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# Emerging Technology Team: Policy Considerations for Continuous Manufacturing

*Pharmaceutical Quality Symposium*

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# Learning Objectives

- Understand major milestones in the history of FDA and continuous manufacturing for drug products (2015 to present)
- Identify the most common type of comments to the public docket for FDA's Draft Guidance for Industry, Quality Considerations for Continuous Manufacturing
- Discuss the current status of the drafting of ICH Q13, Continuous Manufacturing

# Continuous Manufacturing

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

- FDA recognizes that CM has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing
  - Integrated processing with fewer steps
  - Smaller equipment and facilities
  - On-line monitoring and control for increased product quality assurance in real-time


- Benefits to both patients and industry

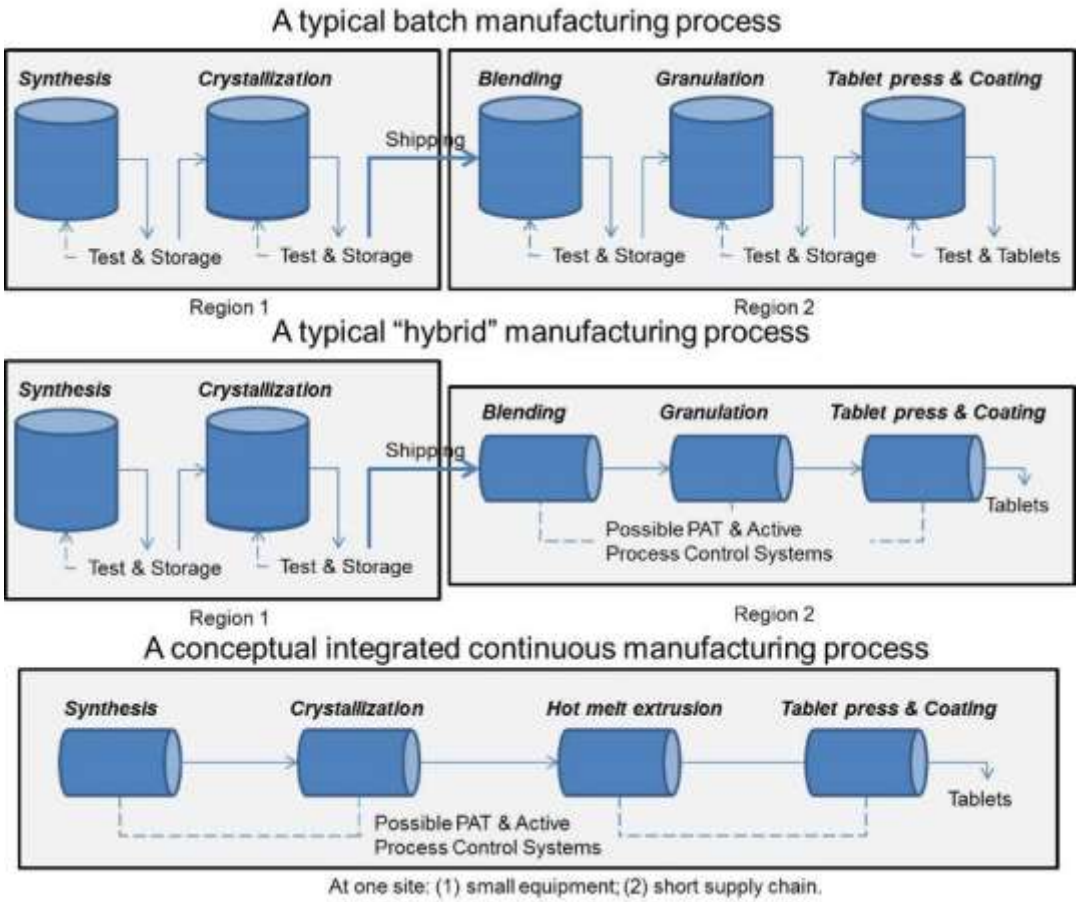
# What is Continuous Manufacturing?

CM is a process based on flow: input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system.

(1) Batch

(2) Hybrid

(3) End-to-End



**2015**

One CM application approved
Two papers published:

- Regulatory and Quality Considerations for Continuous Manufacturing
- Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

**2016**

One CM application approved (batch to CM)

**2017**

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

2018

Two CM applications approved
ICH Q13 endorsed (Step 1)

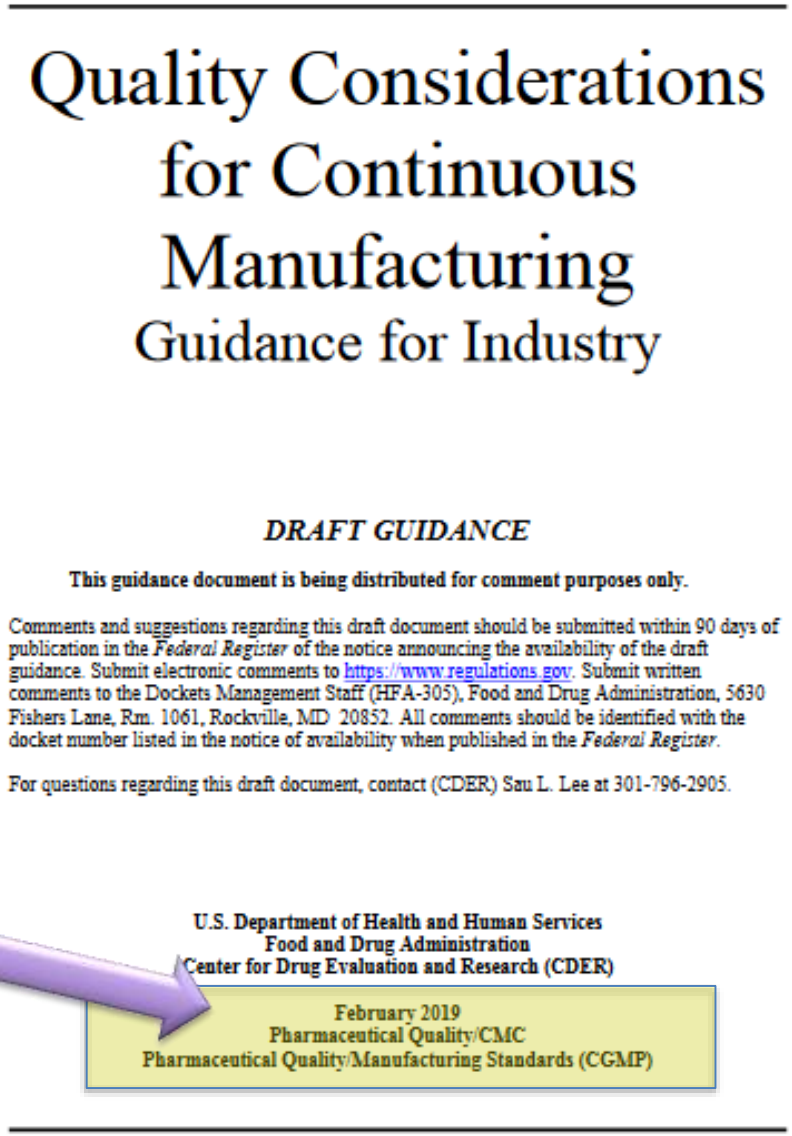
2019

Draft Guidance for Industry: Quality Considerations for Continuous Manufacturing

2020

*Q13 Step 2a/2b (proposed June 2020)*
*Q13 Step 3 (proposed June 2020-November 2021)*

# Continuous Manufacturing Draft Guidance



Quality Considerations for Continuous Manufacturing

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 docket number listed in the notice of availability when published in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sau L. Lee at 301-796-2905.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**February 2019**
**Pharmaceutical Quality/CMC**
**Pharmaceutical Quality/Manufacturing Standards (CGMP)**

1527654 Dft

- Current thinking on quality considerations for continuous manufacturing of *small molecule, solid oral drug products regulated by CDER*
- Recommendations for how applicants should address considerations in NDAs and ANDAs, including supplements
- Recommendations broadly applicable to both batch and continuous manufacturing are generally not covered in this guidance

# Continuous Manufacturing Draft Guidance: Content

- Continuous Manufacturing concepts
- Control strategy
- Process validation
- Pharmaceutical Quality System
- Additional considerations
- eCTD locations for information and definitions

# 24 Letters Received to the Docket

- Industry associations
  - Brand, Generic, APIs, Excipients, OTC
- Individual pharma companies
- Contract manufacturer
- Equipment manufacturer
- Consultants

# 24 Submissions ≈ 44 Categories

## Categories with >10 Occurrences

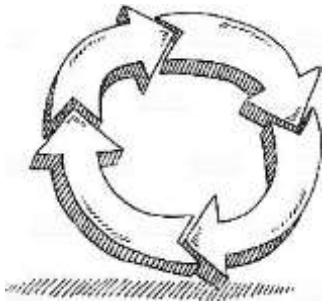
| | |
|---|---|
| Process Monitoring and Control | 49 |
| Process Validation | 23 |
| Scale-up | 14 |
| Input Material Control | 13 |
| System Integration, Data Processing, and Management | 13 |
| Definition of “Batch” | 12 |
| Equipment Qualification | 11 |
| Sampling | 11 |
| PQS v. Filing | 10 |



*Editorial comments, positive/negative comments not included (74)

# Docket Comment Highlights

- Decouple or integrate quality concepts that are traditionally considered "review vs. inspection"
- Process validation and continuous process verification (ICH Q8)
- Request for additional guidance on data integrity and data handling for continuous manufacturing systems
- Expectation of in-line/on-line monitoring
- Run-time extension
- Diversion, investigation, rejection, and partial batch release
- Explain the regulatory process regarding drafting Q13 with simultaneously publishing this draft guidance



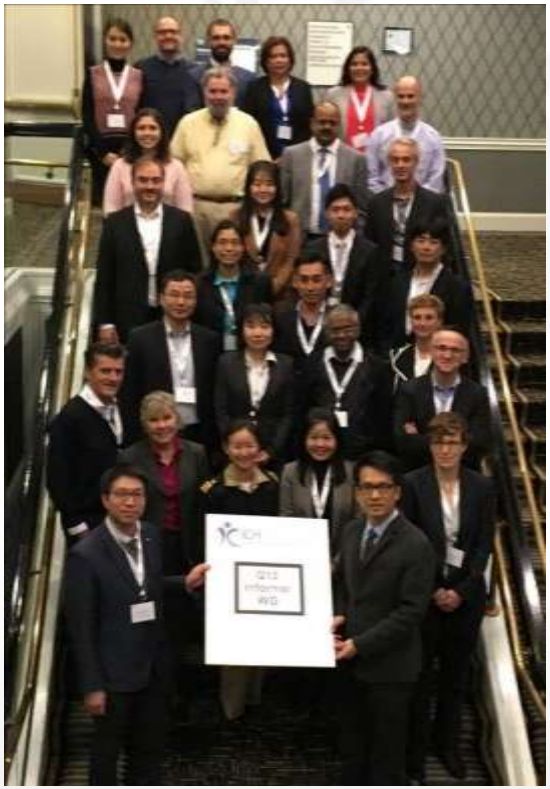
# Need for an ICH Guidance on CM

- **The current ICH Guidelines do not sufficiently address technical and regulatory requirements that are unique to CM.**
- **A harmonized regulatory guideline can facilitate implementation, regulatory approval, and lifecycle management, particularly for products intended for international commercialization.**
- **This approach will benefit industry and regulators, and improve access to medicines.**

# ICH Q13

- **Initiated: September 2018**
- **Concept Paper and Business Plan Endorsed: November 14, 2018, Charlotte, NC, U.S.A.**
- **Organizational Membership:**

- Rapporteur: Dr. Sau (Larry) Lee (FDA, US)
- Regulatory Chair: Dr. Yoshihiro Matsuda (MHLW/PMDA)
- ANVISA, Brazil
- BIO
- EC, Europe
- EFPIA
- FDA, US
- Health Canada, Canada
- HSA, Singapore
- IGBA
- JPMA
- MFDS, Republic of Korea
- MHLW/PMDA, Japan
- NMPA, China
- PhRMA
- Swissmedic, Switzerland
- TFDA, Chinese Taipei
- IFPMA
- APIC
- IPEC
- National Center, Kazakhstan
- *USP*
- *PIC/S*
- *EDQM*



# Scope of ICH Q13

- Intended to inform CM development and implementation for small molecules and therapeutic proteins.
- The general CM-related definitions and regulatory concepts therein may also apply to other biotechnological/biological entities.

# Objectives

- Capture key **technical and regulatory considerations** that promote harmonisation, including certain CGMP elements specific to CM,

- Allow drug manufacturers to employ **flexible approaches to develop, implement, or integrate CM for the manufacture of small molecules and therapeutic proteins** for new and existing products, and

- **Provide guidance to industry and regulatory agencies** regarding regulatory expectations on the development, implementation, and assessment of CM technologies used in the manufacture of drug substances and drug products.


15

# Concept Paper – Content of Q13

- **Definitions and regulatory concepts**
  - Definition of CM, startup/shutdown, state of control, process validation, and continuous process verification.

- **Key scientific approaches**
  - Concepts of system dynamics, monitoring frequency, detection and removal of non-conforming material, material traceability, process models, and advanced process controls.

- **Regulatory expectations**
  - Dossier approval and aspects of lifecycle management.

# ICH Guideline Development Milestones

- **Step 1:** Consensus Building – Develop Technical Document
- **Step 2a:** Confirmation of ICH Parties consensus on the Technical Document/**Step 2b:** Adoption of Technical Document as draft Guideline by Regulatory Members
- **Step 3:** Regulatory consultation and discussion (3 stage process)
- **Step 4**: Adoption of an ICH Harmonised Guideline
- **Step 5:** Implementation

# Business Plan for ICH Q13: Timeline

- ✓ **Step 1:** Initiated November 2018
- ✓ **Step 2a/Step 2b:** June 2020
- ✓ **Step 3:** June 2020 – November 2021
- **Step 4**: November 2021
- **Step 5:** Initiate after November 2021

## Current Status

- Preliminary draft is under development
- Draft to be discussed at the November 2019 ICH meeting

# Special actions to advance guideline development

- **Regionally coordinated site-visits for regulatory EWG members**
- **Engagement with suppliers to understand technology capability**
- **Engagement with external technical experts**

# Keep up with ICH Q13 Online

- **ICH Website:** http://www.ich.org/
- **Status of ICH Q13 Guideline Development:** https://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

# Key Takeaways

- **Key Takeaway 1**
  Docket comments on the FDA draft guidance included many topics, including process control and monitoring, process validation, scale-up, and input material control, and are helpful.
- **Key Takeaway 2**
  The ICH Q13 preliminary draft is under development and to be discussed at the November 2019 ICH meeting.
- **Key Takeaway 3**

  Docket comments will be shared with the ICH Q13 Expert Working Group and could inform the development of ICH Q13.

# Challenge Question

*True/False*

At the present time, FDA is not pursuing finalization of the draft Guidance for Industry, Quality Considerations for Continuous Manufacturing.

# Acknowledgements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