PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry
(provisional draft)

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Introduction

Continuous Manufacturing is a manufacturing method in which raw materials or their blended materials are entered continuously in the manufacturing process throughout the duration of the process, and products are produced continuously through the manufacturing. Quality control procedures (control strategies) that are appropriately established based on the scientific data/knowledge ensure that product made by a continuous manufacturing process is homogenous and of desired quality. Continuous Manufacturing can be used in various cases: Where all the stages of processing are continuous, from charging raw materials to discharging final products; and where only certain stages of the manufacturing process are continuous. Therefore, the control strategy employed should consider how the Continuous Manufacturing process is designed and product characteristics.

It is feasible that Continuous Manufacturing makes it possible to manufacture a desired amount of products with appropriate quality attributes at a desired timing. With its continuous process operation, Continuous Manufacturing will be expected to maintain production efficiency irrespective of the equipment scale.

By adjusting such as the continuous operating time in the process, Continuous Manufacturing can cater for a wide range of batch size. This can allow for the same manufacturing equipment to be used from the developmental phase to the commercial phase, contributing to not only consistent quality production but also labor-saving for scale-up studies and robust technology transfer. Therefore, Continuous Manufacturing is considered an efficient manufacturing technology. In addition, Continuous Manufacturing can be a useful production technology for pharmaceutical manufacturers that require multi-product and low-volume production.

In July 2016, the Pharmaceuticals and Medical Devices Agency (PMDA) established the Innovative Manufacturing Technology Working Group (IMT-WG) as part of the Projects Across Multi-Offices in PMDA. The IMT-WG launched activities to examine desirable regulations that streamline the introduction of new manufacturing technologies, and selected Continuous Manufacturing as our primary target.

This document includes some views on applying Continuous Manufacturing to pharmaceutical products at this time point, which are compiled within the limited practical experience that the IMT-WG has. The contents of this document should be reviewed according to the future experience and

accumulated knowledge. Therefore, it is submitted as a provisional draft. This provisional draft was prepared by anticipating the following cases, (1) through (2).

(1) It is intended for solid oral dosage forms (tablets, etc.) manufactured using drug substances (small-molecule compounds) produced by chemical syntheses.

(2) An ideal production state is achieved. For example, manufacturing equipment is filled up with required amount of raw materials and then raw materials are being supplied.

In addition, this document does not cover matters for GMP controls.

Actual application of Continuous Manufacturing to individual products may require the control of their quality attributes and manufacturing processes, as well as the considerations according to the level of knowledge and understanding of these quality attributes and manufacturing processes. Therefore, the utilization of the PMDA's face-to-face consultation services with the PMDA review division is advised.

I. Control Strategy for Continuous Manufacturing

A control strategy is defined in "Pharmaceutical Quality System" (Pharmaceutical and Food Safety Bureau [PFSB]/Evaluation and Licensing Division [ELD] Notification No. 0219-1 and PFSB/Compliance and Narcotics Division [CND] Notification No. 0219-1 dated February 19, 2010) (ICH Q10) as follows: "A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control." Details of control strategy are explained in Part II Annex of "Pharmaceutical Development" (PFSB/ELD Notification No. 0628-1 dated June 28, 2010) (ICH Q8 [R2]).

For establishing a control strategy for commercial production during the developmental phase of pharmaceutical products, there is no fundamental difference between the Batch Manufacturing and Continuous Manufacturing in terms of factors to ensure Critical Quality Attributes (CQA) of the final products, such as quality attributes of the raw materials and intermediate products, specifications of the products, process parameters, and in-process controls (except for process dynamics which is mentioned below). Therefore, in order to understand the relationship between the factors to be controlled and the CQA, it is useful to acquire knowledge of process parameters and in-process controls that can be obtained during the process of establishing the control strategy in accordance with ICH Q8 [R2]. Additionally, it is necessary to take into consideration the specific factors that have not been anticipated during Batch Manufacturing, through the qualification of equipment or devices to be used in Continuous Manufacturing, regarding their characteristic factors. It is also necessary to consider that multiple factors that need to be controlled should be linked to a CQA not only by handling these factors according to the unit process but also by handling them through the entire manufacturing process.

1. Beneficial control strategy for Continuous Manufacturing

In Continuous Manufacturing, the process inputs, i.e. material attributes of raw materials could change along with the progression of the Continuous Manufacturing process, which may impact the quality of the product or intermediate product. Therefore, more flexible handling could be required compared to the traditional Batch Manufacturing, such as the adjustment of process parameters according to the changes in the material attributes. For this reason, it is important to understand the relationship between process inputs and CQAs, and the knowledge from existing control strategies used for Batch Manufacturing, linked with process parameters, are also considered beneficial for Continuous Manufacturing in the case of switching the manufacturing method.

The control strategy that has been used for traditional Batch Manufacturing ensures the quality attributes of the intermediate products obtained in the process by establishing a Proven Acceptable Range (PAR) of the process parameters or a Design Space. This control strategy that uses the process parameters, not in-process testing, can also be used for the Continuous Manufacturing by

performing the qualification of equipment or devices including their attribute factors on an as-needed and also providing correlation between process parameters and critical quality attributes of intermediates and final products. Rather, in the case of Continuous Manufacturing, where the same manufacturing equipment can be used from the developmental phase to the commercial production, the control strategy with the process parameters established in the developmental phase can be applied easier than the Batch Manufacturing, which requires scale-up for commercial production.

It is also possible to employ a control strategy that ensures the product quality with the constant monitoring of targeted quality attribute of the materials such as intermediate products, by using Process Analytical Technology (PAT), including but not limit to Near-Infrared Spectroscopy (NIRS) or other technics. This control method may be useful for achieving a reduction in end product testing by controlling the range of quality attributes during the monitoring in the relevant process. Moreover, this method will be helpful to ensure the consistency of the product quality attribute during the process if it is possible to establish the Action Limit within the proven acceptable range and maintain the process to the required condition by controlling changes during processing using feedback or feedforward control (Performance-based Approach). The above-mentioned control method may be more useful for Continuous Manufacturing than Batch Manufacturing since Continuous Manufacturing may require the adjustment of process parameters in real time in order to maintain product CQAs within the proven acceptable ranges.

When developing a control strategy for Continuous Manufacturing, it is important to employ controls according to the impact on the quality of products (Fit for Purpose), by utilizing the knowledge obtained during the developmental phase as well as the result of risk assessment, and applying specific considerations for the control strategy for Continuous Manufacturing presented below.

2. Specific considerations for control strategy for Continuous Manufacturing -Understanding of process dynamics-

In Continuous Manufacturing, raw materials and their blended materials continuously enter the manufacturing process and the products are discharged on a continuous basis; therefore, due to any variations that occur during processing, products that do not meet the desired quality may be produced for a period of time if appropriate manufacturing controls are not in place. In order to ensure that the products meet the desired quality consistently throughout the operation time, as in the case of Batch Manufacturing, manufacturers should ensure control for each unit operation (e.g. blending, granulating, tableting) that comprises the manufacturing process, and understand the process dynamics within unit operations (e.g. in the granulation process) or between unit operations (e.g. between the blending process and the granulation process). Understanding of process dynamics (including start-up, hold and shut-down) includes the understanding of the traceability of the raw materials introduced into the process based on the Residence Time Distribution (RTD) and the understanding of the effects of anticipated changes on the quality of downstream products. Before introducing Continuous Manufacturing, it is necessary to establish a robust control strategy that comprehensively covers the entire manufacturing process and demonstrate that a “State of Control”

is maintained. Monitoring the quality attributes of materials during processing using a PAT tool (including soft sensors possibly) is useful as one of the combined control methods to ensure a “State of Control.” Even without utilize a spectroscopic PAT tool, it would be possible to ensure a “State of Control” if the process dynamics can be obtained by simulating the manufacturing process for example using a Residence Time Distribution (RTD) model to estimate blend concentration in the manufacturing line in conjunction with monitoring observed process parameters.

As mentioned above, the control strategy needs to be evaluated individually. Therefore PMDA recommends establishing an early dialogue with regulators during the development stage of Continuous Manufacturing.

II. Batch Definition in Continuous Manufacturing

There is no difference in the definition of "Batch" between Batch Manufacturing and Continuous Manufacturing. However, the concept of batch size is different.

1. Definition of Batch (or Lot)

The definition of Batch (or Lot) is provided in "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" (PFSB Notification No. 1200 dated November 2, 2001) (ICH Q7), which includes remarks on Continuous Manufacturing:

> "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."

2. Concept of Batch (or Lot) Size

The batch (or lot) size in Continuous Manufacturing can be specified based on any of the following aspects:

(1) The run time and the processing speed
(2) The volume of material produced
(3) The feed amount of raw materials

In Continuous Manufacturing, parameters can be modified within a validated range. These parameters include run time, processing speed, volume of material produced, etc. The uniformity of a batch can be ensured by maintaining a "State of Control" through the control based on mathematical models and/or the continuous monitoring with PAT, etc.

III. Validation for Continuous Manufacturing

As is the case in Batch Manufacturing, validation for Continuous Manufacturing needs to be implemented in accordance with the validation standards. For Continuous Manufacturing, it is important to validate the following:

(1) Process performance and quality attributes during Continuous Manufacturing are consistently maintained in a "State of Control" by the pre-established control strategy.

(2) Based on the dynamics of how raw materials or intermediates flow through the process, chronological changes in quality between batches as well as within a batch remain within an acceptable range.

1. Batch size and the number of batches for process validation

Basically, as in the Batch Manufacturing, process validation needs to be performed using the production batch size at the production scale, repeated with at least 3 batches or performed with an equivalent method to ensure the repeatability. In case of being scientifically guaranteed that there are no chronological changes in quality, it may be possible to carry out in 3 batches or more in total including the batch produced with the processing speed or the manufacturing time is changed according to the commercial manufacturing scale in addition to the batch produced at the maximum expected actual production scale. Furthermore validation design that introduces the idea of continuous process verification may be possible in some cases.

The batch size of a product to which Continuous Manufacturing is applied should be established before being manufactured by the manufacturer based on the feed amount of raw materials as in the Batch Manufacturing, desired amount of production volume or the run time at a certain processing speed. In Continuous Manufacturing, the batch size should be established by taking into consideration the operability of manufacturing equipment in a longer operation time and the effects of accumulated substances on manufacturing equipment. Therefore, when manufacturing is performed using an expected range of batch sizes, process validation needs to be performed with the production batch size that can ensure stable performance of the manufacturing process and the product quality during the operating time. This process validation should be repeated with at least 3 batches or performed with an equivalent or superior method.

Additionally, in Continuous Manufacturing, the same equipment or conditions that were used in the developmental stage may be used in commercial production. In such cases, the knowledge acquired in the developmental phase can be used as the data to support commercial production.

2. Validation on changes for an approved product in switching from the Batch Manufacturing to Continuous Manufacturing

Basically, this will be handled in the same manner as stated in 1.

IV. Stability Testing for Continuous Manufacturing

1. Size of the primary batch

In Continuous Manufacturing, the batch size can be varied by changing the operating time of the manufacturing process within the validated range. Therefore, unlike Batch Manufacturing, in the case of Continuous Manufacturing, it is especially important to ensure that products are being manufactured with the equivalent quality regardless of any time point they are sampled from in the manufacturing process. For this reason, it is required to ensure a "State of Control," scientifically proving that chronological changes are within an acceptable range in quality due to transient disturbances or failures in equipment performance. Upon assuring this, it is possible to judge that, in Continuous Manufacturing, batches of any batch size are sufficiently representing the manufacturing methods and processes that are to be applied to the commercial production, and that variation in the batch size will not necessarily pose a major risk to stability of products. With Continuous Manufacturing, a batch that is manufactured with any batch size can be the primary batch. In this case, as is the case with the traditional Batch Manufacturing, it is necessary to understand the potential risks arising from the variation in the batch size by risk assessment, etc., and to explain that the primary batch has the same characteristics as other batches manufactured at the established maximum batch size.

2. Number of primary batches

Even in Continuous Manufacturing, the basic idea for the number of primary batches needed is the same as that in Batch Manufacturing. Basically, at least three batches are required according to "Stability Testing of New Drug Substances and Products" (PFSB/ELD Notification No. 0603001 dated June 3, 2003) (ICH Q1A [R2]). In addition, for Continuous Manufacturing, it is necessary to record information on the sampling points (spot, time etc.) used for the primary batch, as the batch size of the primary batch itself may vary.

V. Glossary

Critical Quality Attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8 [R2])

Proven Acceptable Range (PAR): A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria. (ICH Q8 [R2])

Process Analytical Technology (PAT): A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and intermediate products/in-process materials and processes with the goal of ensuring final product quality. (ICH Q8 [R2])

Action Limit: A reference value established through the integrated considerations for technology and desired product quality within the manufacturing process and the range of product quality specifications. When the production system is in operation, if any monitor data that exceed the established action limits are obtained, it indicates that the manufacturing process has deviated from the control range. In this case, the operation manager of the production system must take corrective action to bring the process back within its normal operating range. Exceeding an action limit does not necessarily indicate that the product quality has been compromised. Note)

Process Dynamics: Traceability of the input materials based on the residence time distribution and effects of expected changes on the quality of the downstream products Note)

State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality (ICH Q10) Note)

Performance-based Approach: Differing from the process control using fixed process parameters, the control method that can achieve the desired product quality by adjusting process parameters as per the control strategy according to any changes that occur during processing based on measuring and assessing quality of the final or intermediate products in real time using PAT, etc. Note)

Fit for Purpose: A risk based weighting of the control strategy based on potential impact on product quality. Note)

Primary batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least a pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps.

However, a primary batch may be a production batch. (ICH Q1A [R2])

Note): The definitions of the terms in the above Glossary are tentative definitions provided for this document. Please note that the interpretation of these terms in relation to Continuous Manufacturing has not been acknowledged internationally; therefore, further discussion is required.