PMDA Perspective

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Innovation in CMC area

- Quality by Design (QbD)
- Design Space (DS)
- Process Analytical Technology (PAT) & Real Time Release Testing (RTRT)
- Nanomedicine (block copolymer micelle, etc.)
- 3D printing
- Continuous Manufacturing (CM) ,etc.

What did QbD bring us?

- Provided a higher level of quality assurance
- Facilitated regulatory assessment
  - Systematic development described in regulatory submissions improved the regulatory assessment
  - Improved the efficiency of the assessment / GMP inspection
- Enabled science and risk based regulatory decisions
  - Provided more operational flexibility
  - Facilitated new technology
- Improved communication
  - Between Regulators and Industry
  - Between Assessors and GMP Inspectors

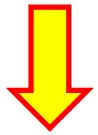
Changes

- At the beginning of ICH Q8,9,10 (Q-trio) implementation
  - Applicants tried to set the Design Space for their flexibility.

- Now
  - Applicants tend not to state the Design Space even if they have developed the Design Space.

Why?

- One of possibilities is
  - The Q&A at FDA-EMA QbD pilot program mentions Design Space Verification.



  - Design Space might allow for less flexibility because of their efforts, such as Design Space verification activities and valid explanation of Design Space.

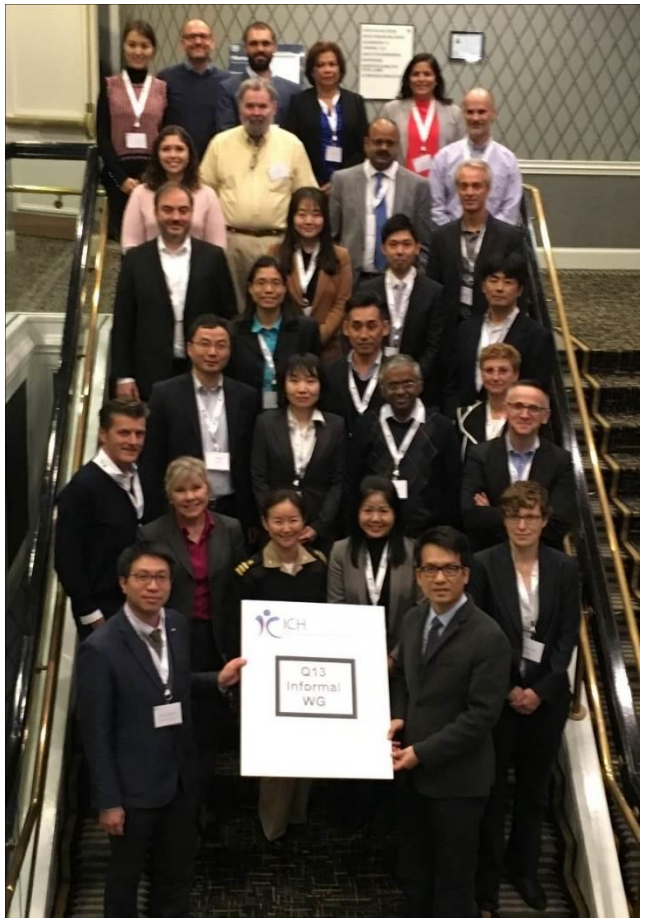
Current situation

- Industry's interest is moving towards
  - Real Time Release Testing
  - Lifecycle Management (ICH Q12)
    - Established Conditions (EC)
    - Post-Approval Change Management Protocols (PACMP)
  - Novel Manufacturing Technologies

Continuous Manufacturing (ICH Q13)

ICH Q13

- Continuous Manufacturing of Drug Substances and Drug Products
- In the meeting held at Charlotte on November 12-15, 2018, the concept paper and business plan were endorsed, and the Expert Working Group (EWG) was determined to formally start drawing up the Q13 guideline.
  - Rapporteur: Dr. Sau (Larry) Lee (US FDA)
  - Regulatory Chair: Dr. Yoshihiro Matsuda (PMDA)



Concept Paper

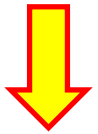
- Issues to be Resolved:
  - CM-related definitions and regulatory concepts
    - Definition of CM, startup/shutdown, state of control, process validation, and continuous process verification.
  - Key scientific approaches for CM
    - Concepts of system dynamics, monitoring frequency, detection and removal of non-conforming material, material traceability, process models, and advanced process controls.
  - CM-related regulatory expectations
    - Dossier approval and aspects of lifecycle management.

Business Plan

- The current ICH Guidelines do not sufficiently address technical and regulatory requirements that are unique to CM. A harmonised regulatory guideline can facilitate implementation, regulatory approval, and lifecycle management; particularly for products intended for commercialization internationally. This approach will benefit industry and regulators, and improve access to medicines.
- The proposed timeline and milestones
  - Step 2b: June 2020
  - Step 4: November 2021

Why is CM drawing attention?

- Are there any problems with conventional batch manufacturing?

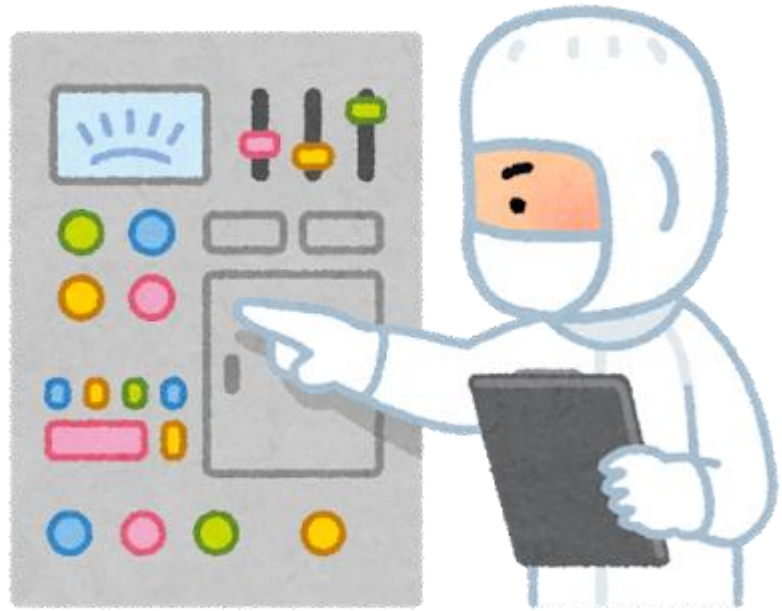


- There is nothing wrong with batch manufacturing, which should remain one of the manufacturing methods to be used in the future.
- However, CM may offer us what is difficult to achieve in batch manufacturing.

Expectations for CM

- Flexible manufacturing
  - Production in response to demand
- Detectability of poor quality products
  - Prevention of drug shortage problem
- Prevention of waste
  - Promotion of Green chemistry
  - Cost reduction

and so on



Offers us a wider choice of manufacturing methods

PMDA's milestones in the study of CM

- 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 from the study

- There are some different views on control strategies of CM between APIs, chemical products and biological products.
  - For example, it would not be easy to monitor all CQAs of biological products by PAT compared to chemical 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

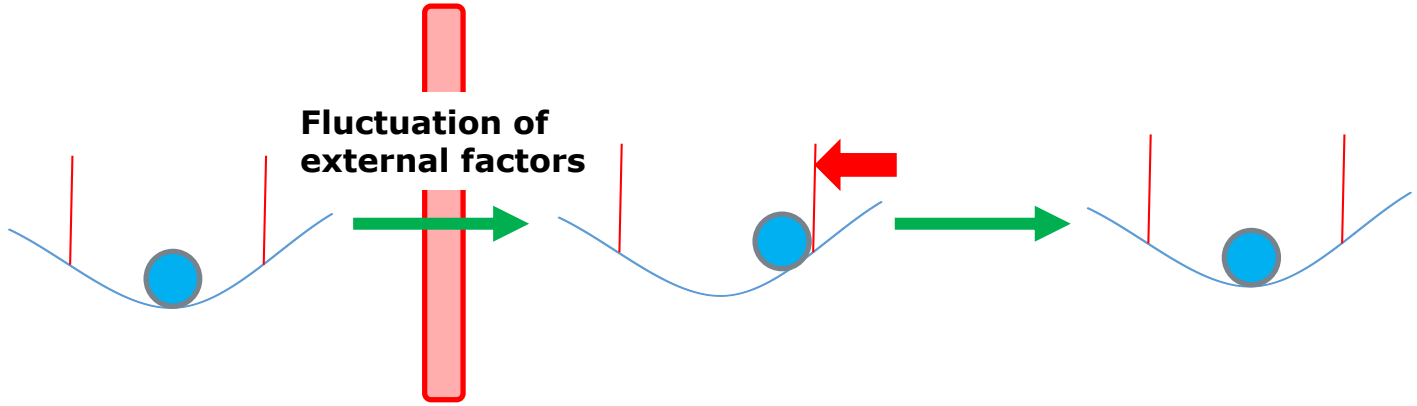
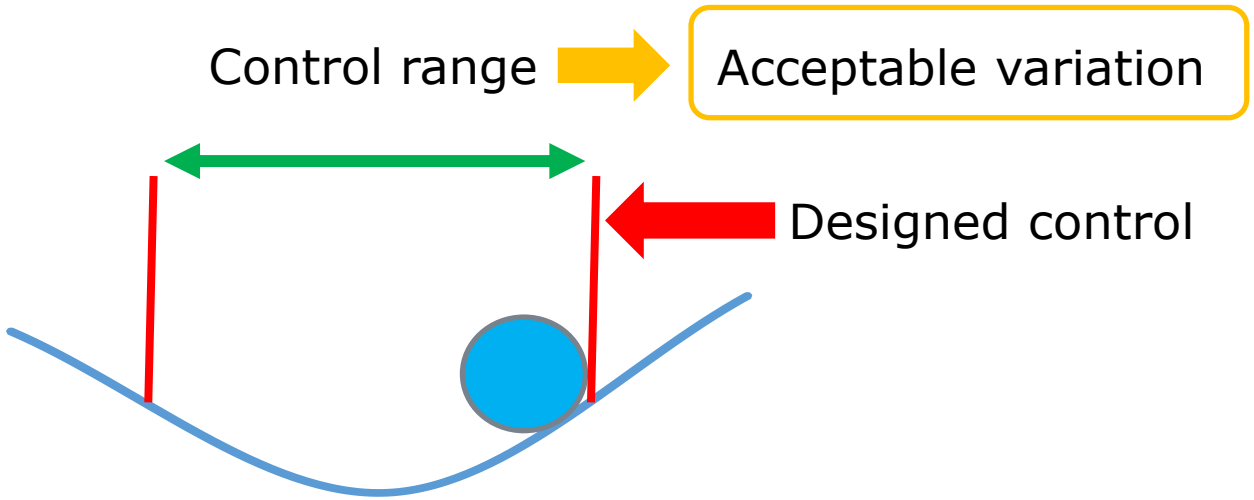


Figure : Conceptual diagram depicting the State of Control
(Note: The red belt indicates the control range and the red arrow indicates the designed control.)

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)

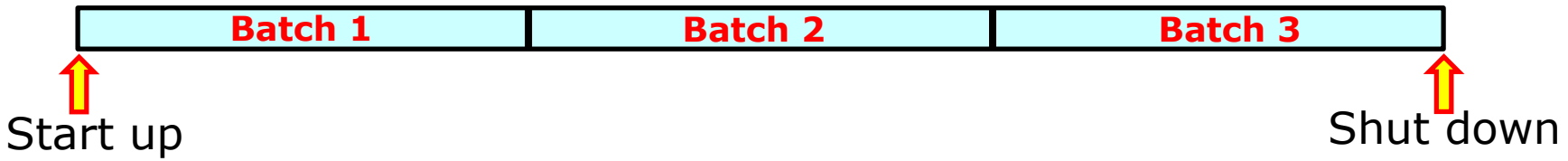
- Specifically for CM
  - The batch size should be established by taking into consideration the operability of manufacturing equipment in a longer operation time and the effects of accumulated substances on manufacturing equipment.

⇩ **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?

Specialized teams for CM at the EMA, FDA and PMDA

EMA

- Process Analytical Technology (PAT) team

US FDA

- Emerging Technology Team (ETT)

PMDA

- Innovative Manufacturing Technology Working Group [July 2016 -]
- AMED research group (for the quality assurance in the continuous manufacturing of pharmaceutical products) [August 2016 -].
- AMED research group (for the quality control methods for the practical application of continuous manufacturing to biopharmaceuticals) [May 2018 -].

Regulatory harmonization and convergence (1)

- It is necessary for pharmaceutical industries to make similar regulatory decisions globally.

- The ICH is among the most effective vehicles of harmonization.
  → ICH Q13

- Are the ICH guidelines (Q13) enough to achieve true harmonization?

- In addition, we also need to consider regulatory convergence.

Reference: Matsuda Y, Global Regulatory Landscape. AAPS PharmSciTech. 2019; 20(1)

Regulatory harmonization and convergence (2)

Refer to: https://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm271079.htm.

Regulatory convergence

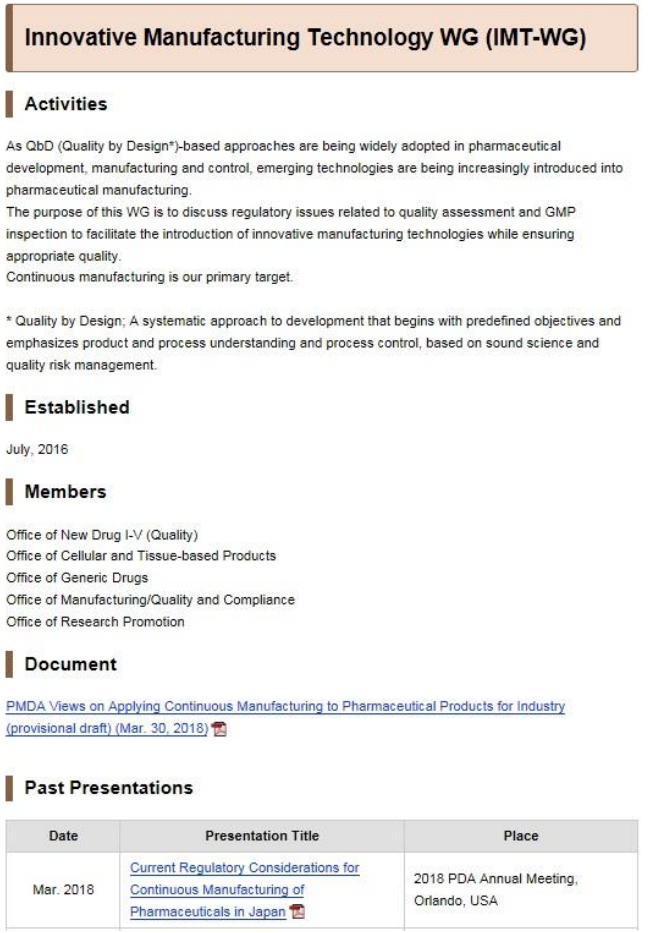
- The process whereby the regulatory requirements across countries or regions become more similar or aligned over time as a result of the gradual adoption of internationally recognized technical guidance documents, standards and scientific principles, common or similar practices and procedures, or adoption of regulatory mechanisms that might be specific to a local legal context but align with shared principles to achieve a common public health goal.

- To this end, it is necessary to share knowledge between regulatory agencies, and particularly, to make opportunities to review real assessments with those of other regulatory agencies.

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

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Thank you for your attention