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FDA Perspective on ICH Q13

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Disclaimer: The opinions discussed in this presentation are those of the authors and do not necessarily reflect FDA policy


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

Continuous Manufacturing

- What makes a process 'Continuous Manufacturing (CM)'
  - 2 or more connected unit operations or process steps
  - Continuous material addition, processing and product formation
- Different risks, control strategies and technical/regulatory aspects compared to batch
  - Mass flow rate
  - Potential for coupled interactions and disturbance propagation
  - Potential for product quality variability, process disturbances, etc., over processing time
  - Many quality decisions need to be made in real-time; cannot stop and test
  - Potential to reject non-conforming material if appropriate systems for detection of variability and material traceability are present

CM Current State

- Slow but steady progress in the adoption of CM technology
- CM facilities in US, Europe and Asia
  - Small molecules, biotech products, contract facilities
- Expanding pool of staff (in both industry and regulatory agencies) with CM knowledge
- Maturity of the scientific and regulatory framework for CM
- Increased knowledge of CM processes for small molecule drug product manufacture and biotech drugs substance manufacturing.
- Significant experience with continuous direct compression processes
  - Nearing 'graduation' out of the CDER Emerging Technology Program

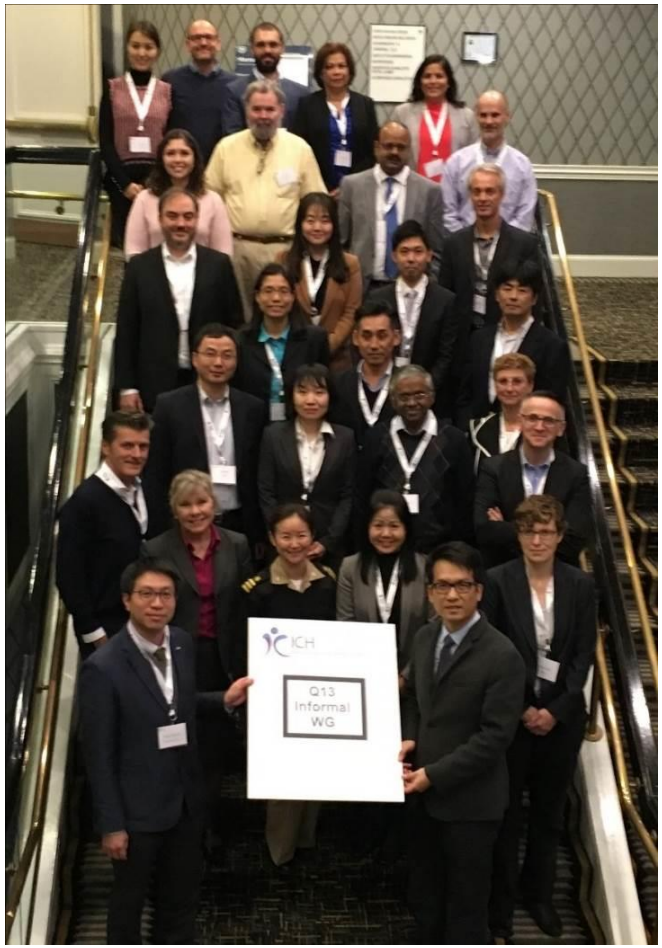
Need for an ICH Guidance on CM

- 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 - First Meeting November, 2018

- 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*



Overview of ICH Q13

- **Scope** – Develop a new guideline to provide harmonisation on technical and regulatory aspects unique to CM of drug substances and drug products for small and large molecules. Main guideline covers fundamental CM aspects and annexes cover special topics with examples
- **Background** – CM is an emergent technology getting a lot of interest from pharmaceutical and biotechnological companies. However, one identified barrier to adoption is a lack of harmonisation of regulatory expectations internationally.
- **Challenges addressed** – variable maturity of technology, harmonisation of operating paradigms, terminology, regional considerations, lifecycle management, etc.

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.

Timeline and Progress

Past completion date	Milestone
Nov. 2018	Initiation, Concept Paper and Business Plan Endorsement Face-to Face Meeting
May. 2019	Outline for technical document developed
Jun. 2019	Face-to-Face Meeting in support of consensus building, outline finalization, and technical document drafting
Nov. 2019	Face-to-Face Meeting in support of development of the technical document; First CM site visit
Apr. 2020	Completed draft distributed to individual organizations for feedback (first internal consultation)
May 2020	Virtual Meeting in support of revisions of the technical document
Sep.–Oct 2020	Three virtual CM site visits
Nov. 2020	Virtual Meeting to continue revisions of the technical document and plan training materials
Dec. 2020	Completed draft distributed to individual organizations for feedback (second internal consultation)
Mar. 2021	Virtual Interim Meeting to continue revisions of the technical document
May 2021	Virtual Meeting to finalize draft for Step 1 sign off

Next Steps – Future Milestones

Expected Completion date	Deliverable
June 2021	• **Step 1 sign-off and Step 2 a/b endorsement** • Initiate regional public consultation period
November 2021	• Virtual Face to Face Meeting for developing training materials
June 2022	• Face to Face Meeting • Review and resolve public comments
November 2022	• **Step 3 sign-off and Step 4 Adoption of final guideline**

Current Status of Document

- Main guideline
- Developed 5 Annexes

- Anticipate additional discussions, comments and further revisions in response to open comment period

ICH Online Information

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

ICH Q13 Expert Working Group

Q13 and FDA's Draft CM Guidance

- FDA's draft guidance development began before the ICH Q13 proposal was accepted by the ICH Committee
- The scope of FDA's draft guidance is limited to small molecule drug product manufacture
- The draft guidance provides transparency of FDA's viewpoints
- External feedback obtained on the guidance via an open docket
  - Received 24 letters
- What to do with FDA's draft guidance will be determined when ICH Q13 is finalized

Docket Comment Highlights

- Clarity on quality concepts that are traditionally considered "review vs. inspection"
- Diversion, investigation, rejection, and partial batch release
- Expectations for in-line/on-line monitoring
- Extension of run-time
- Guidance on data handling and data integrity for CM systems
- Process validation and continuous process verification (ICH Q8)
- Questions on the publication of FDA CM guidance during Q13 development

What is Next?

- Increased interest and activity in CM of biotechnology and biologic products
- Interest in using process models to support development and/or operation of CM processes
- Increased interest in the use of small modular facilities for CM
  - Modular facilities are well-suited for CM systems due to the small footprint
  - Addition of an alternative CM facility is simplified by the use of modular facilities
- Significant interest in domestic manufacture and building redundancy into the drug supply chain through use of CM and modular facilities

FDA CM Team

- Sau “Larry” Lee
- Rapti Madurawe
- Cyrus Agarabi
- Qiao Bobo
- Sarah Rogstad
- Thomas O’Connor
- Sharmista Chatterjee
- Bogdan Kurtyka
- Tara Gooen
- Christina Capacci-Daniel
- Hasmukh Patel
- Many Others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