

## Final Concept Paper

### ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products dated 14 November 2018

*Endorsed by the Management Committee on 15 November 2018*

#### Type of Harmonisation Action Proposed

New Quality Guideline

#### Statement of the Perceived Problem:

There is a general consensus that continuous manufacturing (CM) has potential for improving the efficiency, agility, and flexibility of drug substance and drug product manufacturing. Regulatory agencies have seen more companies engaged in the development and implementation of CM in recent years than in the past. Although current regulatory frameworks allow for commercialization of products using CM technology, a lack of regulatory guidelines can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally. An ICH guideline would facilitate international harmonisation and could reduce barriers to the adoption of CM technology.

#### Issues to be Resolved:

- CM-related definitions and regulatory concepts: Due to differences from batch manufacture, many CM related definitions or terminologies require further clarification or explanation in the regulatory context, for example, definition of continuous manufacturing, startup/shutdown, state of control, process validation, and continuous process verification. Common understanding and consistent usage of terminology across different regions will lead to improved communication amongst stakeholders. Based on the current knowledge, the CM-related definitions and regulatory concepts covered in this guideline are intended to inform CM development and implementation for small molecules and therapeutic proteins. The general CM-related definitions and regulatory concepts therein may also apply to other biotechnological/biological entities.
- Key scientific approaches for CM: Fundamental scientific approaches for CM may differ from those encountered in batch processes, for example, concepts of system dynamics, monitoring frequency, detection and removal of non-conforming material, material traceability, process models, and advanced process controls. A common understanding of the scientific approaches will facilitate consistent science- and risk-based implementation and regulatory assessment of CM across different regions. Based on the current knowledge, the key scientific approaches covered in this guideline are intended to inform small molecules and therapeutic proteins. The general scientific approaches therein may also apply to other biotechnological/biological entities.
- CM-related regulatory expectations: Harmonised regulatory expectations for dossier approval and aspects of lifecycle management that are pertinent to CM can facilitate the adoption of CM and result in consistent regulatory assessment and oversight. Given the current maturity of the

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technology, manufacturing of – drug substances and drug products – small molecules and therapeutic proteins for new and existing products will be addressed. The regulatory expectations with respect to marketing applications and post-approval changes, site implementation, and pharmaceutical quality systems will be addressed.

**Background to the Proposal:**

Objectives: The new ICH guideline document on CM will

- 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 – drug substances and drug products – 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.

The working group will consider multiple approaches to CM, including end-to-end and hybrid approaches to drug substance and drug product manufacturing. This guideline will consider relevant ICH guidelines and how the content of those guidelines applies to CM.

Importance: The new ICH guideline will establish harmonised scientific and technical requirements needed to fulfill regulatory expectations for the implementation and assessment of CM to improve access to medicines.

Feasibility: The level of effort required to complete the ICH guidance on CM is medium with appropriate staffing of the working group. Both industry and regulatory agencies already have personnel with adequate background, expertise and/or experience to form a working group, and drug substances and drug products manufactured with continuous processes have been approved for multiple markets. Although CM is relatively new for pharmaceutical applications, there is sufficient information available to develop an ICH guideline. Fundamental scientific approaches and CM knowledge that is transferrable from other industries (for example, petroleum and food) will be used to develop the Q13 guideline. Additionally, some regulatory agencies are in the process of defining their own best practices for assessment of CM based applications. The benefit of the completed ICH guideline will be immediate as it will help to harmonise regulatory expectations and increase consistency in regulatory assessment and oversight across regions.

**Type of Expert Working Group Recommended:**

The EWG should include regulators and industry representatives with adequate background, expertise and/or experience in both technical and regulatory aspects of CM and with innovative thinking.

**Timing:**

The anticipated time to complete the guideline will be 3 years.