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Current Regulatory Considerations and Challenges for Continuous Manufacturing of Pharmaceuticals

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Today`s Agenda

1. International status of regulatory consideration for CM

- US FDA
- ICH
- International Symposium on Continuous Manufacturing of Pharmaceuticals (MIT)

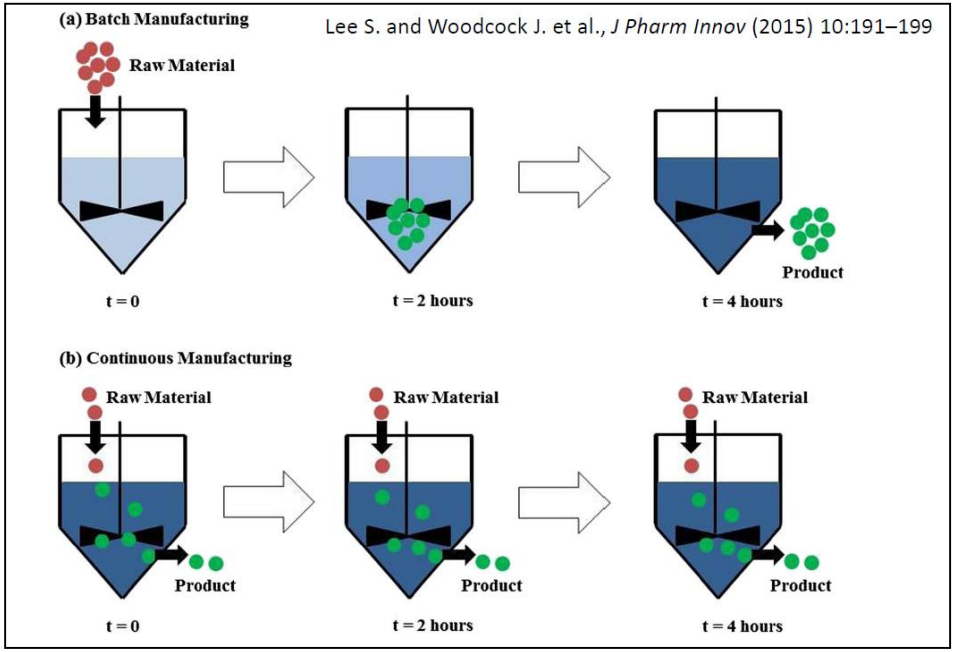
2. Domestic status of regulatory consideration for CM

- Summary of PMDA provisional draft document “PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry”
- Results from AMED sponsored Study Group

3. Challenges and future plan

Continuous Manufacturing is

- A manufacturing method in which raw materials or their blended materials are entered continuously in the manufacturing process throughout the duration of the process, and products are produced continuously through the manufacturing.
- It is feasible that Continuous Manufacturing makes it possible to manufacture a desired amount of products with appropriate quality attributes at a desired timing. With its continuous process operation, Continuous Manufacturing will be expected to maintain production efficiency irrespective of the equipment scale.



Note: However, at present, there are some challenges in the consolidation of all processes, it is assumed that a hybrid type of batch and continuous manufacturing, in which a part of the manufacturing processes are linked.

Trend in US FDA

- As of June 2018, Approvals of Four drug products manufactured by utilizing a continuous manufacturing technology.
  - In July 2015, first approval drug as NDA.
  - In April 2016, first approval drug as sNDA (switching from batch manufacturing to CM)
- ETT GL and MAPP (Manual of Policy & Procedures)
  - Provides recommendations to companies interested in participating in a program involving the submission of CMC information containing emerging manufacturing technology to FDA.（2017.9）
  - Process for Evaluating Emerging Technologies Related to Quality（2017.10）
- Public Docket from C-SOPS（2017.6～9）
  - 24 organization with over 200 comments

ICH Update (1)

- One of the Future ICH Topics proposed by US FDA from 2014 in ICH Informal Quality Discussion Group (IQDG)

- Problem Statement:
  - Continuous manufacturing of pharmaceuticals is a rapidly growing approach for production of both active ingredients and finished products.
  - There is a lack of guidance for regulators and industry on how to implement and regulate continuous pharmaceutical manufacturing.
- Desired State:
  - Clear expectation of scientific and regulatory approaches for continuous manufacturing which will lower perceived barriers and encourage implementation of this emerging technology.

ICH Update (2)

- ICH Assembly, Kobe, Japan, June 2018

The Assembly agreed to begin work on two new Quality topics for ICH harmonization:

- Analytical Procedure Development and Revision of Q2(R1) Analytical Validation (Q2(R2)/Q14)
- Continuous manufacturing (Q13)

Q13 Contents:

- Definitions for CM related concept
- High level scientific principles
- Regulatory requirements (Control strategy, Process Validation, Mathematical model maintenance)

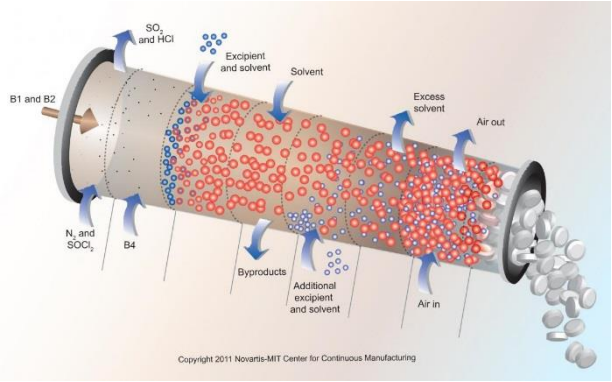
Q13 Scope:

APIs and Drug products (Small molecule and Biotech)

Discussion in ISCMP (MIT)

MIT : Massachusetts Institute of Technology

- International Symposium on Continuous Manufacturing of Pharmaceuticals
- Leading by FDA CDER Director, Dr. Janet Woodcock and hosted by MIT
- Participation from Pharmaceutical industry, Regulators, Academia, Engineering company and so on.
- 1st Sympo in 2014, 2nd Sympo in 2016
- White papers on regulatory requirements for the continuous production of pharmaceutical products were prepared as results of the conference and published in academic journals, respectively



引用元：Novartis-MIT Center for Continuous Manufacturir
（URL: https://novartis-mit.mit.edu/）

1. Gretchen Allison et al, Journal of Pharmaceutical Sciences, 104, p.803–812 (2015)
2. Nasr MM et al, Journal of Pharmaceutical Sciences, 106, p.3199-3206 (2017)

Discussion in 3rd ISCMP (MIT)

Regulatory Presentations from EMA, PMDA and USFDA

Main topics in panel discussion

1. Cooperation between CMC reviewers and GMP inspectors
2. CM for Biotech Products

Regulator updates

US FDA

- Emerging Technology Team (ETT)
- 4 approval products as of June 2018

EMA

- Process Analytical Technology (PAT) team
- Approval product in 2017

  (source : http://www.pharmtech.com/ema-approves-janssen-drug-made-continuous-manufacturing)

PMDA/MHLW

- Innovative manufacturing technology WG in PMDA
- AMED sponsored study groups (Small molecule and Biotech products)
- One approval drug product by global pharma and several consultation experiences (Drug products and small molecule) (As of Sep. 2018)

Progress on regulatory consideration for Continuous Manufacturing in Japan

- 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

PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry

(provisional draft)

March 30, 2018

Pharmaceuticals and Medical Devices Agency

Innovative Manufacturing Technology Working Group

https://www.pmda.go.jp/english/rs-sb-std/rs/0012.html

Contents

-Introduction
-Control Strategy
-Batch Definition
-Validation
-Stability Testing

Summary of the Draft (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.

- This provisional draft was prepared by anticipating the following cases.
  1. Solid oral dosage forms (tablets, etc.) manufactured using drug substances (small-molecule compounds) produced by chemical syntheses.
  2. An ideal production state is achieved.

Summary of the Draft (Control Strategy)

Basic considerations

- There is no fundamental difference between the Batch Manufacturing and Continuous Manufacturing in terms of factors to ensure Critical Quality Attributes (CQA) of the final products.
- In order to understand the relationship between the factors to be controlled and the CQA, it is useful to acquire knowledge of process parameters and in-process controls that can be obtained during the process of establishing the control strategy in accordance with ICH Q8 [R2].

Summary of the Draft (Control Strategy)

CM specific considerations

It is necessary…

- to take into consideration the specific factors that have not been anticipated during Batch Manufacturing, through the qualification of equipment or devices to be used in Continuous Manufacturing, regarding their characteristic factors.
- to consider that multiple factors that need to be controlled should be linked to a CQA not only by handling these factors according to the unit process but also by handling them through the entire manufacturing process.

Summary of the Draft (Control Strategy)

Comparison between Batch and Continuous process

- In Continuous Manufacturing, more flexible handling could be required compared to the traditional Batch Manufacturing, such as the adjustment of process parameters according to the changes in the material attributes.

- The knowledge from existing control strategies used for Batch Manufacturing, linked with process parameters, are also considered beneficial for Continuous Manufacturing in the case of switching the manufacturing method.

Summary of the Draft (Control Strategy)

Control Strategy for CM

It is important…

- to understand the process dynamics within unit operations (e.g. in the granulation process) or between unit operations (e.g. between the blending process and the granulation process).
- to establish a robust control strategy that comprehensively covers the entire manufacturing process and demonstrate that a “State of Control” is maintained.

Keywords for CM control strategy

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.

- Process Dynamics
  - Traceability of the input materials based on the residence time distribution 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
  - A risk based weighting of the control strategy based on potential impact on product quality .

Summary of the Draft (Batch Definition)

There is no difference in the definition of "Batch" between Batch Manufacturing and Continuous Manufacturing.

<Definition of Batch (Lot)>
The definition of Batch (or Lot) is provided in "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" (PFSB Notification No. 1200 dated November 2, 2001) (ICH Q7), which includes remarks on Continuous Manufacturing.

"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."

Summary of the Draft (Batch Definition)

There is no difference in the definition of "Batch" between Batch Manufacturing and Continuous Manufacturing. However, the concept of batch size is different.

<Concept of Batch (Lot) Size>
The batch (or lot) size in Continuous Manufacturing 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

Summary of the Draft (Validation)

For Continuous Manufacturing, it is important to validate the following:

A) Process performance and quality attributes during Continuous Manufacturing are consistently maintained in a "State of Control" by the pre-established control strategy.

B) Based on the dynamics of how raw materials or intermediates flow through the process, chronological changes in quality between batches as well as within a batch remain within an acceptable range.

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Summary of the Draft (Validation)

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

- It is necessary that the batch size can ensure stable performance of the manufacturing process and the product quality during the operating time.
- 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.

Summary of the Draft (Stability Testing)

<Batch Size>

- With Continuous Manufacturing, a batch that is manufactured with any batch size can be the primary batch.
- It is necessary to understand the potential risks arising from the variation in the batch size by risk assessment, etc., and to explain that the primary batch has the same characteristics as other batches manufactured at the established maximum batch size.

Summary of the Draft (Stability Testing)

<Number of Primary Batches>

- Even in Continuous Manufacturing, the basic idea for the number of primary batches needed is the same as that in Batch Manufacturing.
- It is necessary to record information on the sampling points (spot, time etc.) used for the primary batch, as the batch size of the primary batch itself may vary.

Learnings

- There would be some different views on control strategies of CM between APIs, chemical products and biotech 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.

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.

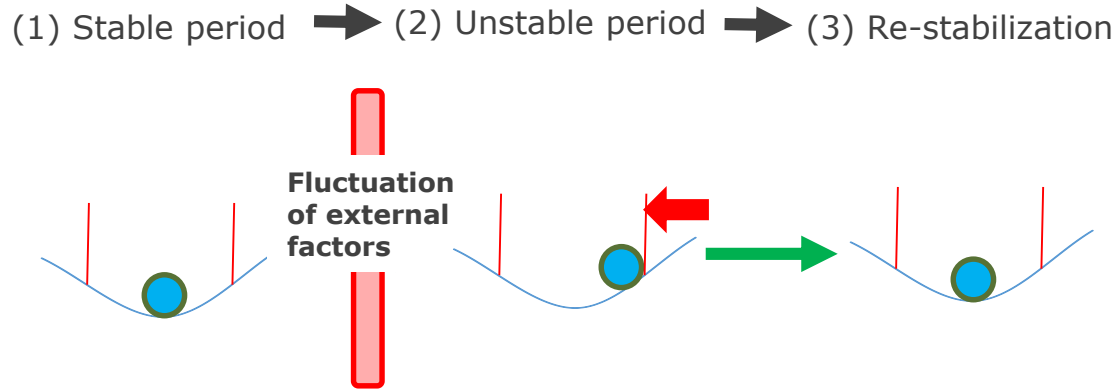
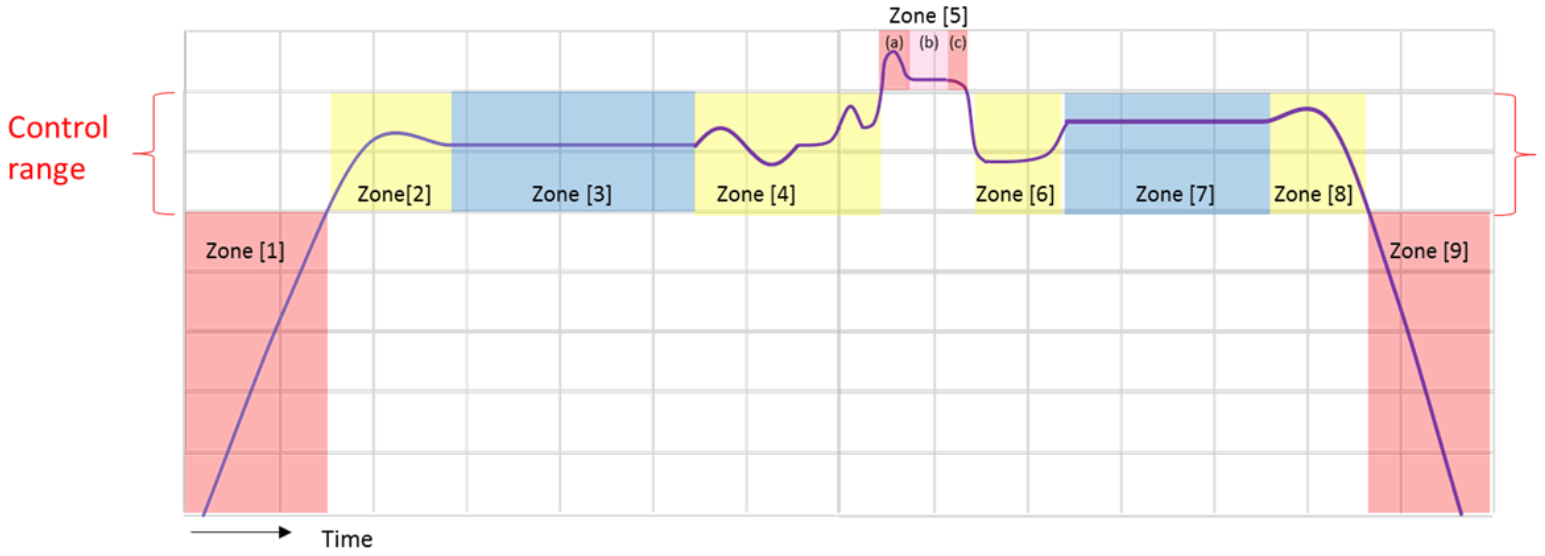


Figure : Conceptual diagram depicting the State of Control
(Note: The red belt indicates the control range and the red arrow indicates the designed control.)

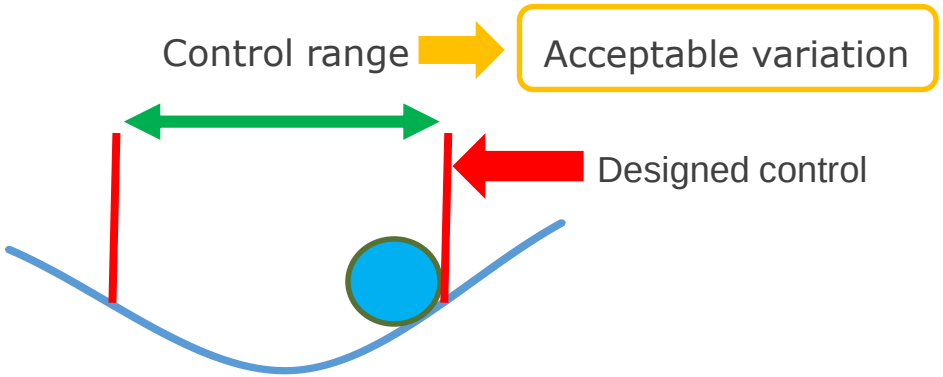
Conceptual diagram depicting relationship between “Steady State” and “State of Control”



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 commen-cement 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 of products	Y	Y/N	N	Y/N	Y	Y	Y	Y/N	N	Y/N	Y

(Y: Yes, N: No, Y/N: Yes or No)

Challenges for State of Control



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)

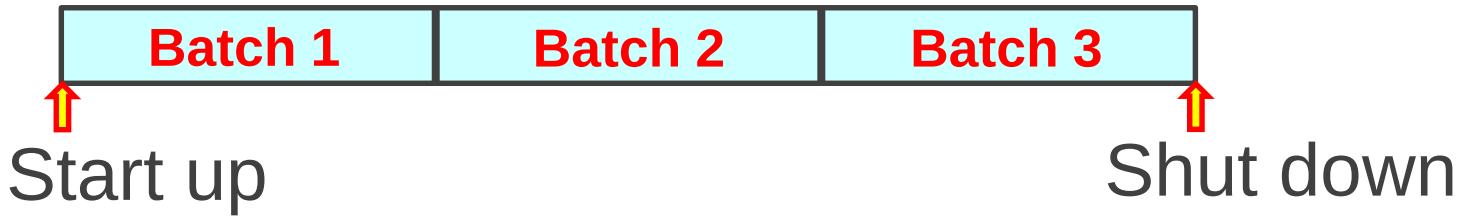
- Specifically for CM
  - The batch size should be established by taking into consideration the operability of manufacturing equipment in a longer operation time and the effects of accumulated substances on manufacturing equipment.

Therefore

Continuous Process Verification

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

Challenges for Validation



- 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?

Future plan

- From 2018 to 2020, New AMED sponsored Study Group
- Strengthen collaboration between CMC review on new technology and GMP inspection（Planning that Reviewers may accompany GMP inspection including the pre/post-application stage）
- Preparation for ICH harmonization
- Preparation for GMP guidance on CM（FY2019, MHLW`s estimated budget request）
- Consideration of CM for chemical API

  - Strengthen collaboration with Academia
- Consideration for introducing CM technology into biotech products

  - Biotech specific technical and regulatory challenges and solutions

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