PMDA Activities for Implementation of Continuous Manufacturing

Yoshihiro Matsuda, Ph.D.

Senior Scientist (for Quality)
Pharmaceuticals and Medical Devices Agency (PMDA)

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 pharmaceutical quality control using the new technologies
  - To draft guidelines

IMT-WG Activities for Continuous Manufacturing (CM)

- IMT-WG had face-to-face meetings with US FDA in 2016 and EMA in 2017.
- IMT-WG visited continuous manufacturing sites of chemical substance and product.
- IMT-WG joined some quality consultations regarding CM across multi-offices in PMDA.
- IMT-WG has effective collaboration with a national research project on pharmaceutical quality control.

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

- Study on quality control techniques in a new development and manufacturing change of pharmaceuticals

It was started on August 15th , 2016.

- Purpose:
  - To facilitate the smooth introduction of the CM in Japan by addressing issues of 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 Outcome (1)

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

The provisional draft document for CM

- PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft) was published in March 30, 2018.
- This provisional draft document was developed by Innovative Manufacturing Technology Working Group (IMT-WG) at PMDA, based on the point-to-consider document.

https://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0018.html

Introduction

- This document includes some views on applying CM 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 updated based on future experience and accumulated knowledge. Therefore, it is submitted as a provisional draft. This provisional draft was prepared by anticipating the following cases,

(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 continuously.

Control Strategy (1)

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..

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 (2)

- Understanding of process dynamics
  - 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 CM, 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.

Control Strategy (3)

- Tools
  - A PAT tool (including soft sensors possibly)
  - An RTD model
- The control strategies need to be evaluated individually. Therefore PMDA recommends establishing an early dialogue with regulators during the development stage of CM.

Batch Definition

- The batch (or lot) size in CM 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 CM, 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.

Validation (1)

- As is the case in Batch Manufacturing (BM), validation for CM needs to be implemented in accordance with the validation standards.
- Batch size and the number of batches for process validation
  - Basically, as in the BM, 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.
  - Validation design that introduces the idea of continuous process verification may be possible in some cases.
  - The batch size of a product to which CM is applied should be established before being manufactured by the manufacturer.

Validation (2)

- Specifically for CM
  - The batch size should be established by taking into consideration the operability of manufacturing equipment for a longer operation time and the effects of accumulated substances on manufacturing equipment.

Therefore

This process validation should be repeated with at least 3 batches or performed with an equivalent or superior method.

Stability Testing

- In CM, the batch size can be varied by changing the operating time of the manufacturing process within the validated range. Therefore, unlike BM, in the case of CM, 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.

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.

CM Research Outcome (2)

- "State of control in continuous pharmaceutical manufacturing" document.
  - "State of control" means a condition in which a change remains within the control range under the predetermined control even if the condition changes over time due to the fluctuation of external factors.

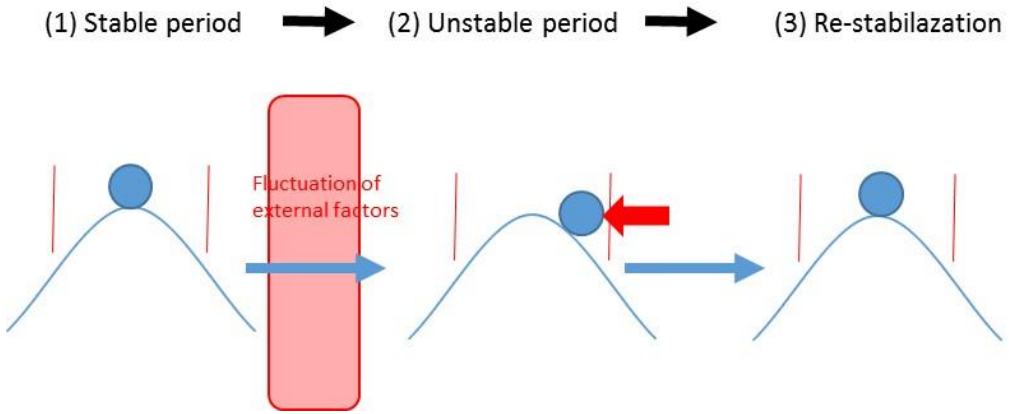
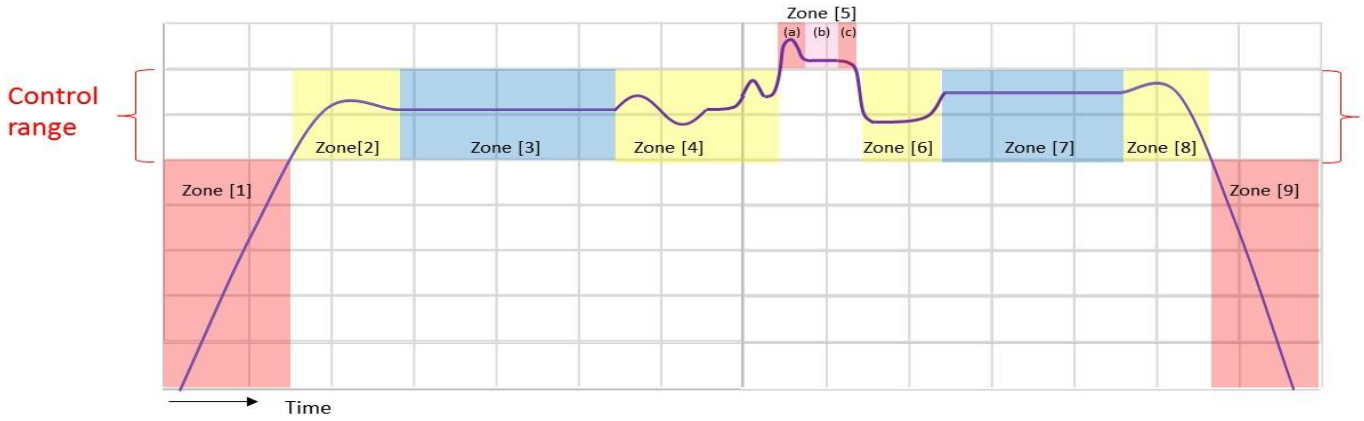


Figure 1: Conceptual diagram depicting State of Control
(Note: The red belt indicates the control range and the red arrow indicates designed control.)

The relationship between State of Control and Steady State



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 unsteady)	Steady state	Condition within the control range despite the fluctuation of external factors	(a)Deviation from the control range (b)Condition where steady state is achieved but which is still out of control range (c)Condition shifts to the unsteady and is still out of control range			Condition which is unsteady after recovery of the control range	Steady state with different values from Zone 3	Condition within the control range despite commencement of shutdown procedure	Shutdown (Deviation from the control range)
					(a)	(b)	(c)				
Steady state	N	N	Y	N	N	Y	N	N	Y	N	N
State of control	N	Y	Y	Y	N	N	N	Y	Y	Y	N
Diversion out of line	Y	Y/N	N	Y/N	Y	Y	Y	Y/N	N	Y/N	Y

Figure 2: Conceptual diagram depicting relationship between "Steady State" and "State of Control"
(Y: Yes, N: No, Y/N: Yes or No)

Q1: "What" and "How" should the assessment criteria be evaluated to ensure whether or not "State of Control" is achieved and guaranteed in CM?

- To the question, "What," the consistency can be evaluated from two viewpoints, "operability of manufacturing processes" and "product quality", which are mentioned in the definition in ICH Q10 guideline.
- As for the question, "How," it is difficult to show unified specific assessment criteria since "How" should be assessed as appropriate for individual cases and differs depending on the control strategies established by the manufacturer. If feedback/feedforward control or PAT-based high-level control strategies are established as part of the quality risk management, for example, a flexible control range may be designated for series of process parameters and targeted/set process control values under real-time monitoring. On the contrary, if control strategies are established at a conventional level (manufacturing based on the pre-determined process parameter), "State of Control" needs to be explained by designating a stricter control range for series of process parameters and targeted/set process control values and frequent quality analyses, etc.

Q2: Does demonstrating "Steady State" assure "State of Control" in CM?

- Even if steady state is maintained, since the operation may be implemented outside the control range for quality assurance, maintaining "Steady State" does not necessarily guarantee "State of Control". It is necessary to guarantee that the operation is maintained within the control range of preset targeted values/set values by following the predefined control strategy. Although "Steady State" is not a requirement for assuring "State of Control", maintaining steady state where the operation is kept under control more easily is considered to be a desirable condition.

Q3: Is it possible to guarantee "State of Control" if variables subject to control are verified within the control range in CM where "Steady State" is not achieved?

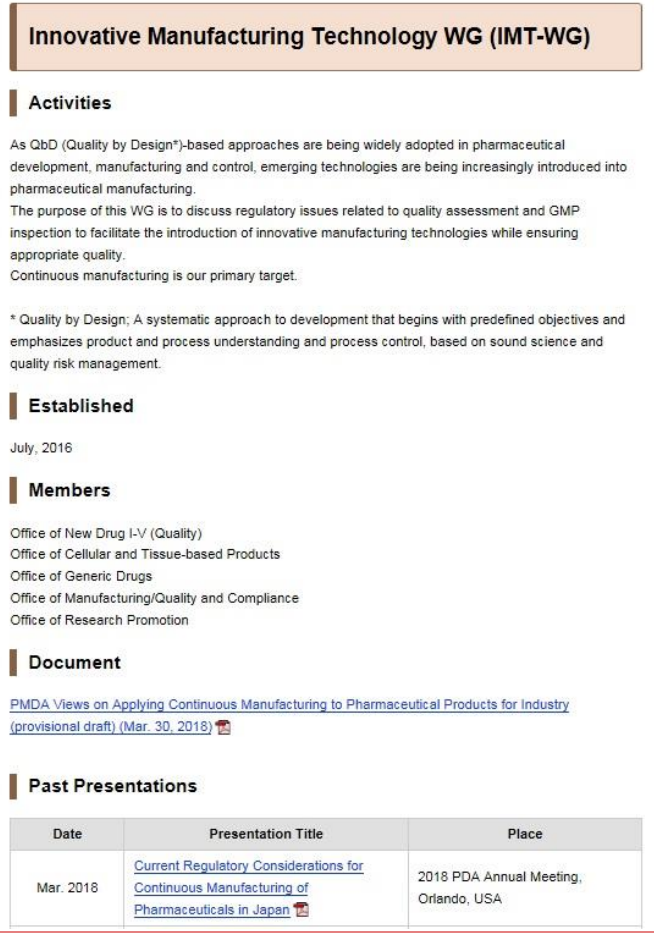
- It would be theoretically possible to guarantee "State of Control" if variables subject to control are verified within the control range and robustness during the process of changes is demonstrated despite the unsteady state. Nevertheless, it should be born in mind that unsteady state has multiple technical problems including the difficulty in establishing an RTD model.

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

How to stay up to date with PMDA

- PMDA posts our presentation files and documents on our website.
- PMDA provides consultations.

http://www.pmda.go.jp/english/rs-sb-std/standards-development/cross-sectional-project/0012.html



Innovative Manufacturing Technology WG (IMT-WG)

Activities

As QbD (Quality by Design*)-based approaches are being widely adopted in pharmaceutical development, manufacturing and control, emerging technologies are being increasingly introduced into pharmaceutical manufacturing.
The purpose of this WG is to discuss regulatory issues related to quality assessment and GMP inspection to facilitate the introduction of innovative manufacturing technologies while ensuring appropriate quality.
Continuous manufacturing is our primary target.

* Quality by Design; A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Established

July, 2016

Members

Office of New Drug I-V (Quality)
Office of Cellular and Tissue-based Products
Office of Generic Drugs
Office of Manufacturing/Quality and Compliance
Office of Research Promotion

Document

PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft) (Mar. 30, 2018)

Past Presentations

Date	Presentation Title	Place
Mar. 2018	Current Regulatory Considerations for Continuous Manufacturing of Pharmaceuticals in Japan	2018 PDA Annual Meeting, Orlando, USA

Acknowledgement

This study was supported by AMED under Grand Number JP17mk0101025h0203.

Yoshihiro Matsuda, PMDA
Atsushi Aoyama, PMDA
Eriko Aoyama, PMDA
Yasuyuki Ikematsu, Eisai Co., Ltd.
Keiji Inoue, GSK
Tomoaki Ohta, Chugai Pharmaceutical Co., Ltd.
Noriko Katori, NIHS
Hiroyuki Kawakita, PMDA
Tatsuo Koide, NIHS
Tomoaki Sakamoto, NIHS
Ryutaro Shimono, Janssen Pharmaceutical K.K.
Yasuhiro Suzuki, Daiichi Sankyo Company, Ltd.
Issei Takayama, PMDA
Kouhei Tahara, Gifu Pharmaceutical University
Katsuhide Terada, Takasaki University of Health and Welfare
Yasuhiro Matsui, Sumitomo Dainippon Pharma
Eiichi Mano, MSD

Thank you for your attention