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Approach to Establishment of Control Strategy for Oral Solid Dosage Forms Using Continuous Manufacturing

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As a result of the research activities of the Japan Agency for Medical Research and Development (AMED), this document aims to show an approach to establishing control strategy for continuous manufacturing of oral solid dosage forms. The methods of drug development, technology transfer, process control, and quality control used in the current commercial batch manufacturing would be effective also in continuous manufacturing, while there are differences in the process development using continuous manufacturing and batch manufacturing. This document introduces an example of the way of thinking for establishing a control strategy for continuous manufacturing processes.

Key words continuous manufacturing; control strategy; state of control; Quality by Design (QbD); solid drug product; regulatory science

Introduction

The pharmaceutical industry must stably supply patients with consistent high-quality drug products. To accomplish this mission, regulatory authorities such as the European Medicines Agency, the U.S. Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA) support new pharmaceutical manufacturing technologies, including continuous manufacturing.¹⁾

A continuous manufacturing process integrates unit operations, such as blending, granulation, drying, and tableting, and ideally processes materials without storing intermediate products after each unit operation. Raw materials are continuously fed into the process, and the intermediate and/or final products are continuously removed from the process. On the other hand, a conventional batch manufacturing process consists of a series of unit operations; it has a warehouse to temporarily

store intermediate products, whose quality is tested off-line using analytical methods, until all quality requirements are fulfilled. Recent review papers on continuous manufacturing processes are found elsewhere.^{2–4)} Some authors compared the novel continuous technology with the conventional batch technology.^{5–8)}

These characteristics of continuous manufacturing, which are different from conventional batch manufacturing, emphasize the importance of the Quality by Design (QbD) approach, which aims at building quality into a product throughout the process instead of testing the quality.⁹⁾ The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8 defines QbD as a systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.¹⁰⁾

Real-time monitoring of critical material attributes (CMAs) and critical process parameters (CPPs) using process ana-

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lytical technology (PAT) is crucial to assure the final product quality, *i.e.*, critical quality attributes (CQAs), of a continuous manufacturing process. It enables one to keep both the process operating condition and the CQAs within their target ranges by manipulating the CPPs through feedback and/or feedforward control.¹¹⁾ PAT aims to enhance the understanding and control of the manufacturing process; various tools and principles are available to meet the regulatory requirements for validating and controlling the manufacturing process.¹²⁾ Recent progress can be found of PAT^{13–15)} and QbD.^{16,17)}

A science-based approach *via* QbD and PAT will help realize real-time release testing (RTRT) and robust manufacturing. Modern quality assurance systems that are implemented for continuous manufacturing processes, relying on PAT for product acceptance and process control, offer the possibility of continual improvement towards a system with minimal deviation from the optimum.⁴⁾

To facilitate continual improvement and innovation throughout the product lifecycle, ICH Q8 guideline⁹⁾ suggests that the pharmaceutical development should include, at a minimum, the following elements:

- Defining the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering *e.g.*, the route of administration, dosage form, bioavailability, strength, and stability;
- Identifying potential CQAs of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled;
- Determining the CQAs of the drug substance, excipients *etc.*, and selecting the type and amount of excipients to deliver drug product of the desired quality;
- Selecting an appropriate manufacturing process;
- Defining a control strategy.

In addition, an enhanced QbD approach to product development would additionally include the following elements:

- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including; [1] Identifying, through *e.g.*, prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs and [2] Determining the functional relationships that link material attributes and process parameters to product CQAs;
- Using the enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing. This guideline is not intended for continuous production but applicable to it.

A key question is how to establish a control strategy for continuous manufacturing. Since all units are more directly integrated in continuous manufacturing than in batch manufacturing, the control strategy should be constructed and examined holistically. Using a direct compression process as an example, the usefulness of control charts, process capability indices, *etc.* for indicating whether the process is in state of control, including its startup and shutdown, was explained.¹⁸⁾ It was emphasized that an appropriate balance between process control and end product testing is needed depending on the level of process understanding. More recently, development of appropriate control strategies for continuous wet granulation was discussed, expecting its increased utilization.¹⁹⁾

In the U.S., FDA has already approved several drug products manufactured by continuous manufacturing. In Japan, drugs manufactured by continuous direct compression was approved for the first time in 2018. Since November 2018, an international guideline for continuous manufacturing has been developed as ICH Q13. At the same time, regulatory authorities are working on the issues to apply the current regulations to continuous manufacturing. For example, FDA published a draft of “Guidance for Industry” on quality considerations for continuous manufacturing.²⁰⁾ In the Japan Agency for Medical Research and Development (AMED) research activities, the document “Points to Consider Regarding Continuous Manufacturing” was published in March 2017²¹⁾; then “State of Control in Continuous Pharmaceutical Manufacturing” was published in March 2018, summarizing the opinions of experts in the industry, regulatory authority, and academia, in order to consolidate the environment where companies may easily apply continuous manufacturing.²²⁾

Based on these activities, this article shows an approach to establishing a control strategy for oral solid dosage forms using continuous manufacturing, highlighting the similarity and the difference between continuous manufacturing and batch manufacturing.

Discussion

Fundamental Concepts for Establishment of Control Strategy In continuous manufacturing, the variations generated in an upstream process will have a direct (and possibly immediate) impact on a downstream process because they are directly connected and raw materials or their mixtures are continuously fed into the process.

As indicated in the document “State of Control in Continuous Pharmaceutical Manufacturing” issued by our former research group, the quality control approach to assure the quality of the lot only by process control and a quality testing of the intermediate and finished product implemented in the current batch manufacturing (Quality by Testing) may not be sufficient as the control strategy for continuous manufacturing.²²⁾

In the process development using continuous manufacturing technology for drug products, the QbD approach is appropriate for understanding the relationship between CQAs, CMAs, and CPPs. It is also recommended to establish a control strategy that can assure the state of control by setting and controlling CMAs and/or CPPs based on the degree of risk affecting the quality.²³⁾ Besides, it is beneficial to adopt [1] feedforward and feedback control utilizing PAT tools and process models, [2] understanding of process dynamics, [3] material diversion of nonconforming materials, and [4] process control using statistical techniques (*e.g.*, multivariate statistical process control), in order to control product quality and manufacturing processes (including in-house control).

Hereafter, the definition of terminology is given.^{9,10)} QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. CQA is 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. CMA is the material attribute of the drug substance, excipient and intermediate product (*e.g.*, concentration of the drug substance in the powder/tablet,

particle size of the drug substance/granules) that affects the critical quality attribute. CPP is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (*i.e.*, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. State of Control is a condition in which the set of controls consistently provides assurance of continued process performance and product quality. Process Performance is defined as the process capability to maintain CMAs and/or CPPs within the specified control range reliably. Evaluation of process performance may include control ranges of CMAs and/or CPPs and confirmation of the impact on variation when a state of change occurs from normal operation. Process Dynamics impacts of traceability of charged materials based on residence time distribution (RTD) and assumed variability on the quality in the downstream process. Action Limits is a reference value that is established within the range of manufacturing processes and product quality specifications by comprehensively taking into account technical aspects, required product quality, *etc.* During the operation of the manufacturing system, monitoring data exceeding the established action limit indicates that the manufacturing process has deviated from its normal control range. In this case, the Manufacturing System Operation Manager shall take corrective actions to restore the system to normal operating ranges. The action limit exceeding does not necessarily mean production of nonconforming material.

Points to Consider in Continuous Manufacturing In this section, three major points to consider in the process development and establishment of the control strategy using continuous manufacturing technology are described.

Change of Lot Size

The advantage of continuous manufacturing over batch manufacturing is that the lot size can be changed flexibly. PMDA has published provisional draft views and showed that the batch size can be varied by changing the operating time of the manufacturing process within the validated range.²⁴⁾

There are four approaches to change the lot size or combinations of them.

Change of Production Run Time

This approach is most expected to be used in continuous manufacturing because it exploits the advantage of continuous manufacturing. The lot size can be changed without waste by merely changing the run time under the control strategy already employed. However, when the run time is increased, risks not observed in the short run time, *e.g.*, accumulation of powder, heat generation of equipment, may appear. Hence, it is necessary to evaluate such risks arising from the increase of run time in the development stage.

Parallel Manufacturing Using Multiple Manufacturing Processes (Scale-Out)

This approach is effective, especially when a significant increase in production volume is required or when residence time is significantly long. Although the same manufacturing equipment is used in parallel, it is necessary to establish the control strategy taking into consideration how to assure the uniformity between drug products manufactured from parallel manufacturing processes.

Change of Throughput

This approach changes the throughput in continuous manufacturing as a method of changing the manufacturing volume with the same manufacturing equipment and run time. However, changing the throughput would affect the process dynamics and the residence time distribution of the manufacturing process. Thus it is necessary to evaluate process parameters, process control, sampling frequency, sampling size, and time and quantity of diversion, and also the control strategy needs to be rebuilt appropriately.

Change of the Size of Manufacturing Equipment (Scale-Up/Down)

This approach is the same strategy taken for current batch manufacturing. When the size of manufacturing equipment is changed, based on prior knowledge, it is necessary to evaluate the current process parameters, process control, sampling frequency, sampling size, and time and quantity of material diversion, and then to establish the control strategy appropriately again. Since this approach is used in batch manufacturing, it does not fully utilize the advantage of continuous manufacturing. However, the knowledge and experience in batch manufacturing that we have cultivated so far can be utilized.

Process Dynamics The process dynamics in continuous manufacturing of pharmaceutical products refer to traceability such as residence time distribution of materials and the influence of expected perturbations on the products.

In continuous manufacturing, raw materials or mixtures are continuously fed into the manufacturing process, and products are continuously extracted. Therefore, it is expected that the process parameters are always maintained at the target values and the quality of intermediate products satisfies the predetermined criteria regardless of the elapsed time. In actual manufacturing, however, they are not always constant and continuously fluctuates due to variation of process parameters and disturbances such as physical properties of raw materials, state of manufacturing equipment, and environmental changes. Although these variations are usually within a certain control range, large variations beyond the control range may occur, and products not conforming to the intended quality may be produced. Therefore, it is required to understand how the supplied raw materials/their mixtures or intermediates are distributed in the manufacturing equipment and how they are affected by variation, and then to establish the control strategy that finally evaluates and assures the product quality.

PAT In continuous manufacturing, the product is continuously taken out from the process; therefore, the quality of intermediates and final products sampled at a time point like in batch manufacturing is supposed not to be representative of the entire lot. Thus, it may be necessary to set the sampling frequency in continuous manufacturing higher than in batch manufacturing. In such cases, it is desirable to measure and evaluate the quality attributes/material attributes of intermediates/products in real time by PAT using an optical sensor or soft sensor, or to verify and understand them by a model. In addition, if the relationship between measurements of sensors and final product quality is known, a control method using the sensor measurements such as torque and temperature is also considered effective.

Quality Control by CPPs or CMAs Figure 1 shows two examples of the establishment of the control strategy through the QbD approach in the development of a drug product using

Fig. 1. Overview of Control Strategies Utilizing CPPs (Left) and CMAs (Right)
(p-CPP: potential CPP, p-CMA: potential CMA)

continuous manufacturing. One is the control strategy utilizing CPPs, and the other is the control strategy utilizing CMAs instead of CPPs. Even in continuous manufacturing, it is necessary to identify CPPs or CMAs to be controlled to assure the required product quality.

Generally, in batch manufacturing, the manufacturing equipment size needs to be changed from the development stage to the commercial manufacturing stage. Whenever the equipment is scaled up, if the CPPs-based control strategy is adopted, it is necessary to confirm the relationship between CQAs and the control range of CPPs because the control range of CPPs varies. To solve this problem, the “Sakura Bloom Tablet P2 Mock” document²³⁾ suggests a different approach to establishing the control strategy utilizing CMAs. This CMAs-based control strategy, which identifies and controls CMAs affecting CQAs, is also effective to construct feedforward and feedback control, in which PPs are adjusted based on the pre-set control strategy according to real-time measurement/control utilizing PAT and variability during process operation.

In the continuous manufacturing, on the other hand, it is easier to use the same manufacturing equipment from the development stage to the commercial manufacturing stage than the batch manufacturing, and the production volume can be increased without changing the size of manufacturing equipment. Therefore, both the control strategy utilizing CMAs and the control strategy directly controlling CPPs can be easily adopted in comparison with the batch manufacturing.

Scheme for Establishment of Control Strategy in Continuous Manufacturing Figure 2 shows an example of a scheme for the establishment of the control strategy in continuous manufacturing. The control strategy is established by the following steps:

- Step 1: Identification of CMAs and/or CPPs affecting CQAs
Step 2: Development/verification of control strategy

Step 3: On-going Process Verification

Step 1: Identification of CMAs and/or CPPs Affecting CQAs

- [1] Define the quality target product profile (QTPP) as it relates to quality, safety, and efficacy.
- [2] Identify potential critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled.
- [3] Extract potential critical material attributes (p-CMAs) and/or potential critical process parameters (p-CPPs) that may affect CQAs by risk assessment using such as failure mode and effect analysis (FMEA).
- [4]–[5] Verify the relationship between the p-CMAs and/or p-CPPs and CQAs and identify CMAs and/or CPPs.

In the continuous manufacturing, it is possible to use the same manufacturing equipment from the development stage to the commercial manufacturing stage; therefore, it becomes easier to accumulate the data for setting the control range of process parameters and to verify it compared with the batch production in which the manufacturing equipment is changed at each scale-up. Therefore, it is easy to establish a control strategy to control CPPs without identifying CMAs from an early stage directly.

Step 2: Development/Verification of Control Strategy

- [6] Develop control strategy using the knowledge gained in Step 1. The control strategy can be classified into three levels depending on the approaches.^{25,26)}

Level 1 Control strategy based on minimal parameter-based approach: This is a control strategy to perform a release test and establish appropriate setting point/tight ranges for identified CMAs or CPPs that can assure CQAs with a limited understanding of the relationship between inputs and resulting quality attri-

Fig. 2. Scheme for Establishment of Control Strategy

butes.

Level 2 Control strategy based on enhanced parameter-based approach: This is a control strategy to ensure CQAs by flexible CMAs or CPPs based on increased understanding of interaction between inputs and product quality attributes (e.g. design space). In continuous manufacturing, it is easier to establish a design space using commercial equipment from the early stage of development with a smaller amount of drug substance than in batch manufacturing.

Level 3 Control strategy based on Performance-based approach: This is a control strategy to ensure CQAs by automatic control of the process by real-time monitoring of CQAs or CMAs using PAT to detect quality variation due to unintended disturbance such as raw material attributes variation. By setting the action limits that trigger the feedforward and feedback control within the control ranges of CQAs or CMAs, the quality can be controlled constantly without producing nonconforming materials. In this control strategy, it is

considered possible to utilize knowledge gained from an enhanced approach, a data-rich environment, and an enhanced control strategy (e.g., chemometrics approach using spectral data, statistical methods to analyze process status, models such as residence time distribution (RTD))

In addition to the above level 1, 2 and 3 control strategies, as a control method specific to continuous manufacturing, there is a diversion of nonconforming material based on the understanding of process dynamics. If this control method is used, the locations of monitoring point for judgment of diversion and the point for executing diversion and amount (time) to be diverted shall be determined. In this case, for example, it is effective to utilize a model such as RTD.

Select appropriate control methods according to the fit for purpose, integrate them, and develop the control strategy. In case of developing the control strategy, it is important to evaluate the justification for control method using risk assessment for the matters especially happened in continuous manufacturing such as material diversion during startup and

shutdown, control method for disturbance, and influence of increasing run time (long time operation) assumed in commercial manufacturing.

- [7] Verify whether the “state of control” can be assured by the control strategy developed in [6]. Verify the consistency of the process by considering the lot size assumed to be used in commercial manufacturing. If process control and a real-time release test (RTRT) utilizing PAT, process model, and statistical method are performed, the possibility that the justification of the model may be decreased due to variations of raw materials and processes shall also be evaluated. Process validation can be included in this step. The expected verification items are as follows:

- Impact of variations of raw materials/drug substances
- Justification of control ranges for CMAs/CPPs
- Verification of in-process control test method/acceptance criteria
- Verification of model/analytical procedure
- Verification of sampling points/frequency/size
- Verification of material diversion point/size
- Verification of feedforward and feedback control

Step 3: On-Going Process Verification

- [8] Confirm that the state of control is maintained continuously even at commercial manufacturing. It is vital to verify periodically and continuously assure control strategy in commercial manufacturing because it is challenging to verify all variations happen in commercial manufacturing in the development phase. In order to verify periodically and assure the control strategy, it is necessary to accumulate data in commercial manufacturing. These data should include information such as the drug substance/raw materials used, results of process control and the product test, CPPs and CMAs related to the product quality. Analyze the accumulated data periodically, maintain the control strategy to assure the intended product quality, and assess the trend change in commercial manufacturing. In this case, it is also useful to use a method to analyze the conformance to the control value/ range of individual parameter and similarity to the trend of the past production (Univariate Statistical Process Control: USPC) or a method to analyze the overall index calculated by multivariate analysis such as principal component analysis (Multivariate Statistical Process Control: MSPC.²⁷⁾ If a model is utilized as a control method, moreover, it is necessary to verify the justification of the model continuously and to update the model as needed.

Conclusion

The concept of QbD introduced in ICH Q8 is useful for establishing the control strategy in continuous manufacturing. It is also important to utilize a model to understand the process dynamics, especially because materials move continuously within and between manufacturing equipment.

This article describes an example of a concept and scheme for the establishment of the control strategy for oral solid dosage forms using continuous manufacturing. It is expected that continuous manufacturing, which is a new manufacturing technology, will be generalized when pharmaceutical manufacturers themselves well-understand the element of continu-

ous manufacturing different from batch manufacturing and gain experience in establishing the control strategy.

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