Working document QAS/24.957
January 2025

World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

WHO Points to consider in continuous manufacturing of pharmaceutical products

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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/24.957:

WHO Points to consider in continuous manufacturing of pharmaceutical products

Description of activity	**Date**
Preparation of first draft working document.	June 2024
Discussion of the feedback received on the working document in a virtual meeting with an informal consultation group.	July 2024
Review and finalization of the first draft working document with an informal drafting group.	August – November 2024
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	January - March 2025
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	March – April 2025
Discussion of the feedback received on the working document in a virtual meeting with an informal drafting group.	April - May 2025
Preparation of a working document for discussion and possible adoption by the ECSPP.	June 2025
Presentation to the fifty-ninth meeting of the ECSPP.	October 2025
Any other follow-up action as required.	

WHO Points to consider in continuous manufacturing of pharmaceutical products

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1. Introduction

Pharmaceutical manufacturers have predominantly used batch processing as a means to manufacture active pharmaceutical ingredients (APIs), excipients and finished pharmaceutical products (FPPs).

In recent years, several manufacturers have opted to introduce continuous manufacturing (CM) in pharmaceutical production. Although CM is a relatively new approach in pharmaceutical product manufacturing, this concept has been used in other industries for nearly a century. There are several examples of industries and products utilizing this approach and including, oil refinery, metal smelting, petrochemical product manufacturing, as well as certain food and beverage manufacturing.

CM (including flow chemistry, where appropriate) can be applied to the production of certain chemicals, starting materials (excipients and APIs) as well as FPPs.

Flow chemistry, or continuous flow chemistry (hereafter referred to as flow chemistry), enables the control of a wide range of parameters, making reactions much safer. It further facilitates ease to scale up, high throughput, and increased control of reaction parameters, such as, reagent and reactant quantity, mixing, temperature, time, and the solvent amount.

Automated systems should be considered when applying flow chemistry. Appropriate instruments, including flow reactors where required, should be used to ensure a sustainable manufacturing method.

In a CM process, the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system. This description can be applied to an individual unit operation or the entire manufacturing process consisting of a series of unit operations.

There are different approaches for the integration of unit operations in CM. In an end-to-end approach, the drug substance and drug product process steps are fully integrated into a single continuous process in which there is no isolated drug substance or intermediate.

CM does not have to be end-to-end in production of a product. It could be applied to some (semicontinuous) or all unit operations in a manufacturing process. As an example, in the production of simple oral solid dosage forms (OSDs), some steps (such as feeding and mixing) or all steps can be included in CM.

Although the amount of material being processed at any given instance may be relatively small in a continuous manufacturing process, the process can run over a period of time to generate desired quantities of finished material meeting the necessary quality standard.

Many pharmaceutical companies are currently developing and applying a hybrid approach, in which CM steps may be incorporated for portions of a drug substance or drug product process, or for an entire drug substance or drug product process.

Uncertainties in adopting CM processes in the pharmaceutical industry include material traceability, process design, monitoring, and control.

In the traditional batch manufacturing process, sampling and testing of samples after certain processing steps are the norm. This often leads to down times and hold times. The relatively new approach of CM, utilizing sensors for in-line, and on-line analytical testing may reduce such down and hold times. It may further facilitate utilizing the full capacity of equipment and production lines, reduce human error, and support quality control and testing.

This document presents points to consider for manufacturers implementing CM in the production of pharmaceutical products. The principles contained in this document may be useful where chemicals, excipients used in pharmaceutical products, (APIs), and FPPs are produced by CM. Although the examples given in the document focus on oral solid dosage forms, the principles may be applied to other dosage forms, biologicals and vaccines.

2. Glossary

at-line. Refers to the case where samples are collected manually and the analyser is located next to the process.

batch. A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

continuous manufacturing. Continuous feeding of input materials into a process with processed output materials continuously removed from the system, whether from an individual unit operation or the entire manufacturing process consisting of a series of unit operations.

flow chemistry. Flow chemistry is also known as continuous flow or plug flow chemistry; and it involves a chemical reaction run in a continuous flow stream rather than a batch production.

industrial Internet of things (IIoT). Industrial applications and devices which gather data from their environment and share it with other connected devices and analytical software. It may be used in predictive analytics and supply chain optimization.

in-line. Process analytical technology systems that are incorporated into the flow of the process and produce continuous data without sampling using capacitance, light scattering, spectroscopy, on-line liquid chromatography, and other types of sensors.

on-line. Systems which are connected directly to the process and collect and automatically analyse samples, which are never returned to the process.

process analytical technology (PAT). A mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of critical process parameters (CPP) which affect the critical quality attributes (CQA).

process control. Process control is the practice of monitoring and adjusting a process to achieve a desired outcome. It is a combination of engineering and statistics that involves using algorithms, mechanisms, and architectures to maintain a process's output within a specific range.

process dynamics. The response of a manufacturing process to changing inputs or conditions or transient events (A transient event is a temporary condition in which a process goes through a dynamic

change. This change may be due to a disturbance or an intentional alteration in the selected operating conditions (for example, start-up, shutdown, changes from one operating condition to another).

quality by design (QbD). A scientific and mathematical framework that aims to ensure a product's quality and efficacy from the beginning of the manufacturing process.

r**eal-time release testing (RTRT).** The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

residence time distribution (RTD). A measure of the range of residence times experienced by material passing through a specific process environment/vessel/unit operation.

state of control. A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

steady state. A stable condition that does not change over time.

For other definitions, see the *WHO Quality Assurance of Medicines Terminology Database*: https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

3. Benefits and challenges in continuous manufacturing

The benefits and challenges of CM have been described in various guidelines and articles (see Further Reading section).

CM may result in increasing output of product in a shorter timeframe than traditional batch processing. It may also provide safety benefits due to lower exposure risk to operators.

CM may also present challenges to manufacturers. These include, for example, providing specialized training of personnel in the new concept, managing product changeover and cleaning of such lines.

With the technical, operational, and economic challenges, as well as risks associated with CM, it is important that manufacturers wanting to move from batch manufacturing to CM processes ensure that there is sufficient process knowledge to facilitate risk management and the development and implementation of an appropriate control strategy.

Challenges to adopting CM in the pharmaceutical industry include, for example:

- technological issues (for example, process knowledge);
- logistical concerns (for example, new equipment and computerized systems);
- advanced control strategies comprising complex analytical instrumentation and technology for improved process control using robust and reliable methods (for example, in-line, on-line and at-line analytics);
- real-time data strategies for critical quality attributes (CQAs) and critical process parameters (CPPs), (for example, to maintain a steady state or state of control);
- regulatory uncertainty;
- integrating downstream unit operations such as semi-continuous manufacturing;
- personnel (for example, specific training and qualification);
- risks (including actual and perceived risks);
- economic issues (for example, return on investment);
- flexibility issues (for example, adjusting process and upscale or downscale).

Technical and operational challenges

The lack of commercially available equipment suitable for small-scale CM lines presents a challenge to formulation and development facilities as well as commercial manufacturers.

The importance of the link between batches produced and used during clinical trials (including bio-equivalence studies) and commercial batches should also not be underestimated.

The operation of CM equipment may further present a challenge. Operators should have knowledge of the complexities relating to process control as there may be risks of lack of continuous flow of materials, overfilling, over-pressurization, material spills, failure of equipment or sensors or

computerized systems, and backflow of material. Hence qualification and training of operators should get the required attention.

Regulatory challenges

In a highly regulated environment, some pharmaceutical companies fear that any significant changes to existing manufacturing processes could create regulatory delays. This may have led to a slow adoption of the CM approach by manufacturers.

Furthermore, while CM aligns strongly with international guidelines such as United States Food and Drug Administration (USA FDA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, pharmaceutical manufacturing is a global enterprise, and companies must gain approval for their products in multiple countries with their own regulatory bodies. Not all regulatory agencies may have established requirements and standards for CM.

When changing from an existing batch manufacturing process to a CM process, the continuous process can be introduced as a new process for a new molecular entity or as a post-approval manufacturing change. For the latter approach, it should be necessary to establish that the product is physiochemically equivalent as it is produced by the continuous process. For low-risk changes to product CQAs, such as polymorphicity, dissolution, impurities, and stability, demonstration of chemical equivalence could be sufficient to support the change from batch to CM. For high-risk changes, such as significant formulation changes or drug release characteristics, bioequivalence studies may be needed.

More work and harmonization may likely be required to resolve issues related to regulatory challenges and requirements in CM.

Workforce challenges

Designing, implementing, and adequately regulating new approaches in manufacturing require skilled and well-trained personnel in manufacturing as well as in the regulatory environment.

Additional training may be required for personnel in production, quality control, quality assurance, engineering and regulatory as, for example, specialized equipment, sensors, feedback systems, computerized systems and data management may be required in CM.

4. Good practices considerations

Good practice considerations in CM should start at product and process development stage.

CM may require manufacturers to acquire new equipment; implement new ways of managing existing equipment; acquire new instruments and computerized systems as well as software; and establish new modes of operation. This may further include a move to apply process analytical technology (PAT) and principles of quality by design (QbD).

The premises and equipment should be appropriate to support CM. Equipment should remain within operating specifications over the duration of the CM process.

The Pharmaceutical Quality System (PQS) should be suitably designed, appropriately implemented and maintained (*Ref: WHO GMP Main principles*). This includes material and process management; qualification and validation; maintenance and calibration. Other PQS elements include risk management, process capability index, process performance index, managing deviations, managing incidents and non-conformities (including material diversion and disturbance), product stability and a control strategy.

Raw and starting materials used in a product should be traceable and consistently meet predefined specifications.

Systems should be in place for product collection, control and managing of product rejections.

Other systems to be considered include:

- detailed start up and shutdown procedures;
- how production collection and in-process sampling will occur as a means of assuring continued process performance and product quality;

- process validation and continued process verification procedures;
- personnel training procedures;
- cleaning and cleaning validation.

Appropriate resources should be provided.

Consideration should be given to current good practices where the use of advanced tools based on artificial intelligence (AI) such as predictive analytics, predictive maintenance, and robotic process automation (RPA), are used. This further includes using data from smart devices and Industrial Internet of Things (IIoT) sensors.

Process parameters (including their settings and real time data) should be controlled and monitored as part of the control strategy. Manufacturers should ensure that where settings are adjusted during manufacturing, that this is done within the design space.

5. Risk management

CM may pose additional risks opposed to traditional batch processing. Risk identification, risk and harm assessment, risk control and risk communication should be integral parts of the PQS where CM is employed (*1, 2*).

Quantitative or qualitative analysis using, for example, FMEA or a risk matrix may be considered when doing risk assessment.

Risk assessment should be done at various stages in the life cycle of a product; from development through transfer of technology to commercial CM .

Risks relating to the sourcing and control of material, equipment, processing steps and cleaning, as a minimum, need to be included in the assessment. Each processing step or unit operation should be mapped out indicating, as appropriate, quality attributes and process parameters. Risks and harms can then be assessed and controls identified.

Consideration should be given to, for example:

- Input material attributes: for example, their impact on process operations and product quality. Note: Process performance may vary where input material attributes are not consistent. Flowability, particle size, particle size distribution, cohesion, flowability, hygroscopicity and other attributes should be considered in the selection of material and manufacturer of the materials as part of vendor qualification;
- Process steps: such as operating parameter settings (for example, time, temperature, rotation per minute, amperage, speed, and pressure during sifting, milling, blending, granulation, drying, compression, filling, sealing, and coating;
- Unexpected disturbances, possible deviations and non-conformances (for example, poor material flow, vibration, product build up and material diversion).

The performance of computerized systems and the risks and impact associated with failure of such systems should be considered.

Appropriate means should be identified for the detection and handling of non-conforming material.

Risk assessment should be thorough to provide assurance that the required controls are identified and are effective to ensure that a state of control is achieved.

6. Control strategy

The control strategy for commercial production should be initiated during the developmental phase of pharmaceutical products.

The control strategy should be based on the outcome of the risk assessment.

The control strategy should be clearly defined and describe all steps to ensure that the state of control is achieved. This includes, but is not limited to input materials, process monitoring, material diversion, real-time release testing (RTRT), specification, and process equipment.

The control strategy should have the ability to detect process departures thereby enabling timeous corrective actions to be taken to bring the process back into conformance.

Achieving and maintaining a state of control require appropriate measures to be taken relating to the management of raw and starting materials; specifications; traceability; process monitoring; sampling; intermediates; equipment; and product collection and rejection.

Mechanisms should be in place to identify any drift in parameters or trend of data that may be of concern. The root cause should be identified to ensure that appropriate action is taken.

For raw materials and intermediates, it may be necessary to have additional controls when multiple lots of a raw material are used during CM.

Maintaining a state of control should provide assurance of consistent and desired product quality.

In ensuring that the manufacturing process is in a state of control, at least the following aspects should be considered and be clearly defined:

- start-up, pauses and shut-down;
- in process monitoring and control with material collection and rejection of non-conforming materials;
- critical process parameters and critical quality attributes at various stages in the process.

Note: Flow charts indicating processing steps, continuous and semi-continuous steps and clear indication of location of sensors and probes may be useful.

The appropriate means of monitoring the process should be implemented. Sampling should be defined. This includes a clear description of the number of samples; frequency of sampling; sample size; sample location; in-line, on-line or at line sampling; limits and acceptance criteria.

The objectives of sampling, collection and processing of data should be clear, as data may be used in statistical analysis and trending. Setpoints and control limits should be appropriate. It may be possible to apply new approaches in technology and methodology in CM. CM requires more flexible handling compared to the traditional batch manufacturing. Process parameters may be adjusted during

processing based on measuring and results of quality attributes of the intermediate or in-process material, in real time, using for example process analytical technology. In-line sensors and devices may be useful to enable real-time identification of departures from expected results.

Validated systems should be in place to manage rejection of non-conforming materials.

Based on process knowledge and understanding, the elements of a control strategy for CM include, for example:

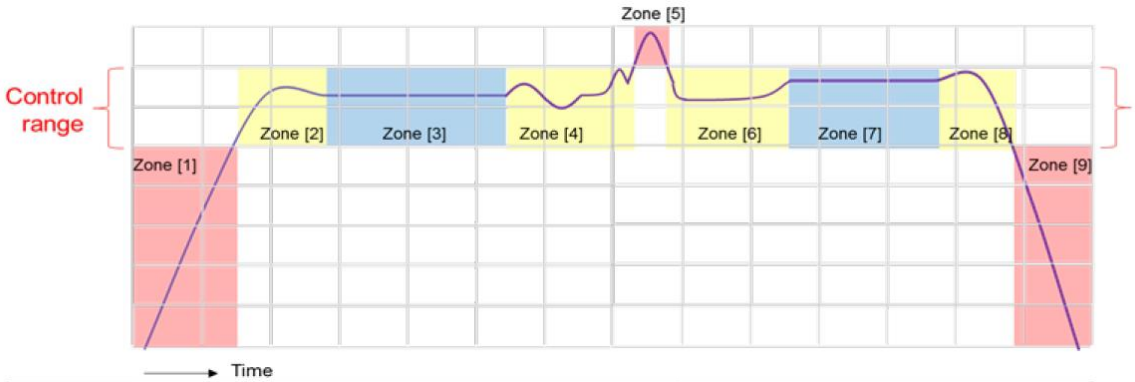
- measuring process parameters and CQAs in a timely manner;
- maintaining the process in a state of control;
- maintaining the product attributes within specifications;
- optimizing process operation;
- realization process operation;
- realizing process efficiency improvements.

The control strategy should normally support a system of real time release.

Figure 1 below presents a conceptual presentation of the control strategy

Fig. 1. Conceptual presentation of the control strategy[1]

[1] Issei TAKAYAMA, Yoshihiro MATSUDA and Noriko KATORI. Current Regulatory Considerations for Continuous Manufacturing of Pharmaceuticals in Japan. 2017



Zone	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]
Description of condition	Startup (Condition where control range is not yet achieved)	Startup (Condition where control range is achieved but is unstable)	Steady state	Condition within the control range despite the fluctuation of external factors	Deviation from the control range	Condition which is unstable after recovery of the control range	Steady state with different values from Zone 3	Condition within the control range despite commencement of shutdown procedures	Shutdown (Deviation from the control range)
Steady state	N	N	Y	N	N	N	Y	N	N
State of Control	N	Y	Y	Y	N	Y	Y	Y	N
Discharge out of line	Y	Y/N	N	Y/N	Y	Y/N	N	Y/N	Y

Y: Yes, N: No, Y/N: Yes or No

7. Process dynamics

Scientific knowledge supported by experimental data of the process dynamics and variables are needed to ensure that CM processes are appropriately designed, managed, and operate within a state of control. This includes knowledge of the differences that may exist between developmental batch and commercial batch processing.

Processing steps in CM need to be well controlled to ensure the production of uniform products and thus require different approaches in process parameter control and monitoring. As an example, fluctuation in feed of raw material may impact on the quality of a blend. For improved monitoring and control of the processing parameters, manufacturers may have to consider specifically designed equipment and instrumentation; computerized systems and feedback systems. The selection of equipment and instrumentation should be suitable for its intended purpose and process for semi-continuous and continuous manufacturing, as applicable (Note: Refer to the use of Near Infrared (NIR); Raman spectroscopy; soft sensor and gravimetric controls).

To obtain meaningful results, consideration should be given to, for example:

- instrument selection;
- analytical procedure;
- analytical procedure development;
- appropriate placement of sensors and probes;
- process parameters (for example, flow rate, particle size and distribution, compression force), maintenance, service and calibration;
- system accuracy, operating range, sensitivity;
- data reliability (meeting ALCOA+);
- meeting GxP including requirements for computerized systems;
- sampling method, sample collection location, sampling frequency, representativeness of the sample, and sample size;
- consistency in analysis over the range of expected concentration;
- acceptance criteria.

8. Computerized systems

Smart machinery that uses AI and machine learning (ML) together with data from IIoT sensors facilitate continuous manufacturing. These further aid in production of customized products, traceability of materials and data management.

Computerized systems should be appropriate for their intended use.

Computerised systems should be appropriately validated and be able to ensure the integrity of data (*3, 4*).

9. Validation and verification

The principles of process validation as described in WHO guidelines, should be considered (*5*). In addition, specific attention should be given to start-up and shutdown of the process, process run-time evaluation, and the ability to detect process excursions. The number of start-ups and shutdowns could

be determined based on risk analysis and the unique critical considerations for that process. Examples may include process robustness, process flow rate and residence time.

In CM, careful consideration should be given to the manner in which process performance and quality attributes are consistently controlled by the control strategy.

Frequent process monitoring (see Sampling section above) with in-line, on-line, at-line monitoring and control facilitate the real-time collection of data and adoption of continuous performance verification.

Where a traditional approach in process validation is followed, consideration should be given to the number of batches required for process validation. Any variation in results of attributes between different batches, should be within an acceptable range. Consideration should be given to the possible impact on the process capability where differences in quantities and times (resulting in different batch sizes) in different batches are employed in CM.

Where CM is applied and a batch is produced over a period of time, the effects of accumulated material on manufacturing equipment should be taken into consideration.

10. Stability testing

Stability data for products manufactured by means of CM should be available. The same principles for stability testing as outlined in WHO guidelines for stability testing, apply (*6*).

The selection of batches, and number of batches of product that should be subjected to stability testing should be justified.

Consideration should be given to variables that may be impacting on batches such as the number of batches of input material to the batch and batch size.

Stability data from commercial batches should be available and derived from batches where the state of control had been demonstrated.

Consideration should also be given to the inclusion of scale up batches in the stability testing program, where appropriate.

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Further reading

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