PMDA Update

Yoshihiro Matsuda, Ph.D.

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

Progress on Continuous Manufacturing

- PMDA Innovative Manufacturing Technology Working Group (IMT-WG)
  - PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft)

    https://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0018.html
- Japan Agency for Medical Research and Development (AMED) sponsored study group
  - "Points-to-consider" document

    http://www.nihs.go.jp/drug/section3/AMED_CM_PtC.pdf
  - "State of control in continuous pharmaceutical manufacturing" document

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

Learnings

- There would be some different views on control strategies of CM between APIs, chemical products and biological products.
- We need further discussion about how we can define the acceptable variation of CM as the state of control.
- What kinds of PV strategies would be allowed.
- Issues of lifecycle management such as a batch size change, a formulation change, model maintenance, a change from CM to BM, etc.

Performance based approach

- We are able to measure and access the final and intermediate products in real time using PAT, etc. according to any changes that occur. Therefore the process parameters can be adjusted in order to achieve the desired product quality.

In order to achieve this,

- Need to understand the "Process Dynamics"
- Need to ensure the "State of Control"
- Need to consider the "Fit for Purpose"

State of Control

- "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.

(1) Stable period → (2) Unstable period → (3) Re-stabilization

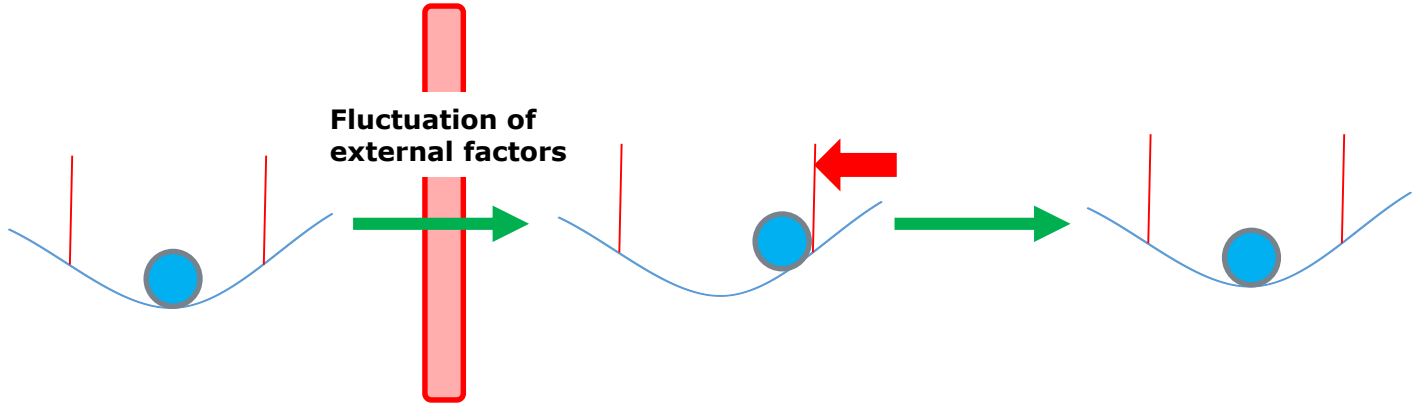
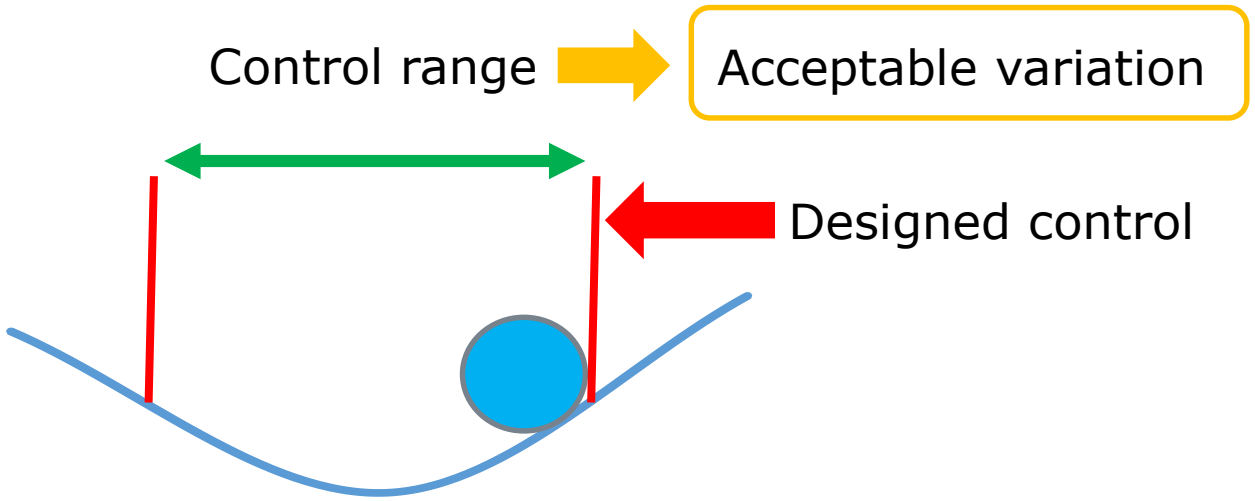


Figure : Conceptual diagram depicting the State of Control
(Note: The red belt indicates the control range and the red arrow indicates the designed control.)

Challenges



How much variation of CM can be accepted as the state of control?
And is it possible to fit the batch definition
(uniform character and quality)?

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.
  - A 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)

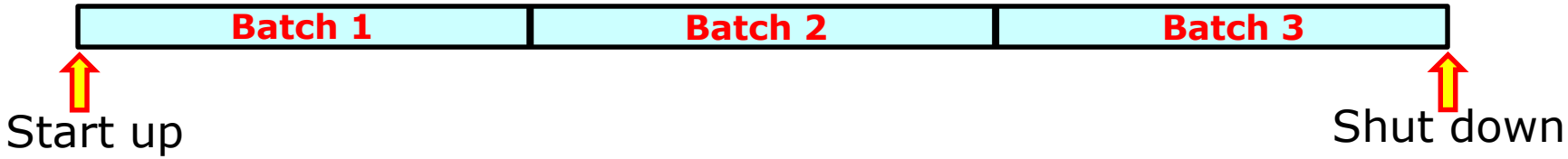
- Specifically for CM
  - The batch size should be established by taking into consideration the operability of manufacturing equipment in a longer operation time and the effects of accumulated substances on manufacturing equipment.

⇩ **Therefore**

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

Continuous Process Verification

Challenges



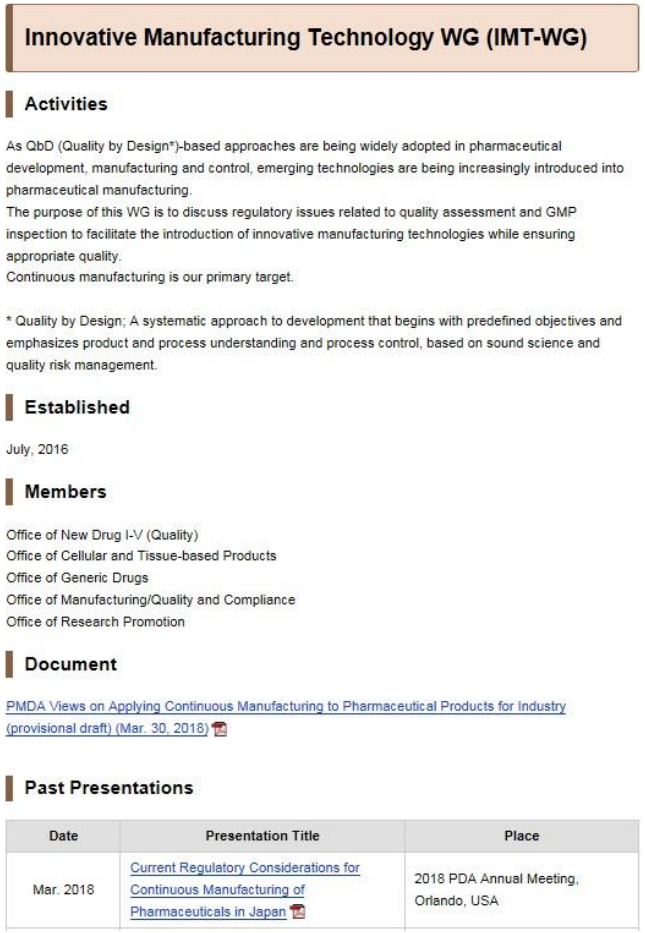
- Qualification of start up and shut down will be verified three times during the operational qualification (OQ).

Is it possible to achieve the objective of PV by using 3 sequential batches?

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

Thank you for your attention