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Pharmaceuticals and Medical Devices Agency

ICH Q13 Update: Continuous Manufacturing of Drug Substances and Drug Products

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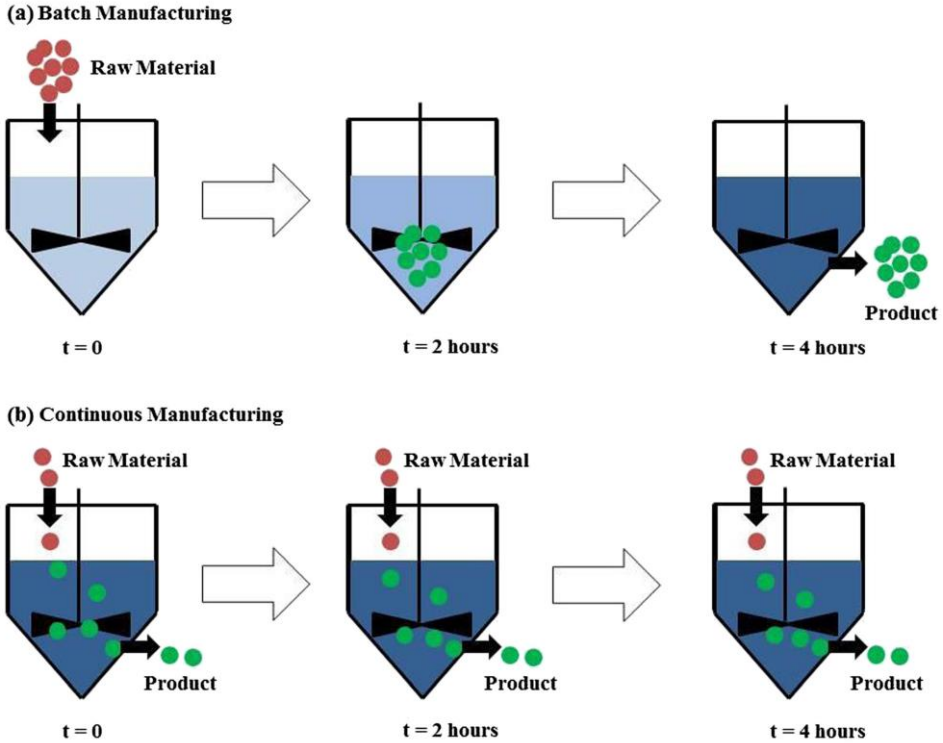
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Outline

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

What is CM?



Lee S. and Woodcock J, et al., *J Pharma Innov* (2015)10; 191-9

CM is a manufacturing method in which raw materials or their blended materials are entered continuously in the manufacturing process throughout the duration of the process, and products are produced continuously through the manufacturing.

Why is CM drawing attention?

- Are there any problems with conventional batch manufacturing?

- No. The batch manufacturing is still working well in pharmaceutical area and should remain one of the manufacturing methods to be used in the future.
- However, we expect the CM to bring us additional opportunities.

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

Expectations for CM

- 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

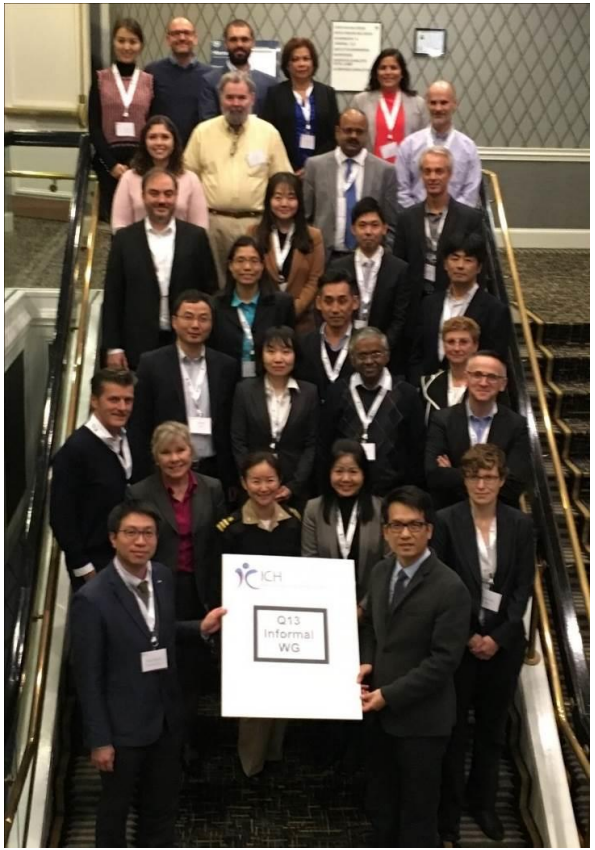
Need for New guideline

- 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 commercialization internationally.
- This approach will benefit industry and regulators, and improve access to medicines.

ICH Q13 - First Meeting in 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*



Objectives

- Capture key technical and regulatory considerations that promote harmonization, including certain Current Good Manufacturing Practices (CGMP) elements specific to Continuous Manufacturing (CM).
- Allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for the manufacture – drug substances and drug products – of small molecules and therapeutic proteins for new and existing products.
- 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.

Progress

Past completion date	Milestone
Nov. 2018	Concept Paper and Business Plan Endorsement
Nov. 2018	Initiation of consensus building
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
June – July 2021	• **Step 1 sign-off and Step 2 a/b endorsement** • Initiated regional public consultation period
Nov. 2021	Virtual Meeting to discuss about training materials

Endorsement of Q13 Step 2 document

ICH Q13 draft guidance has been signed off as a *Step 2* document (27 July 2021) to be issued by the ICH Regulatory Members for public consultation.

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

Draft version

Endorsed on 27 July 2021

Currently under public consultation

Table of Contents –

Part I: Main Guideline

Part II: Annexes

1. Introduction – Objective and Scope

- This guideline describes scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing (CM). Building on existing ICH Quality guidelines, this guideline provides clarification on CM concepts, describes scientific approaches, and presents regulatory considerations specific to CM of drug substances and drug.
- This guideline applies to CM of drug substances and drug products for chemical entities and therapeutic proteins. It is applicable to CM for new products and the conversion of batch manufacturing to CM for existing products.
- The principles described in this guideline may also apply to other biological/biotechnological entities.

1. Introduction – Objective and Scope

- CM involves the continuous feeding of input materials into, the transformation of in-process materials within, and the concomitant removal of output materials from a manufacturing process. This guideline focuses on the integrated aspects of a CM system in which two or more unit operations are directly connected.

- Fundamental aspects of CM that are generally not specific to technology, dosage form, or molecule type are described within the main body of this guideline (Part I).
- Annexes(Part II) are provided to augment the main guideline by providing illustrative examples and considerations specific to certain modalities, technologies, and production methods.

2. CM Concepts

Different Mode of CM

- CM can be applied to some or all unit operations in a manufacturing process (e.g., hybrid, E2E, integrated across the boundary of DS and DP).

Batch Definition

- The ICH Q7 definition of a batch is applicable to all modes of CM, for both drug substances and drug products (e.g., quantity of output or input material, run time). Other approaches to define batch size can also be considered, if scientifically justified.
- A batch size can also be defined as a range.

3. Scientific Approaches

Control Strategy

- The development of a successful control strategy for CM is enabled by a holistic approach, considering aspects specific to CM (discussed below) and the principles described in ICH Q8–Q11.
  - State of Control
  - Process Dynamics
  - Material Characterisation and Control
  - Equipment Design and System Integration
  - Process Monitoring and Control
  - Material Traceability and Diversion
  - Process models

3. Scientific Approaches

Changes in Production Output

- Several considerations associated with some common approaches to production changes are discussed.
  - Change in run time with no change to mass flow rates and equipment
  - Increase mass flow rates with no change to overall run time and equipment
  - Increase output through duplication of equipment (i.e., scale-out)
  - Scale up by increasing equipment size/capacity
- For already approved products, it is important to justify the selected approach, understand its impact on the overall control strategy and process performance, and, as needed, update the control strategy. Some changes may require process modification and process validation.

Continuous Process Verification

- Continuous process verification is highlighted as an alternative approach for process validation.

4. Regulatory Considerations

- The regulatory expectations with respect to marketing application, post-approval changes, site implementation, and pharmaceutical quality systems are provided by describing the important aspects below:
  - Process description
  - Control strategy (input material attributes, process monitoring and control, system operation, material diversion and collection, real time release testing, and equipment and system integration)
  - Batch description
  - Process models
  - Drug substance and drug product stability
  - Conversion of a batch process to CM
  - Process Validation
  - Pharmaceutical quality system
  - Lifecycle management
  - Submission of CM-specific information in the CTD

Table of Contents –

Part I: Main Guideline

Part II: Annexes

Annex III: Continuous Manufacturing of Therapeutic Drug Substances

- Augments the main guideline by providing additional considerations for therapeutic protein drug substances(DS) and DS used as intermediates for subsequent conjugation (e.g., pegylation).

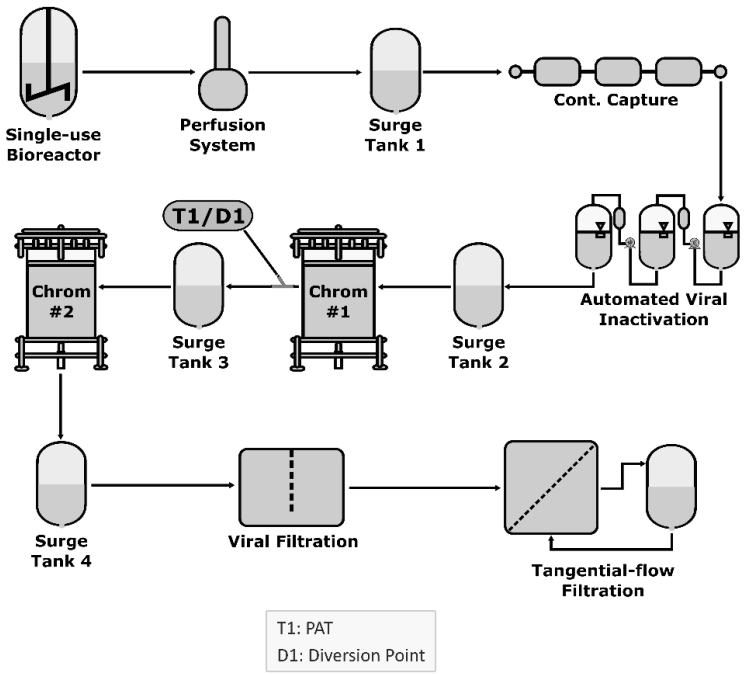


Fig. Example of a DS CM System for Therapeutic Proteins

Annex III: CM of Therapeutic Drug Substances -Control Strategy-

Adventitious Agent Control

- In general, all principles used to ensure safety in batch manufacturing are applicable to CM. Safety is demonstrated by a threefold approach based on the principles outlined in ICH Q5A. A strategy should be developed to include the type and frequency of adventitious agent testing undertaken to demonstrate that the process remains free of contamination during cell culture and other downstream steps.
- An aspect unique to CM is extended cell culture duration and continuous processing of harvested cell culture material to obtain DS. This means that measures should be in place to demonstrate the acceptability of all cell culture material used to generate a given DS batch.
- Rapid testing for adventitious agents, when possible, may enable real-time decision-making to mitigate the impact of contamination events during continuous operation.

Annex III: CM of Therapeutic Drug Substances -Control Strategy- (cont.)

Equipment Design and System Integration

- The integrity of single-use equipment during use should be ensured to prevent contamination. The potential weak points and typical locations where single-use systems require changing out over a potentially extended time frame or at a higher frequency for a CM process should be evaluated for potential contamination risks.
- Filtration steps in CM may be subject to longer filtration periods and potentially increased throughput per unit area or a greater number of filter changes than those under batch manufacturing. Given these factors, a control strategy and a clearly defined scheme should be put in place to allow for filter changes and post-use integrity testing, as appropriate, without interrupting the process. In the event of a filter failure, a clear strategy for material diversion and refiltration (reprocessing) should be defined.

Annex III: CM of Therapeutic Drug Substances -Control Strategy- (cont.)

Equipment Design and System Integration(cont.)

- The CM system should contain appropriate sampling locations based on risk assessment.
- When surge tanks are used, the relevant RTD, uniformity and microbial risks to the product in these surge tanks should be evaluated and defined in advance.

Process Monitoring and Real-Time Release Testing

- Appropriate monitoring at suitable stages of the CM process enables timely data analysis to ensure operations are in a state of control.
- Conventional offline testing for product release is necessary for quality attributes for which analytical technologies are not available for online or in-line measurements (e.g., potency). Likewise, conventional tests for monitoring and control (e.g., microbiological analytical methods and other tests that require long processing times) might also be needed.

Annex III: CM of Therapeutic Drug Substances -Process Validation-

Approaches to Process Validation

- Process validation approaches used in batch mode are also applicable to CM processes. Alternative approaches (e.g., continuous process verification) may be considered when justified.
- Variability between batches from a single cell bank thaw, as well as the potential variability between different batches purified from harvests of multiple cell bank thaws should be considered.
- Variability may be evaluated either as part of process qualification or through alternative studies, if justified. For some unit operations, the use of scale-down models remains an alternative approach to validation (e.g., viral clearance), if justified.

Annex III: CM of Therapeutic Drug Substances -Process Validation- (cont.)

Run Time Consideration

- The approach to establish a limit of *in vitro* cell age (LIVCA) for production cells does not differ, regardless of the mode of bioreactor operation. Previously established LIVCA for a bioreactor operating in a batch mode run may not be applicable to a bioreactor operating in a continuous mode under different culture conditions.
- Run time considerations should include the control of all adventitious agents and the impact of resin and membrane lifetimes. Viral testing should be conducted as outlined by ICH Q5A, and an appropriate microbial control strategy should be established.

Viral Clearance Validation

- The general recommendations outlined in ICH Q5A remain applicable for CM. Considerations specific to CM in aspects such as qualification of small-scale models are addressed in ICH Q5A(under revision).

Public Consultation

Public consultation dates:

ANVISA, Brazil - Deadline for comments by 7 December 2021
EC, Europe - Deadline for comments by 20 December 2021
FDA, US - Deadline for comments by 13 December 2021
HSA, Singapore - Deadline for comments by 30 November 2021
Health Canada, Canada - Deadline for comments by 27 December 2021
MFDS, Republic of Korea - Deadline for comments by 30 November 2021
MHLW/PMDA, Japan - Deadline for comments by 17 December 2021
NMPA, China - Deadline for comments by 31 December 2021
SFDA, Saudi Arabia - Deadline for comments by 28 October 2021
Swissmedic, Switzerland - Deadline for comments by 20 December 2021
TFDA, Chinese Taipei - Deadline for comments by 30 November 2021 (As of 18 November 2021)

ICH HP https://www.ich.org/page/quality-guidelines
PMDA HP https://www.pmda.go.jp/int-activities/int-harmony/ich/0097.html

Next Steps – Future Milestones

Expected Completion Date	Deliverable
June 2022	• Face to Face Meeting • Review and resolve comments from public consultation
November 2022	• Face to Face Meeting • **Step 3 sign-off and Step 4 Adoption of final guideline**

Acknowledgements

ICH Q13 EWG

Thank you for your attention!

Pharmaceuticals and Medical Devices Agency

http://www.pmda.go.jp/ (日本語)
http://www.pmda.go.jp/english/index.html (English)