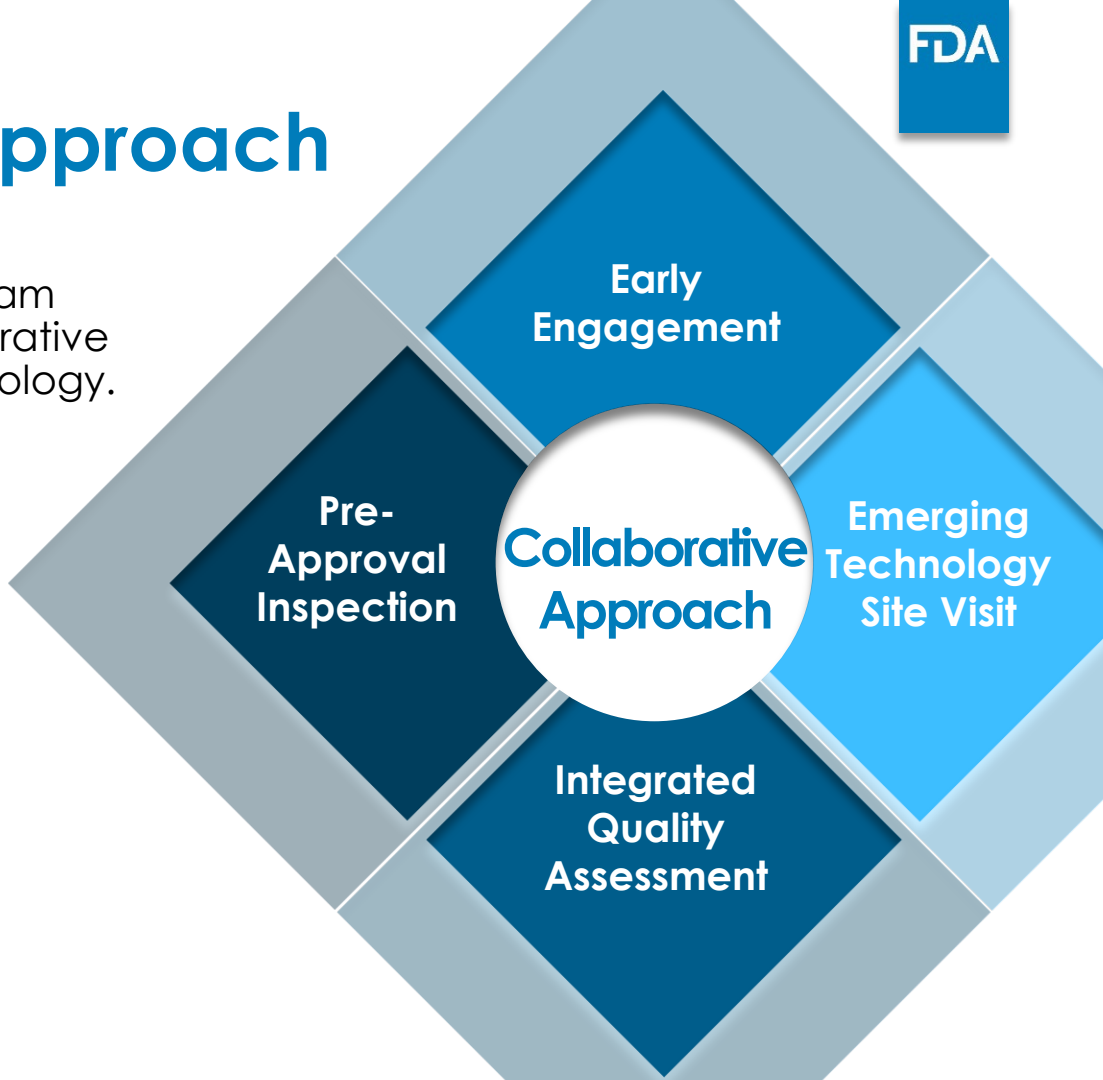
To help **establish scientific standards and policy**, as needed

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

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

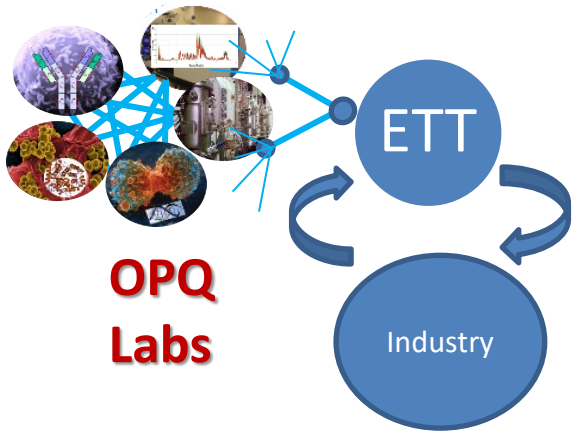
- Deviations, level of investigation, root cause analysis, corrective and preventive action, understanding diversion event (common vs. unexpected) for continuous improvement, etc.

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

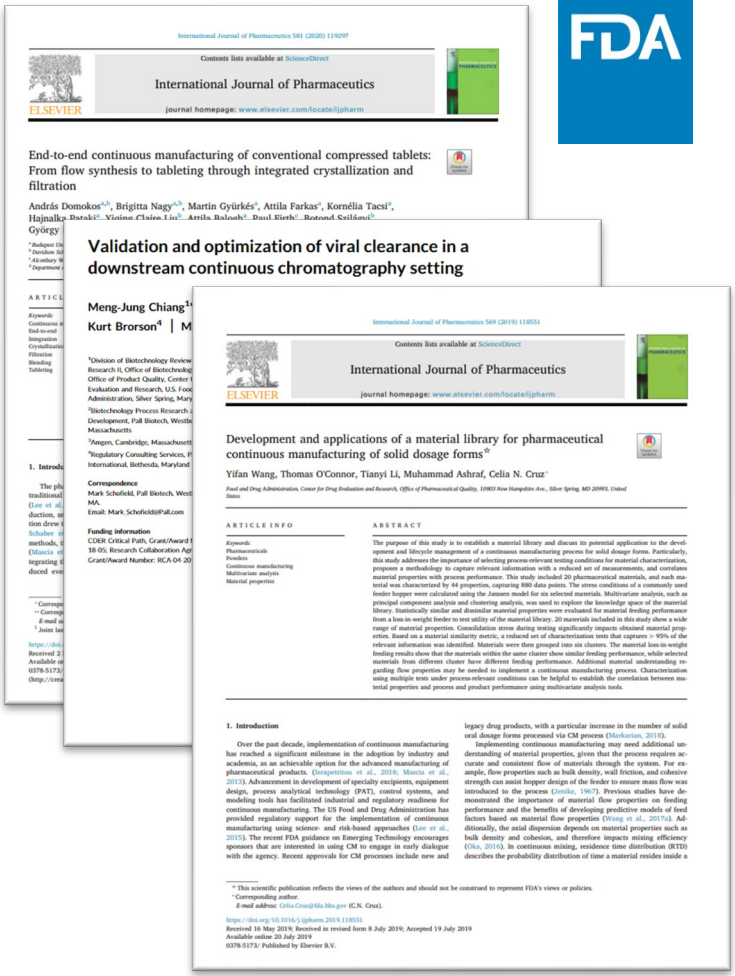
Continuous perfusion bioreactor

3D Printing

High resolution mass spectrometry

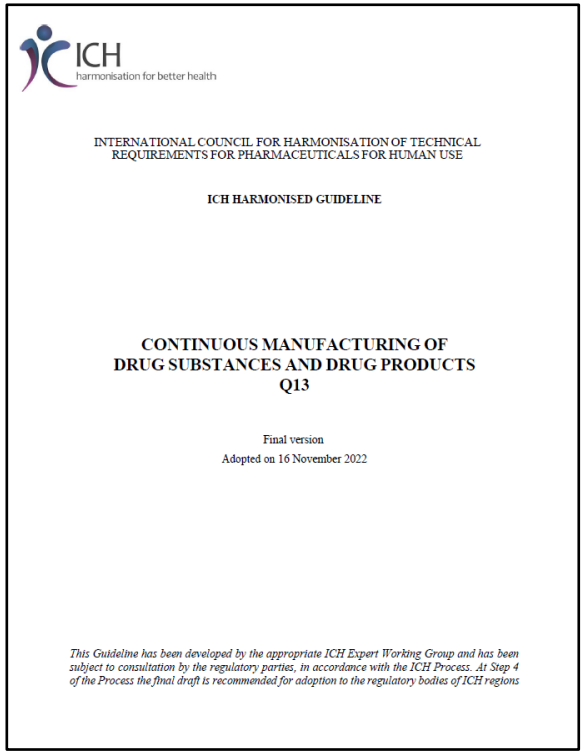
The Impact of CM Research

- **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
harmonisation for better health

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

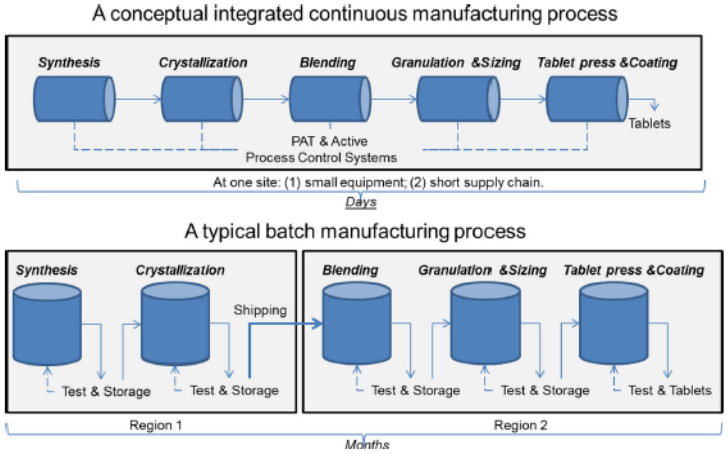
- Covers **fundamental aspects of CM** that are not specific to technology, dosage form, or molecule type
  - CM Concepts
  - Scientific Approaches
  - Regulatory Considerations

Annex I	Annex II	Annex III	Annex IV	Annex V

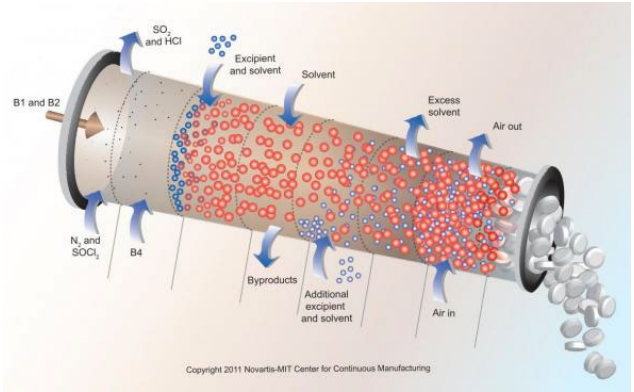
Provide illustrative examples and considerations specific to certain modalities (e.g., chemical entities, therapeutic proteins), technologies, and production methods

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

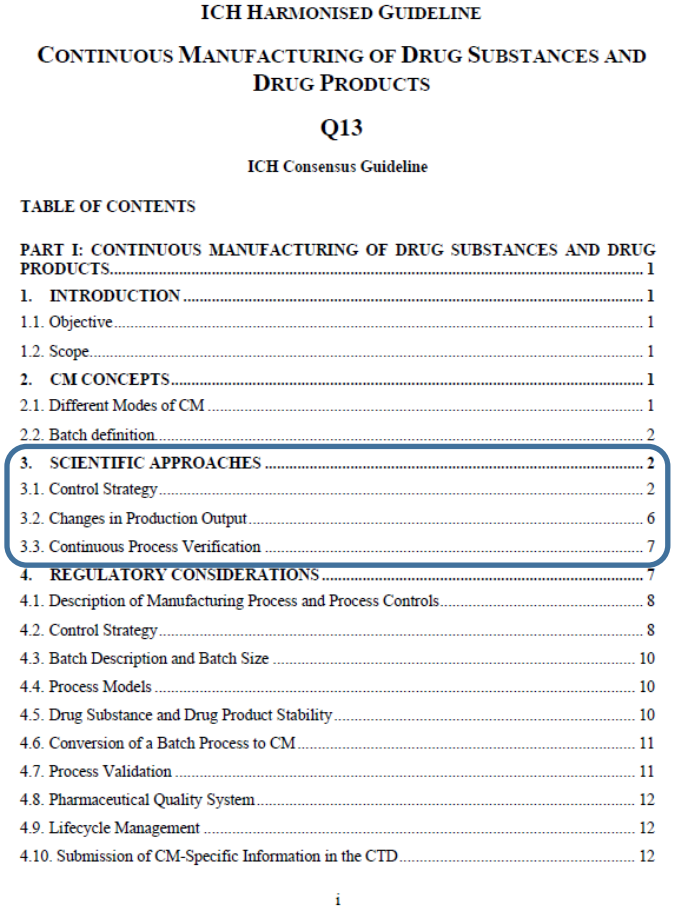


Lee et al., J Pharm Innov 2015 (DOI 10.1007/s12247-015-9215-8)



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

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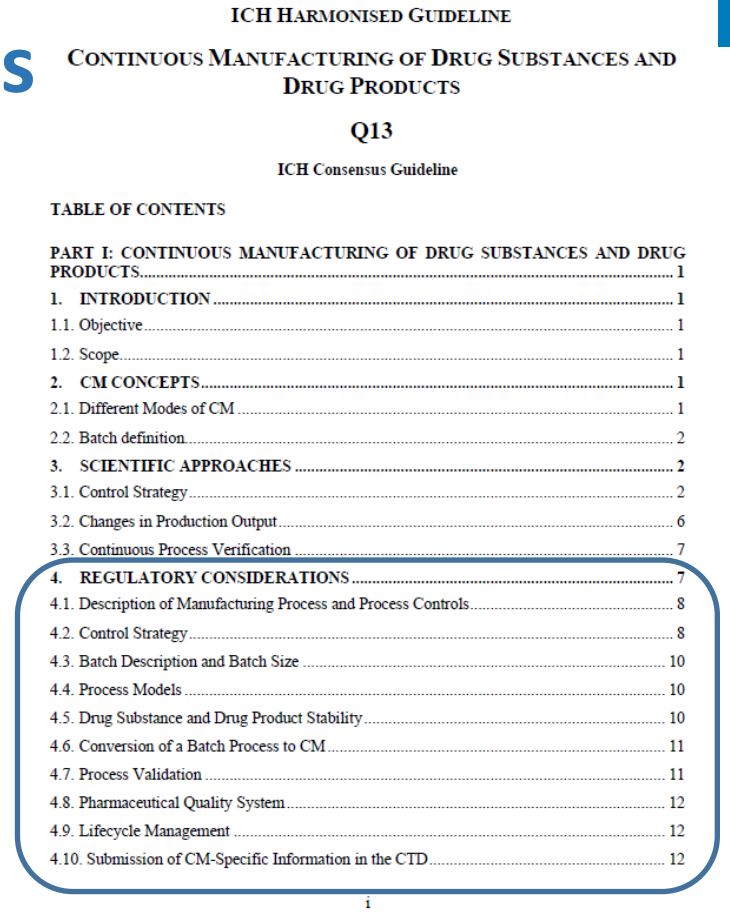
Regulatory Considerations

- 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**



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CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

Q13

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Concluding Statements

Impact of Continuous Manufacturing

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

Adam C. Fisher, William Liu, Andreas Schick, Mahesh Ramanadham, Sharmista Chatterjee, Raphael Brykman, Sau L. Lee, Steven Kozlowski, Ashley B. Boam, Stelios C. Tzinontides*, Michael Kopcha

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ABSTRACT

Continuous manufacturing (CM) sends materials directly and continuously to the next step of a process, eliminating hold times and reducing processing times. The potential benefits of CM include improved product quality, reduced waste, lower costs, and increased manufacturing flexibility and agility. Some pharmaceutical manufacturers have been hesitant to adopt CM owing to perceived regulatory risks such as increased time to regulatory approval and market entry, more difficulty submitting postapproval changes, and higher inspectional scrutiny. An FDA self-audit of regulatory submissions in the U.S. examined the outcomes, at approval and during the product lifecycle, of continuous manufacturing applications as compared to traditional batch applications. There were no substantial regulatory barriers identified for CM applications related to manufacturing process changes or pre-approval inspections. CM applicants had relatively shorter times to approval and market as compared to similar batch applications, based on the mean or median times to approval (8 or 3 months faster) and marketing (12 or 4 months faster) from submission, translating to an estimated $171–537 M in early revenue benefit.

1. Introduction

Continuous manufacturing (CM) is a technology that sends materials produced during each process step directly and continuously to the next step for further processing. In such a process, input materials are continuously fed into production and transformed, and processed output materials are continuously removed. CM has been adopted in many industries (e.g., petroleum, commodity chemicals), while the pharmaceutical industry has been slower to adopt CM (Lee et al., 2015; Rosi, 2022). The U.S. landscape of prescription drug products made using a CM process was roughly $3.09B in 2020 (Fig. 1), representing a small but growing portion of the $172B total market for branded, solid oral prescription drugs. The leading firm in the CM sector captures around 65% of total sales, with 20% of sales captured by the next largest firm. Many have pointed to the slow adoption of advanced manufacturing technologies, including CM, as one of the reasons that the pharmaceutical industry has not achieved the consistent six sigma manufacturing capability (i.e., <3.4 errors per million opportunities) common in other industries (Politis and Rekhas, 2011; Yu and Kopcha, 2017).

The United States Food and Drug Administration (FDA) has long championed the development and implementation of advanced manufacturing technologies like CM for drug substances and finished drug products because of the potential to improve product quality and reliability, lower manufacturing costs, reduce waste, decrease inventory, and increase manufacturing flexibility and agility in response to fluctuations in product demand. The cumulative effects of CM adoption could reduce or mitigate drug shortages (Lee et al., 2015). CM can be applied to all classes of products: new drugs submitted in New Drug Applications (NDAs) (Hernandez, 2015), generic drugs filed in Abbreviated New Drug applications (ANDAs) (Chaudhary et al., 2017), drug substances filed in Drug Master Files (DMFs) (Stauffer et al., 2019), biotechnology products filed in Biologics License Applications (BLAs) (Fisher et al., 2019), and nonprescription drugs (Griffin et al., 2016). There is now a rich source of scientific literature describing the benefits of CM in pharmaceutical manufacturing relating mostly to decreases in production/operating costs and improvements in product quality and reliability (Rosi, 2022; Beckman et al., 2019). Perhaps most importantly for patients and consumers, CM has the potential to impact product availability; for example, by avoiding drug shortages due to manufacturing problems or expediting patient access through improved

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- **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

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