PMDA's Perspectives on Continuous Manufacturing

Yoshihiro Matsuda, Ph.D.

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

Continuous Manufacturing

- Continuous Manufacturing is a manufacturing method in which raw materials or blended materials enter the manufacturing process continuously, and products are discharged continuously throughout the duration of the process.
- Continuous Manufacturing includes various options: those with all stages of processing from charging raw materials to discharging products are continuous, and those with only certain parts of the manufacturing process are continuous.

A Background – ICH

- One of the Future ICH Topics proposed by FDA
  - Continuous Manufacturing
- Problem Statement
  - There are perceived challenges to implement continuous manufacturing technologies and receive approval of such emerging technologies at the global scale.
  - The potential lack of global harmonization has been identified as the number one barrier to adopting this promising emerging technology in industry surveys.

It will be discussed wheather this proposal should be adapted at ICH Montreal meeting in 2017.

Pharmaceuticals and Medical Devices Agency (PMDA)

A Background – MIT(1)

- International Symposium on Continuous Manufacturing of Pharmaceuticals
- MIT on May 20-21, 2014
- This meeting was brought about by FDA CDER Dr. Janet Woodcock to open up Novartis-MIT Center for Continuous Manufacturing vision to a wider industry view.
- 8 white papers were finally published after discussion at the symposium.
  - (White paper #3) Regulatory and Quality Considerations for CM.

PMDA can support the outcome from the first CM symposium, although PMDA did not join the discussion

A Background – MIT(2)

- (White Paper #3) Regulatory and Quality Considerations for CM
  - Continuous manufacturing(CM) provides multiple opportunities for improvements in pharmaceutical manufacturing →Agree
  - The current regulatory environment supports advancing regulatory science and innovation, including CM →Agree
  - Traditional concepts need to be further explored or modified, to advance the implementation of continuous processes →Agree

(Reference: https://iscmp.mit.edu/sites/default/files/documents/ISCMP2014_WP3_Slides.pdf)

Pharmaceuticals and Medical Devices Agency (PMDA)

A Background – MIT(3)

- The regulatory expectations for assurance of quality and reliable and predictive processing, are the same for batch and continuous processing →Agree
- CM provides additional opportunities to design the appropriate controls into the system, rather than current industry practice on relying mostly on testing materials at the end of the process →Agree
- The flexibility of cGMPs supports new manufacturing technologies including CM →Agree

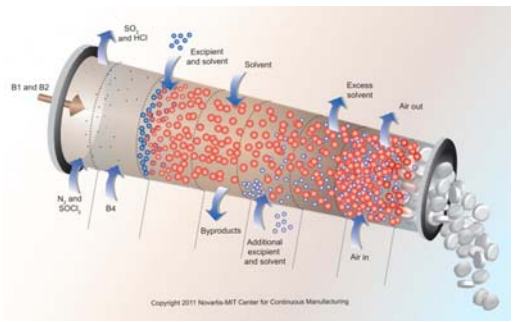
A Background – MIT(4)

- Risk analysis techniques and/or modeling tools should be employed to fully understand the process, the impact on product quality, and to develop the appropriate controls →Agree
- Continuous Quality Verification is well suited to the validation of CM processes →Agree
- Regulatory expectations for cleaning and cleaning validation are the same →Agree

A Background – MIT(5)

- 2nd International Symposium on Continuous Manufacturing of Pharmaceuticals
- September 26-27, 2016
- Attendee: more than 300 people
- Regulatory and Quality Session

  Chair: Dr. Moheb Nasr
  Industry: Dr. Markus Krumme
  US FDA: Dr. Larry Lee
  PMDA: Dr. Yoshihiro Matsuda



A Background – MIT(6)

- Key words;
  - State of control
  - Fitness for Purpose
  - Performance based approach
- Concerns;
  - Regulatory agency's understanding/acceptance of CM with Real Time Release Testing (RTRT)
  - Different control strategies for different regulatory regions(Batch vs. CM, different RTRT models for the same test etc.)
  - Allowance for parallel production of CM and Batch

We are preparing a regulatory white paper.

Expectations for CM

- Opportunities:
  - To avoid poor quality product with PAT etc.
    → Prevention of drug shortage problem
  - To avoid scale-up issues
    → Rapid development
  - To operate multiple scales and dosage manufacturing
    → Personalized medicines
  - To reduce inventory
    → Cost reductions

PMDA would like to support industry to introduce the innovative manufacturing technology.

PMDA's Approaches to CM

We are learning about CM technology.

- Collaboration with AMED sponsored Study Group in Japan.
- Communication between PMDA and Industry that is studying CM.
- Professional Training together with GMP Inspectors.
  - External specialists/scientists give us lectures.
- Collaboration with related societies.
  - PAT, Multivariate analysis etc.
- Collaboration with other regulators.

(AMED: Japan Agency for Medical Research and Development)

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 Regulatory Science

IMT-WG Activity Plan

- To organize face-to-face meeting(s) with FDA and EMA
- To visit continuous manufacturing sites
- To discuss with stakeholders including industries and academia
- To collaborate with a national research project on pharmaceutical quality control
- To publish a draft points-to-consider document about CM in spring, 2017

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 Sites Visit (1)

- A visit to a Drug Product CM site in late Oct-Nov, 2016
  - Discussion Points
    - Control Strategy for CM
      - Feeding, PAT tools, RTRT,
    - Material Properties influence in CM
    - Impurity
    - Tracking and Tractability of materials
    - Batch definition
    - Process validation etc.

It's not PMDA activity. This site visit is a part of AMED sponsored Study Group activities

Pharmaceuticals and Medical Devices Agency (PMDA)

CM Sites Visit (2)

- A visit to a Drug Substance CM site in late March, 2017
  - Discussion Points
    - Process Development
    - Equipment Design (Flow Reactor)
    - Control Strategy for CM
      - Kinetics approach, PAT tools, Design Space, Divert-to-waste, Productivity Rates
    - Impurity
    - Material Traceability (Residence Time)
    - State of Control
    - Process validation etc.

A Face-to-Face Meeting with Regulators

- We had a meeting with FDA in Nov, 2016.
  - Discussion Points
    - Product specific matters
    - Emerging Technology Team
    - Training for staffs
    - Collaboration
- We had a meeting with EMA (PAT Team) in Feb, 2017.
  - Discussion Points were the same as with FDA.

Clarification for CM Implementation

A draft Points-to-consider document.

- We are focusing on 4 topics
  - Control Strategy
  - Batch Definition
  - Process Validation
  - Stability Testing

Note : This document assumes drug products of chemically synthesized drug.

Control Strategy (draft) (1)

- Factors to ensure CQAs are the same between CM and Batch Manufacturing(BM)
- But some different CS for CM can be taken

↓

Performance based Approach

- Unlike the manufacturing with fixed process parameters, process parameters can be adjusted flexibly for variables detected by PAT etc.

↓

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

Control Strategy (draft) (2)

- 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)
- Fitness for Purpose
  - Weighting of control depending on the influences on pharmaceutical products.

Batch Definition (draft)

- 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 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 (draft) (1)

- The basic concept of process validation for CM is not different from that for BM. Specifically for CM;
  - To maintain the state of control by control strategy
  - For example, the assurance that the quality's time-dependent variation can be controlled within allowance range not only among batches, but also in a batch.
- 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.

Process Validation (draft) (2)

- Scale for PV batches/lots
  - 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.
- 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 (draft)

- 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

- How to gain experience of CM?
- How to share our experience of CM?
- How to encourage industries?
- How to return profits to patients?

Let's move forward!

Thank you for your attention