

DRAFT WORKING DOCUMENT FOR COMMENTS: WHO Points to consider in continuous manufacturing of pharmaceutical products

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 36 SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/24.957:
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 38 WHO Points to consider in continuous manufacturing 39 of pharmaceutical products
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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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61 **1. Introduction**

62

63 Pharmaceutical manufacturers have predominantly used batch processing as a means to manufacture 64 active pharmaceutical ingredients (APIs), excipients and finished pharmaceutical products (FPPs).

65

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.

71

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

74

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.

79

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.

83

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.

88

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.

93 CM does not have to be end-to-end in production of a product. It could be applied to some 94 (semicontinuous) or all unit operations in a manufacturing process. As an example, in the production 95 of simple oral solid dosage forms (OSDs), some steps (such as feeding and mixing) or all steps can be 96 included in CM.

97

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.

101

102 Many pharmaceutical companies are currently developing and applying a hybrid approach, in which

103 CM steps may be incorporated for portions of a drug substance or drug product process, or for an

104 entire drug substance or drug product process.

105

106 Uncertainties in adopting CM processes in the pharmaceutical industry include material traceability,107 process design, monitoring, and control.

108

109 In the traditional batch manufacturing process, sampling and testing of samples after certain 110 processing steps are the norm. This often leads to down times and hold times. The relatively new 111 approach of CM, utilizing sensors for in-line, and on-line analytical testing may reduce such down and 112 hold times. It may further facilitate utilizing the full capacity of equipment and production lines, reduce 113 human error, and support quality control and testing.

114

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.

120

121 **2. Glossary**

122

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

125 batch. A specific quantity of material produced in a process or series of processes so that it is expected 126 to be homogeneous within specified limits. In the case of continuous production, a batch may 127 correspond to a defined fraction of the production. The batch size can be defined either by a fixed 128 quantity or by the amount produced in a fixed time interval.

129

130 continuous manufacturing. Continuous feeding of input materials into a process with processed 131 output materials continuously removed from the system, whether from an individual unit operation 132 or the entire manufacturing process consisting of a series of unit operations.

133

134 flow chemistry. Flow chemistry is also known as continuous flow or plug flow chemistry; and it

- 135 involves a chemical reaction run in a continuous flow stream rather than a batch production.
- 136

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.

140

141 **in-line.** Process analytical technology systems that are incorporated into the flow of the process and

142 produce continuous data without sampling using capacitance, light scattering, spectroscopy, on-line

143 liquid chromatography, and other types of sensors.

144

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

147

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).

151

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.

155

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

158	change. This change may be due to a disturbance or an intentional alteration in the selected operating
159	conditions (for example, start-up, shutdown, changes from one operating condition to another).
160	
161	quality by design (QbD). A scientific and mathematical framework that aims to ensure a product's
162	quality and efficacy from the beginning of the manufacturing process.
163	
164	real-time release testing (RTRT). The ability to evaluate and ensure the quality of in-process and/or
165	final product based on process data, which typically include a valid combination of measured material
166	attributes and process controls.
167	
168	residence time distribution (RTD). A measure of the range of residence times experienced by material
169	passing through a specific process environment/vessel/unit operation.
170	
171	state of control. A condition in which the set of controls consistently provides assurance of continued
172	process performance and product quality.
173	
174	steady state. A stable condition that does not change over time.
175	
176	For other definitions, see the WHO Quality Assurance of Medicines Terminology Database:
177	https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.
178	
179	3. Benefits and challenges in continuous
177	of Denemits and chanenges in continuous
180	manufacturing
181	
182	The benefits and challenges of CM have been described in various guidelines and articles (see Further
183	Reading section).
184	
185	CM may result in increasing output of product in a shorter timeframe than traditional batch
186	processing. It may also provide safety benefits due to lower exposure risk to operators.
187	
188	CM may also present challenges to manufacturers. These include, for example, providing specialized
189	training of personnel in the new concept, managing product changeover and cleaning of such lines.

190

191 With the technical, operational, and economic challenges, as well as risks associated with CM, it is 192 important that manufacturers wanting to move from batch manufacturing to CM processes ensure 193 that there is sufficient process knowledge to facilitate risk management and the development and 194 implementation of an appropriate control strategy. 195 196 Challenges to adopting CM in the pharmaceutical industry include, for example: 197 technological issues (for example, process knowledge); ٠ 198 logistical concerns (for example, new equipment and computerized systems); 199 advanced control strategies comprising complex analytical instrumentation and technology for 200 improved process control using robust and reliable methods (for example, in-line, on-line and 201 at-line analytics); 202 real-time data strategies for critical quality attributes (CQAs) and critical process parameters • 203 (CPPs), (for example, to maintain a steady state or state of control); 204 regulatory uncertainty; 205 integrating downstream unit operations such as semi-continuous manufacturing; ٠ 206 personnel (for example, specific training and qualification); • 207 • risks (including actual and perceived risks); 208 economic issues (for example, return on investment); • 209 flexibility issues (for example, adjusting process and upscale or downscale). • 210 211 Technical and operational challenges 212 213 The lack of commercially available equipment suitable for small-scale CM lines presents a challenge 214 to formulation and development facilities as well as commercial manufacturers. 215 216 The importance of the link between batches produced and used during clinical trials (including bio-217 equivalence studies) and commercial batches should also not be underestimated. 218 219 The operation of CM equipment may further present a challenge. Operators should have knowledge 220 of the complexities relating to process control as there may be risks of lack of continuous flow of 221 materials, overfilling, over-pressurization, material spills, failure of equipment or sensors or

- computerized systems, and backflow of material. Hence qualification and training of operators shouldget the required attention.
- 224

225 Regulatory challenges

226

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.

230

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.

237

238 When changing from an existing batch manufacturing process to a CM process, the continuous process 239 can be introduced as a new process for a new molecular entity or as a post-approval manufacturing 240 change. For the latter approach, it should be necessary to establish that the product is 241 physiochemically equivalent as it is produced by the continuous process. For low-risk changes to 242 product CQAs, such as polymorphicity, dissolution, impurities, and stability, demonstration of 243 chemical equivalence could be sufficient to support the change from batch to CM. For high-risk 244 changes, such as significant formulation changes or drug release characteristics, bioequivalence 245 studies may be needed.

246

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

249

250 Workforce challenges

251

252 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.
- 258

259 4. Good practices considerations

- 260
- 261 Good practice considerations in CM should start at product and process development stage.
- 262

263 CM may require manufacturers to acquire new equipment; implement new ways of managing existing 264 equipment; acquire new instruments and computerized systems as well as software; and establish 265 new modes of operation. This may further include a move to apply process analytical technology (PAT) 266 and principles of quality by design (QbD).

267

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

270

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.

- 277
- Raw and starting materials used in a product should be traceable and consistently meet predefinedspecifications.
- 280
- 281 Systems should be in place for product collection, control and managing of product rejections.
- 282

283 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;

287	 process validation and continued process verification procedures; 	
288	 personnel training procedures; 	
289	cleaning and cleaning validation.	
290		
291	Appropriate resources should be provided.	
292		
293	Consideration should be given to current good practices where the use of advanced tools based on	
294	artificial intelligence (AI) such as predictive analytics, predictive maintenance, and robotic process	
295	automation (RPA), are used. This further includes using data from smart devices and Industrial	
296	Internet of Things (IIoT) sensors.	
297		
298	Process parameters (including their settings and real time data) should be controlled and monitored	
299	as part of the control strategy. Manufacturers should ensure that where settings are adjusted during	
300	manufacturing, that this is done within the design space.	
301		
302	5. Risk management	
303		
304	CM may pose additional risks opposed to traditional batch processing. Risk identification, risk and	
305	harm assessment, risk control and risk communication should be integral parts of the PQS where CM	
306	is employed (1, 2).	
307		
308	Quantitative or qualitative analysis using, for example, FMEA or a risk matrix may be considered when	
309	doing risk assessment.	
310		
311	Risk assessment should be done at various stages in the life cycle of a product; from development	
312	through transfer of technology to commercial CM .	
313		
314	Risks relating to the sourcing and control of material, equipment, processing steps and cleaning, as a	
315	minimum, need to be included in the assessment. Each processing step or unit operation should be	
316	mapped out indicating, as appropriate, quality attributes and process parameters. Risks and harms	
317	can then be assessed and controls identified.	
318		

319 Consideration should be given to, for example:

320 •	Input material attributes: for example, their impact on process operations and product quality.
321	Note: Process performance may vary where input material attributes are not consistent.
322	Flowability, particle size, particle size distribution, cohesion, flowability, hygroscopicity and
323	other attributes should be considered in the selection of material and manufacturer of the
324	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).
- 330

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

333

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 andare effective to ensure that a state of control is achieved.
- 338

339 6. Control strategy

340

341 The control strategy for commercial production should be initiated during the developmental phase

342 of pharmaceutical products.

343

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

345

346 The control strategy should be clearly defined and describe all steps to ensure that the state of control

347 is achieved. This includes, but is not limited to input materials, process monitoring, material diversion,

348 real-time release testing (RTRT), specification, and process equipment.

350 The control strategy should have the ability to detect process departures thereby enabling timeous 351 corrective actions to be taken to bring the process back into conformance. 352 353 Achieving and maintaining a state of control require appropriate measures to be taken relating to the 354 management of raw and starting materials; specifications; traceability; process monitoring; sampling; 355 intermediates; equipment; and product collection and rejection. 356 357 Mechanisms should be in place to identify any drift in parameters or trend of data that may be of 358 concern. The root cause should be identified to ensure that appropriate action is taken. 359 360 For raw materials and intermediates, it may be necessary to have additional controls when multiple 361 lots of a raw material are used during CM. 362 363 Maintaining a state of control should provide assurance of consistent and desired product quality. 364 365 In ensuring that the manufacturing process is in a state of control, at least the following aspects should 366 be considered and be clearly defined: 367 start-up, pauses and shut-down; 368 in process monitoring and control with material collection and rejection of non-conforming 369 materials; 370 critical process parameters and critical quality attributes at various stages in the process. • 371 372 Note: Flow charts indicating processing steps, continuous and semi-continuous steps and clear 373 indication of location of sensors and probes may be useful. 374 375 The appropriate means of monitoring the process should be implemented. Sampling should be 376 defined. This includes a clear description of the number of samples; frequency of sampling; sample 377 size; sample location; in-line, on-line or at line sampling; limits and acceptance criteria. 378 379 The objectives of sampling, collection and processing of data should be clear, as data may be used in 380 statistical analysis and trending. Setpoints and control limits should be appropriate. It may be possible 381 to apply new approaches in technology and methodology in CM. CM requires more flexible handling 382 compared to the traditional batch manufacturing. Process parameters may be adjusted during

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- 383 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
- 385 be useful to enable real-time identification of departures from expected results.
- 386
- 387 Validated systems should be in place to manage rejection of non-conforming materials.
- 388
- 389 Based on process knowledge and understanding, the elements of a control strategy for CM include,
- 390 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.
- 397
- 398 The control strategy should normally support a system of real time release.
- 399
- 400 Figure 1 below presents a conceptual presentation of the control strategy
- 401
- 402 **Fig. 1**. Conceptual presentation of the control strategy¹

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



403

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

405

404 **7. Process dynamics**

406 Scientific knowledge supported by experimental data of the process dynamics and variables are 407 needed to ensure that CM processes are appropriately designed, managed, and operate within a state 408 of control. This includes knowledge of the differences that may exist between developmental batch 409 and commercial batch processing.

410

411 Processing steps in CM need to be well controlled to ensure the production of uniform products and 412 thus require different approaches in process parameter control and monitoring. As an example, 413 fluctuation in feed of raw material may impact on the guality of a blend. For improved monitoring and 414 control of the processing parameters, manufacturers may have to consider specifically designed 415 equipment and instrumentation; computerized systems and feedback systems. The selection of 416 equipment and instrumentation should be suitable for its intended purpose and process for semi-417 continuous and continuous manufacturing, as applicable (Note: Refer to the use of Near Infrared (NIR); 418 Raman spectroscopy; soft sensor and gravimetric controls). 419

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

421	•	instrument selection;
422	•	analytical procedure;
423	•	analytical procedure development;
424	•	appropriate placement of sensors and probes;
425	•	process parameters (for example, flow rate, particle size and distribution, compression force),
426		maintenance, service and calibration;
427	•	system accuracy, operating range, sensitivity;
428	•	data reliability (meeting ALCOA+);
429	•	meeting GxP including requirements for computerized systems;
430	•	sampling method, sample collection location, sampling frequency, representativeness of the
431		sample, and sample size;
432	•	consistency in analysis over the range of expected concentration;
433	•	acceptance criteria.
434		
435		
436	8.	Computerized systems
437		
438	Smart	machinery that uses AI and machine learning (ML) together with data from IIoT sensors
439	facilitate continuous manufacturing. These further aid in production of customized products.	
440	tracea	bility of materials and data management.
441		
442	Comp	uterized systems should be appropriate for their intended use.
443		
444	Comp	uterised systems should be appropriately validated and be able to ensure the integrity of data
445	(<i>3,</i> 4).	
446		
447	9.	Validation and verification
448		
449	The p	rinciples of process validation as described in WHO guidelines, should be considered (5). In
450	additio	on, specific attention should be given to start-up and shutdown of the process, process run-time

451 evaluation, and the ability to detect process excursions. The number of start-ups and shutdowns could

- 452 be determined based on risk analysis and the unique critical considerations for that process. Examples
 453 may include process robustness, process flow rate and residence time.
- 454
- 455 In CM, careful consideration should be given to the manner in which process performance and quality
- 456 attributes are consistently controlled by the control strategy.
- 457
- 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.
- 466
- Where CM is applied and a batch is produced over a period of time, the effects of accumulatedmaterial on manufacturing equipment should be taken into consideration.
- 469

470 **10. Stability testing**

- 471
- 472 Stability data for products manufactured by means of CM should be available. The same principles for 473 stability testing as outlined in WHO guidelines for stability testing, apply (6).
- 474
- The selection of batches, and number of batches of product that should be subjected to stabilitytesting should be justified.
- 477
- 478 Consideration should be given to variables that may be impacting on batches such as the number of479 batches of input material to the batch and batch size.
- 480
- 481 Stability data from commercial batches should be available and derived from batches where the state
- 482 of control had been demonstrated.
- 483

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

485 where appropriate.

486



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