Q13: Continuous Manufacturing of Drug Substances and Drug products

Step 2

Step 2 document – to be released for comments

Date: 12 August 2021

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Legal Notice

Background

- This document has been signed off as a *Step 2* document (27 July 2021) to be issued by the ICH Regulatory Members for public consultation.
- This document was developed based on a Concept Paper (15 November 2018) and a Business Plan (15 November 2018).
- Anticipating finalization as a *Step 4* document to be implemented in the local regional regulatory system: November 2022.

Key Principles

- Continuous manufacturing (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.
- The Guideline:
  - Building on existing ICH Quality Guidelines, provides clarification on CM concepts, describes scientific approaches, and presents regulatory considerations specific to CM of drug substances and drug products.
  - Focuses on the integrated aspects of a CM system in which two or more unit operations are directly connected.
  - Describes scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of CM.

Guideline Objectives

- Capture key scientific and regulatory considerations that promote harmonisation, including certain GMP elements specific to CM.
- 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.
- Describe fundamental aspects of CM that are generally not specific to technology, dosage form, or molecule type within the main Guideline (Part I).
- Use Annexes (Part II) to augment the main Guideline by providing illustrative examples and considerations specific to certain modalities (e.g., chemical entities, therapeutic proteins), technologies, and production methods (e.g., integration of drug substance and drug product manufacturing).

Expected Benefits

- Harmonise regulatory expectations for drug substance and drug product production using CM, which will increase the likelihood of its implementation by industry internationally. This will result in the following likely benefits:
  - Enable the development of new methods for production of medicines and increase access for patients.
  - Increase manufacturing options available to address public health needs.
  - Develop new approaches for the control of drug manufacturing to enhance assurance of quality.
  - Increase operator safety (process safety risk reductions) for manufacturing.
  - Reduce resource consumption (for example, materials) and waste generation by shrinking equipment and facility footprints.
  - Improve the robustness, efficiency, and capability of manufacturing processes.

Table of Contents – Part I: Main Guideline

Table of Contents – Part II: Annexes

Section 1: Introduction

- Objective
  - Describes scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing (CM).
  - Building on existing ICH Quality Guidelines, provides clarification on CM concepts, describes scientific approaches, and presents regulatory considerations specific to CM of drug substances and drug products.
- Scope
  - Applies to CM of drug substances and drug products for chemical entities and therapeutic proteins.
  - Applies to CM for new products (e.g., new drugs, generic drugs, biosimilars) and the conversion of batch manufacturing to CM for existing products. The principles described in the Q13 Guideline may also apply to other biological/biotechnological entities.

Section 2: CM Concepts

- Different Modes of CM
  - CM can be applied to some or all unit operations in a manufacturing process.
- Batch Definition
  - The ICH Q7 definition of a batch is applicable to all modes of CM, for both drug substances and drug products.
  - The size of a batch produced by CM can be defined in terms of quantity of output material, quantity of input material, and run time at a defined mass flow rate.
  - Other approaches to define batch size can also be considered, if scientifically justified based on the characteristics of the CM process.

Section 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 including state of control, process dynamics, material characterisation and control, equipment design and system integration, process monitoring and control, material traceability and diversion, and process models.
- Changes in production output
  - Some common approaches to CM production changes are discussed. These include 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), and scale up by increasing equipment size/capacity.
- Continuous process verification
  - Continuous process verification is highlighted as an alternative approach for validating CM processes.

Section 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

Annexes

- Annex I: CM of Drug Substances for Chemical Entities
  - Provides an example of an approach to implement CM of drug substances for chemical entities based on the scientific principles described in the main Guideline.
- Annex II: CM for Drug Products
  - Provides an example of an approach to implement CM for a solid dose drug product based on the scientific principles described in the main Guideline.
- Annex III: CM of Therapeutic Protein Drug Substances
  - Augments the main Guideline by providing additional considerations for therapeutic protein drug substances and drug substances used as intermediates for subsequent conjugation (e.g., pegylation).

Annexes

- Annex IV: Integrated Drug Substance and Drug Product CM
  - Augments the main Guideline by providing additional considerations for the development and implementation of an integrated drug substance and drug product CM process using a small molecule tablet dosage form as an example.
- Annex V: Perspectives on Managing Disturbances
  - Describes examples of approaches for managing transient disturbances that may occur during CM.

Other Considerations

- The ICH Q13 Guideline should be applied in conjunction with other ICH “Q” Guidelines, including Q8–Q12.
- See Section 4 of the main Guideline for recommendations regarding the appropriate location for information to be submitted within a dossier.

Next Steps – Future Milestones

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

Conclusions

- The ICH Q13 Guideline establishes harmonised scientific and technical requirements to fulfill regulatory expectations for the implementation and assessment of CM, thereby facilitating a wider adoption of CM technologies and improving access to medicines.

Contact

- **For any questions please contact the ICH Secretariat:**

admin@ich.org