ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products

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Background

- This document has been signed off as *Step 4* document (16 November 2022) to be implemented by the ICH Regulatory Members
- This document was developed based on a Concept Paper (15 November 2018) and Business Plan (15 November 2018)

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

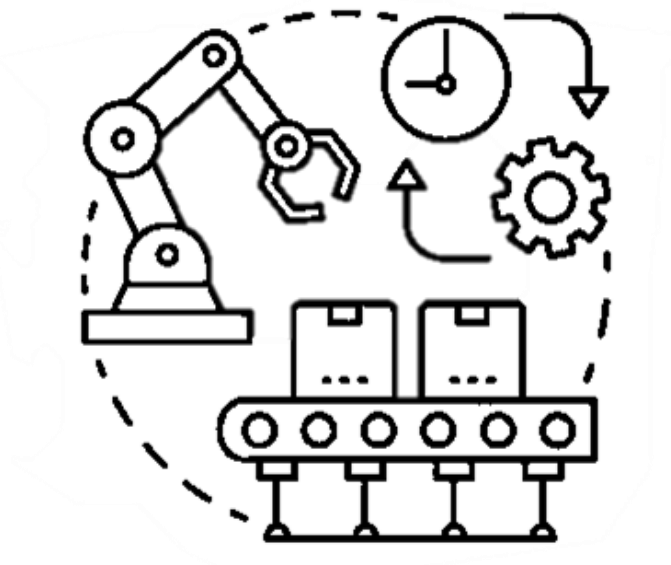
CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Final version
Adopted on 16 November 2022

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions

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.
  - Focuses on the integrated aspects of a CM system in which two or more unit operations are directly connected.



Key Principles

- 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.
  - 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.

Guideline Objectives

- 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).

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.

Section 1: Introduction

- 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 defined mass flow rates.
  - 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
  - Holistic approach, considering 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
  - 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
  - Alternative approach for validating CM processes.

Section 4: Regulatory Considerations

- 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 (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 (Chemical Entities)
  - 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 Drug Substances (Therapeutic Proteins)
  - 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 Continuous Manufacturing
  - 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.

Next Steps – Milestones

Adoption of Q13 IWG Concept Paper by the ICH Management Committee	January 2023
Establishment of the ICH Q13 IWG	January 2023
IWG development of training materials and approach	January 2023 – December 2023
IWG to finalize training materials and approach	June 2024