CM Research Outcomes

-Control Strategy, Batch Definition, Process Validation and Stability Testing-

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Introduction of PMDA

Headquarters, Tokyo

- Name : Pharmaceuticals and Medical Devices Agency
- Date of Establishment : In April 2004
- Established as an Incorporated Administrative Agency

Kansai branch

Hokuriku branch

http://www.pmda.go.jp/en/index.html

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

PMDA: Pharmaceuticals and Medical Devices Agency
MHLW: Ministry of Health, Labour and Welfare

Innovative Manufacturing Technology Working Group (IMT-WG)

- Has been established in PMDA since July, 2016.
- Purpose
  - To establish PMDA's perspective on the latest technologies of pharmaceutical quality control
  - To propose a new regulatory framework for the pharmaceutical quality control by the new technologies
  - To draft guidelines
- Members
  - Senior Scientist (for Quality); Dr. Yoshihiro Matsuda
  - From Office of New Drugs
  - From Office of Manufacturing/Quality and Compliance
  - From Office of Generic Drugs
  - From Office of Cellular and Tissue-based Products
  - From Office of Regulatory Science

IMT-WG 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

Japan Agency for Medical Research and Development (AMED) sponsored study group

- Research into Quality Assurance of Pharmaceutical Continuous Manufacturing
  - It was started on August 15th , 2016.
  - 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:
    - PMDA (assessors, GMP inspectors)
    - National Institute of Health Science (researchers)
    - Universities
    - Industries (Daiichi-Sankyo, Eisai, Sumitomo Dainippon Pharma, Chugai, GSK, Janssen, MSD etc.)

CM Research Outcomes

A Points-to-consider document.

- We focused on 4 topics by following inputs from The Japan Pharmaceutical Manufacturers Association (JPMA) members.
  - Control Strategy
  - Batch Definition
  - Process Validation
  - Stability Testing

http://www.nihs.go.jp/drug/section3/AMED_CM_PtC.pdf

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.

Control Strategy (1)

- 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.

Control Strategy (2)

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"

Control Strategy (3)

- 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.

Control Strategy (4)

- 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.

Batch Definition

- The definition of Batch is the same between CM and BM.
- 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.

Process Validation (1)

- 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.

Process Validation (2)

- 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.

Process Validation (3)

- 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.

Why?

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.

Process Validation (4)

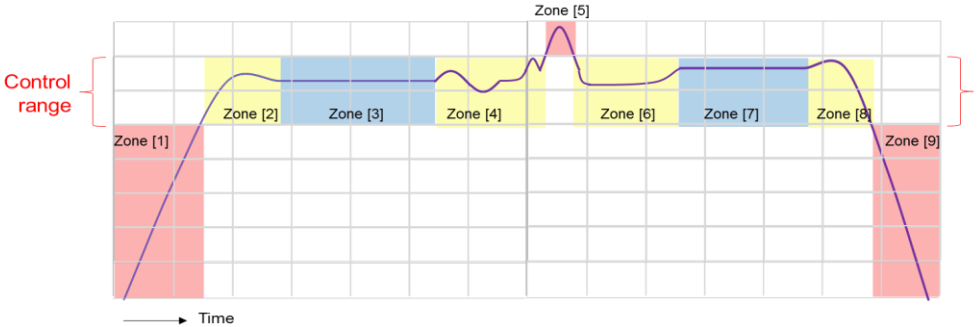
- Change of the maximum batch size after PV
  - When the maximum batch size needs to be changed (e.g., by extension of the processing time) after PV is performed, at least one batch validation (prospective validation or concurrent validation) is required.

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.

Next step

- We are discussing on “State of control” and a difference between “State of control” and “Steady State” in CM.



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	Devia-tion 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 commenc ement of shutdown proce-dures	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

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Thank you for your attention