ISPE Singapore Affiliate

Update on ICH Q13

Continuous Manufacturing of Drug Substances and Drug Products

Yoshihiro Matsuda, Ph.D.

Senior Scientist (for Quality)

Pharmaceuticals and Medical Devices Agency (PMDA)

December 9, 2020

Agenda

1. Expectations for Continuous Manufacturing (CM)
2. ICH Q13
3. Current Status

Why is CM drawing attention?

- Are there any problems with conventional batch manufacturing?

- There is nothing wrong with batch manufacturing, which should remain one of the manufacturing methods to be used in the future.
- However, CM may offer us what is difficult to achieve in batch manufacturing.

Expectations for CM

- Prevents inferior quality at an early stage by combining it with highly accurate monitoring technologies (e.g. PAT) → to avoid the risk of product shortage
- Easy to scale up or down → (a) shorter development period (CM can be implemented from the phase of manufacturing investigational new drugs), (b) enables the adjustment of yield
- Flexible yield control in response to demand → lower costs in manufacturing, warehousing, and others
- Enables low-volume manufacturing → applicable to generic drugs and personalized medicine
- More compact manufacturing equipment → allows for the installation of containment to reduce the operators' risk
- Enables the relocation of manufacturing sites (transportation of manufacturing equipment) → thus securing an alternative site in the event of earthquakes
- Lower usage of solvents → thus achieving green chemistry
- Reduces manufacturing costs → new investment in the development of new drugs, and lower drug price

Offers us a wider choice of manufacturing methods

ICH

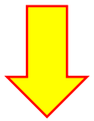
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- The ICH is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration
- The ICH began with representatives of the regulatory agencies and industry associations of Europe, Japan and the US in April 1990 →As of 2020, 17 members and 33 observers

Regulatory Agencies：

MHLW/PMDA, US FDA, EC/EMA, HC, Swiss Medic, ANVISA, CFDA, HSA, MFDS, TFDA, TITCK

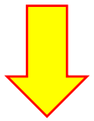
Road to ICH Q13

- In 2014, the CM was selected as a topic which would be developed into a guideline.



- The CM was chosen as a nominee of the future ICH quality topics.

（As of the ICH Minneapolis meeting, 2014）



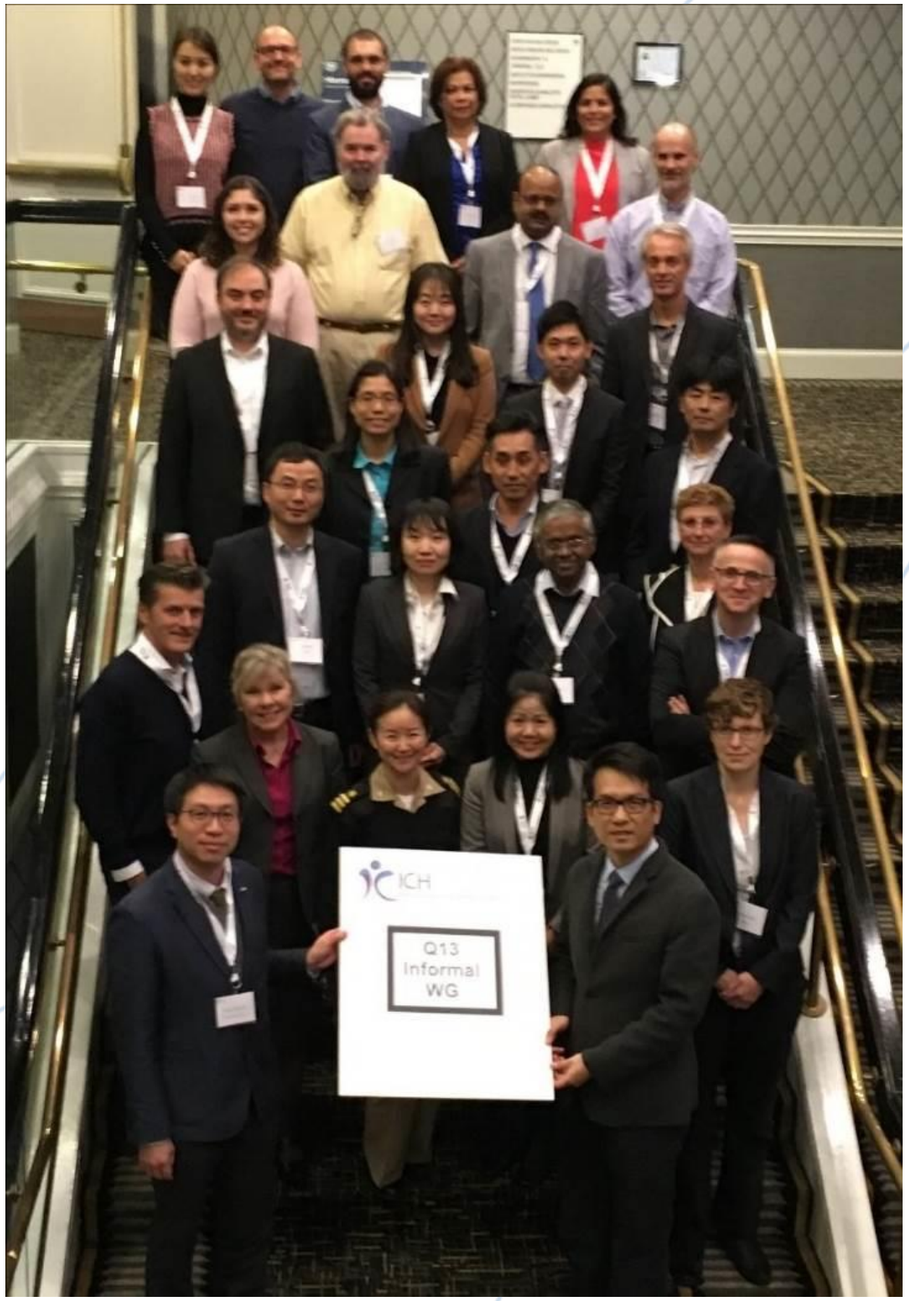
- In June, 2018, the CM was endorsed as a new topic at the ICH Kobe meeting.（ICH Q13）

ICH Q13

First Meeting on 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*



November 2018 (1st meeting)

- Finalized the Concept Paper, the Business Plan, and the Work Plan
- Moved from Informal Working Group (IWG) to Expert Working Group (EWG)
- Developed the draft outline
- Identified key topics, and areas of alignment or regional differences

Concept paper （1）

- The CP describes the perceived problems and the issues to be resolved by a harmonization project. Based on the description of the CP, the guideline will be developed.
- The perceived problem:
  - A lack of regulatory guidelines regarding the CM.

  - It can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally.

  - An ICH guideline would facilitate international harmonization and could reduce barriers to the adoption of CM technology.

Concept paper （2）

Scope

- Small molecules
- Therapeutic proteins
  - At the present time, our CM research/development for biotechnological/biological entities is limited to antibody drugs; but to avoid the exclusion of other biotechnological/biological entities, we use the expression “therapeutic proteins”.

We will state that the general definitions and regulatory concepts, as well as scientific approaches in this guideline may also apply to other biotechnological/biological entities.

Concept paper （3）

Issues to be Resolved:

- CM-related definitions and regulatory concepts

  Due to differences from batch manufacturing, matters require further clarification or explanation:

  （Definition of CM, startup/shutdown, state of control, process validation, and continuous process verification.）

- Key scientific approaches for CM

  CM specific matters:

  （Concepts of system dynamics, monitoring frequency, detection and removal of non-conforming material, material traceability, process models, and advanced process controls.）

- CM-related regulatory expectations

  The regulatory expectations with respect to marketing applications and post-approval changes, site implementation, and pharmaceutical quality systems.

Concept paper （4）

Objectives:

1. Capture key technical and regulatory considerations that promote harmonization, including certain GMP elements specific to CM.
2. Allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for the manufacture.
3. Provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies.

- To consider multiple approaches to CM, including end-to-end and hybrid approaches to drug substance and drug product manufacturing.
- To consider relevant ICH guidelines and how the content of those guidelines applies to CM.

Business plan （1）

BP outlines the costs and benefits of harmonizing a topic that was previously proposed by a CP and focuses on regulatory feasibility. Based on the BP, the ICH finally decides whether the topic should be developed as an ICH guideline.

Problem/Issue expected to tackle:

1. Harmonise CM-related definitions
2. Articulate key scientific approaches for CM
3. Harmonise regulatory concepts and expectations for CM across the regions

Business plan （2）

Specific costs from lack of action by ICH include:

1. Issuance of final regional guidelines/guidances with differing regulatory expectations.
2. Multiple filing strategies required to comply with different regulatory expectations.
3. Increased risk and costs for CM implementation due to the lack of harmonized regulatory expectations.
4. Uncertainty resulting in ad hoc special meetings and consultations between industry and regulators to resolve technical and regulatory questions.
5. Lost opportunities for patients to have improved access to medicines.

Business plan （3）

Plan

1. The main deliverable is a new quality guideline, ICH Q13, on CM for drug substances and drug products.
2. The EWG includes approximately 35 experts. We anticipate the need for six face-to-face meetings and multiple interim teleconferences to complete the new guideline.
3. The new guideline is anticipated to take three years to achieve Step 4, from November 2018 – November 2021.
4. Proposed timeline and milestones
   - Final CP and BP endorsed: November 2018
   - Step2b：June 2020 →May 2021?
   - Step4：November 2021 →November 2022?

Business plan （4）

Potential special actions

- Site-visits to CM facilities by regulatory working group members.
- Understanding of technologies' state-of-the-art capabilities.
- Presentations at major technical conferences on the ICH guideline during the consultation phase.
- Engagement with external, technical experts.

Potential actions that may be taken to advance or promote implementation of the guideline:

- Creation of formal training materials related to the ICH Q13 guideline and their distribution.
- Development of example case studies.

June 2019 (2nd meeting)

- Completed the Q13 Outline.
- Began drafting the document.
  - Four sub-teams formed to begin drafting of each session
  - Multiple teleconferences to develop and review the content
- Continued consensus building for key scientific and regulatory concepts.
- Completed first draft in October 2019.
- Identified CM facilities in North America, Asia and Europe for site visits by Q13 EWG regulatory members.

November 2019 (3rd meeting)

- Further refined the scope and content of three major document sections (Definition and Regulatory Concepts, Scientific Approaches and Regulatory Considerations).
- Continued consensus building.
- Identified topics for Annexes, and developed plans for their drafting.
  - Annexes elaborate and/or provide examples on the application of some CM topics discussed in the guidance.
  - Annexes address key aspects associated with different modalities.
  - Annexes provide further information regarding regulatory expectations.

May 2020 (4th meeting)

- Virtual meeting to continue development of the technical document.
- Comments from EWG organizations were collated and distributed to EWG.
- Critical areas to be discussed were identified from comments.
- Continued consensus building.
- Continued revision of guideline and annexes over the summer.

November 2020 (5th meeting)

- Virtual meeting to continue development of the technical document.
- Discussed and addressed key topic-specific issues identified during the second-round revision of ICH Q13 Guideline.
- Clarified approaches and expectations for collecting, organizing and filtering organizations' feedback on the third draft of ICH Q13 Guideline.

Current Status

- Continue editing the draft of the guideline and annexes issued to EWG for review and discussion within their respective organizations.
- The 2nd internal consultation will start.
- Before the next ICH meeting in May 2021, we will almost finish the drafting, and we expect to proceed with a public consultation after the next ICH meeting.

Acknowledgements

Thank you for your attention

matsuda-yoshihiro@pmda.go.jp