Current Regulatory Considerations for Continuous Manufacturing of Pharmaceuticals in Japan

Issei TAKAYAMA*[1], Yoshihiro MATSUDA*[2] and Noriko KATORI**
*Office of New Drug VI[1], Senior Scientist (for Quality)[2], Pharmaceuticals and Medical Devices Agency, Japan
** Division of Drugs, National Institute of Health Sciences, Japan

Contact information:
Issei TAKAYAMA, Ph. D (Reviewer)
Address: Shin-kasumigaseki Bldg, 3-3-2 Kasumigaseki, Chiyoda-Ku, Tokyo 100-0013, JAPAN
TEL: +81-3-3506-9487
E-mail: takayama-issei@pmda.go.jp

Summary

Continuous Manufacturing (CM) can produce variable quantities of products with desired quality at a required time by continuous process operation. Compared to the traditional Batch Manufacturing, the manufacturing process can be more integrated, requiring smaller number of individual unit operations. The facility space can be reduced because of smaller size of manufacturing equipment. The scale-up study from the developmental phase to the commercial production phase may be reduced. As such, the CM technique is greatly expected. While Continuous Manufacturing can be a major innovative manufacturing technique of the pharmaceutical industry in the future, however, in the pharmaceutical industry, the manufactures of pharmaceutical products are strictly regulated to prevent low quality products and shortage. Thus, the production system for continuous manufacturing that meets these existing regulatory requirements is actively being discussed around the world.

First, we reviewed the domestic and overseas status of regulatory requirements for continuous manufacturing. At the end of 2016, although vigorous discussions are being held, mainly in the Office of Pharmaceutical Quality Division, US FDA, no official guidelines have been published from regulatory agencies. In addition, international harmonization activities such as ICH are still under consideration. Based on these backgrounds, the AMED sponsored study group that PMDA Innovative manufacturing technology working group (IMT WG) participated requested the CM project team in Japan Pharmaceutical Manufacturers Association to input the priority issues in introducing this new technology and obtaining regulatory approvals for the continuous manufacturing of Pharmaceuticals. To solve these issues and support the development, we proposed 4 topics of Points to consider in the introduction of continuous manufacturing (Control strategy, Definition of Batch/Lot, Process Validation, and Stability Test), assuming drug products of chemically synthesized drug substances. Moreover, we reviewed the internationally discussed important concepts for continuous manufacturing such as “Performance based Approach”, “Process Dynamics”, “State of Control”, and “Fit for Purpose” with domestic stakeholders and proposed the current interpretation of these concepts in this presentation.

Please note that this presentation is based on the personal opinion of the authors and does not indicate the official view of PMDA/MHLW.

Introduction

1. Briefing of Japan regulatory system

Regulatory authorities for drugs and medical devices in Japan

PMDA
- ☐ Scientific assessment of drugs and medical devices
- ☐ Consultation on clinical trials etc.
- ☐ Inspection (GCP, GLP, GMP, QMS etc.)
- ☐ Supporting MHLW’s activities

MHLW
- ☐ Authorization of applications
- ☐ Publication of guidelines
- ☐ Supervision of PMDA activities

MHLW: Ministry of Health, Labour and Welfare

2. Global discussions on regulatory considerations for CM

US FDA:
US FDA has actively recommended the introduction of CM technology, in anticipation of the current situation that major technological innovation is not seen in the method of manufacturing drug products for this past half century, and expecting new efforts in the pharmaceutical industry.
They have set up the Emerging Technology Team within Office of Pharmaceutical Quality to provide a platform for FDA and industry to accelerate the development and adoption of emerging technology. CM has been identified as target of this team and an opinion paper on CM of pharmaceutical products was published in academic journal in 2015 (1). Moreover, As a concrete example, they announced in their website that they approved one product as a NDA in July 2015, and one product as a partial change of approved manufacturing method (sNDA) in April 2016. They also established a public docket to invite discussion of issues related to the adoption of CM by industry, based on the proposal from Engineering Research center for Structured Organic Particulate System (C-SOPS) in June 2017.
(1) J Pharm Innov (2015) 10:191–199

ICH perspective:
As one of future topics in the quality field, the guideline on CM has been suggested from 2014, since the regulatory requirements in each region are not well developed. However, at the time of Geneva meeting in November 2017, the working group for the guideline on CM has not officially been adopted in ICH.

Academic perspective (MIT CM Symposium):
In 2014 and 2016, the international symposiums on CM of pharmaceuticals were held mainly hosted by the Massachusetts Institute of Technology. Based on the discussions at that time, “White Papers” including regulatory considerations were proposed and finally they were published in academic journal as opinion papers. (2)(3)
(2) J Pharm Sci (2015) 104: 803–812
(3) J Pharm Sci (2017) 106:3199-3206

Topics 1

JPN domestic discussions on regulatory considerations for CM

PMDA Innovative Manufacturing Technology WG

☐ Members

Senior Scientist (for Quality); Dr. Yoshihiro Matsuda, Reviewers from Office of New Drugs, Generic Drugs, Cellular and Tissue-based Products, and Regulatory Science and Inspectors form Office of Manufacturing/Quality and Compliance

☐ Activity Plan for Continuous Manufacturing(CM)
- To organize face-to-face meeting(s) with US FDA and EMA
- To visit continuous manufacturing sites of chemical substance and product
- To discuss with stakeholders including industries and academia
- To collaborate with a national research project on pharmaceutical quality control
- To publish a provisional draft document for CM in spring, 2018

JPN Pharmaceutical Manufacturers Association CM Project

Activity Plan :
- ☐ Understanding the CM (Technical aspects, QA aspects, RA aspects) : Share examples of application to R&D and Commercial production, and experience of regulatory submission
- ☐ Extracting issues in introducing and obtaining regulatory approval for the CM: Technical aspects, QC aspects (QbD and PAT) and Process Validation.
- ☐ Establish industry thinking about issues on CM and discuss them with regulators and academia: RA aspects
  - Batch definition and Application dossier
  - Drafting the mock of “Application Form” for JPN NDA.
  - Input to future ICH discussion

Refer to presentation slides from Mr. Ohta in 18th Pharmaceutical Quality forum in Feb. 2016.

JPN Agency for Medical Research & Development (AMED) sponsored study group

Research into Quality Assurance of Pharmaceutical Continuous Manufacturing

☐ Purpose:
To facilitate the smooth introduction of the CM in Japan by addressing issues of the CM together with industries, regulators and academia and by sharing our knowledge.

☐ Members:
National Institute of Health Science (NIHS), Universities, JPMA and PMDA

☐ Proposing a Points to consider document in 2017
We focused on 4 topics by following inputs from the JPMA members.
- Control Strategy
- Batch Definition
- Process Validation
- Stability Testing

English report available from NIHS Website; http://www.nihs.go.jp/drug/section3/AMED_CM_PtC.pdf

Topics 2

Points to Consider Regarding Continuous Manufacturing (Key messages from each chapter)

Introduction

- ☐ While Continuous Manufacturing could be a major innovative manufacturing technique of the pharmaceutical industry in the future, official documents such as guidelines for Continuous Manufacturing have not been issued. Therefore, the key points to consider for the introduction of Continuous Manufacturing are summarized in this document.
- ☐ Note that this document assumes drug products of chemically synthesized drug substances and summarizes basic concepts of Continuous Manufacturing based on the latest scientific knowledge; therefore, the contents presented in this document should be updated as needed to reflect scientific advances in a step-by- step manner.

#1 Control Strategy

- ☐ For establishing a control strategy for commercial production during the developmental phase of pharmaceutical products, there is no 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. However, in Continuous Manufacturing, it is considered possible to apply new approaches (technology and methodology) for ensuring the above-mentioned factors.
- ☐ Continuous Manufacturing requires more flexible handling, compared to the traditional Batch Manufacturing, such as adjustment of process parameters as needed, since the process is continuously in operation.

Performance based Approach
- Differing from the process control using fixed process parameters, the control method that can achieve the desired product quality by flexibly adjusting process parameters 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..

For the achievement
- Need to understand the “Process Dynamics”
- Need to ensure the “State of Control”
- Need to consider the “Fit for Purpose”

- ☐ Process Dynamics
  - Traceability traits such as residence time distribution of the input materials, and effects of expected changes on the quality of the downstream products.
- ☐ State of Control
  - A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)
- ☐ Fit for Purpose
  - Weighting of control depending on the influences on pharmaceutical products.

- ☐ Understanding of process dynamics
  - Understanding of process dynamics includes ensuring traceability such as residence time distribution of the input materials in the process, and investigation of effects that expected changes have on the quality of downstream products.
- ☐ Handling of products obtained during process disturbance
  - Online monitoring by PAT is beneficial for judging the need of rejection from the process. If a certain portion of the product forms physical fractions, control on the basis of the fraction is considered effective. However, in this case, it is necessary to ensure that all fractions considered unacceptable are properly removed from the process.

#2 Batch Definition

☐ The definition of Batch is the same between CM and Batch M.

Definition from ICH Q7

“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.”

☐ How to set the Batch size can be different.
- The run time and the throughput speed
- The amount materials manufactured
- The charge amount of the raw materials

The batch size can be changed by specifying the run time at a certain throughput speed or the total amount of manufacturing in the manufacturing order for each production. However the maximum batch size can be determined based on the risk assessment on quality at an extended run time and the result of the process validation.

#3 Process Validation

- ☐ The basic concept of process validation for CM is not different from that for BM. Specifically for CM;
  - Process performance and quality attributes during Continuous Manufacturing are consistently controlled by the control strategy established in advance.
  - Variations in quality between batches remain within an acceptable range. Variations in quality over time within a batch also remain within it.
- ☐ The number of PV batches
  - Basically a minimum of three batches are required for the PV to ensure the repeatability, as in the BM in Japan.
  - However, since the batch size in Continuous Manufacturing can be adjusted by changing the processing time even with the same manufacturing equipment, it is not considered necessary to manufacture three batches at the maximum batch size as specified, if it is scientifically proven that no time-series changes occur in the quality upon examination during the developmental stage before the process validation.
- ☐ Scale for PV batches
  - it is not always necessary to perform process validation on all batches at the maximum batch size. However, at least one batch should be manufactured at the expected maximum batch size to ensure the quality.

Because the operation of manufacturing equipment in a longer time and the effects of accumulated substances on manufacturing equipment need to be taken into consideration.

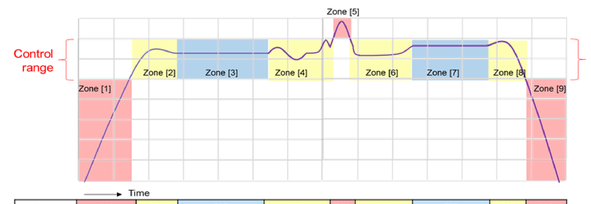
- ☐ Change of the maximum batch size after PV
  - When the maximum batch size needs to be changed (e.g., by extension of the processing time) after PV is performed, at least one batch validation (prospective validation or concurrent validation) is required.

#4 Stability Testing

- ☐ Size of the primary batch
  - A view that batches of any batch size can be employed for the primary batch will be acceptable.
  - However it is necessary to explain that the primary batch has the same characteristics as other batches manufactured at a commercial production scale.
- ☐ Number of primary batches
  - The basic idea for the number of primary batches needed is the same as that in BM; basically, at least three batches are required according to ICH Q1A(R2).
  - It is necessary to record information on the sampling points intended for the primary batch, as the batch size of the primary batch itself may vary unlike the case in BM.

Conclusion and Next step

1. Based on the accumulated knowledge of the AMED sponsored study and review experience on CM now and future, PMDA should draft the regulatory requirements and prepare the international harmonization activities of the CM in advanced.
2. Although we only reported regulatory considerations of CM for drug products of chemically synthesized drug substances in this presentation, R&D of CM in the field of biopharmaceuticals has already started. Upon introducing CM, it will be urgent to consider the regulatory issues unique to biopharmaceuticals such as ensuring viral safety.
3. Currently, the AMED study group is preparing a commentary document to promote common understanding of the concept of "State of Control" in CM among stakeholders. The preliminary result of discussion is summarized as follows:



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

Figure 1 Conceptual diagram of “State of Control” in the CM

Acknowledgement

This study was supported by AMED under Grand Number JP17mk0101025h0203.

Thanks to study group members and PMDA colleagues;

NIHS and Academic Researchers;
Tatsuo KOIDE, National Institute of Health Sciences
Tomoaki SAKAMOTO, National Institute of Health Sciences
Kouhei TAHARA, Gifu Pharmaceutical University
Katsuhide TERADA, Takasaki University of Health and Welfare

JPMA CM Project members;
Yasuyuki IKEMATSU, Eisai Co., Ltd.
Keiji INOUE, GSK K.K.
Eiichi MANO, MSD K.K.
Yasuhiro MATSUI, Sumitomo Dainippon Pharma Co., Ltd.
Tomoaki OHTA, Chugai Pharmaceutical Co., Ltd.
Ryutaro SHIMONO, Janssen Pharmaceutical K.K.
Yasuhiro SUZUKI, Daiichi Sankyo Company, Ltd.

PMDA Staff;
Atsushi AOYAMA, Eriko AOYAMA, Ryusei ISHII, Hiroyuki KAWAKITA