Continuous Manufacturing PMDA's Perspective

Yoshihiro Matsuda, Ph.D.

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

A Background – ICH(1)

- One of the Future ICH Topics proposed by FDA
  - Continuous Manufacturing of Pharmaceuticals
- 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.

A Background – ICH(2)

- Desired State:
  - Clear expectation of scientific and regulatory approaches for continuous manufacturing which will lower perceived barriers and encourage implementation of this emerging technology.
- Timelines:
  - Start in the Spring of 2018
  - The target completion is in the Fall of 2020

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.

A Background – MIT(2)

- (White Paper #3) Regulatory and Quality Considerations for Continuous Manufacturing
  - 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)

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

A Background – MIT(4)

- The flexibility of cGMPs supports new manufacturing technologies including CM →Agree
- 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

Approaches to CM at PMDA(1)

- Before ICH activity for CM, we have a lot to learn regarding CM.

- Collaboration with AMED sponsored Study Group.
- Communication between PMDA and Industries who are studying CM.
- Collaboration with other regulators.

(AMED: Japan Agency for Medical Research and Development)

Approaches to CM at PMDA(2)

- Professional Training together with GMP Inspectors.
  - External specialists/scientists give us lectures.
- Collaboration with a society, e.g. JSPME(Japan Society of pharmaceutical Machinery and Engineering).
  - PAT, Multivariate analysis etc.

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 Regulatory Science

IMT-WG Activity Plan (J-FY 2016*)

- 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 points-to-consider about CM

*; April, 2016 – March, 2017

Perspective on CM(1)

- 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 medicine
  - To reduce inventory
    → Cost reductions

Perspective on CM(2)

- PMDA is positive towards CM
- Issues to solve
  - Definition of Batch/Lot
    - How to determine reference/representative batch/lot for PV or Stability Test?
  - Handling deviations
    - How to restart manufacturing?
  - Cleaning Strategies
    - How to set a timing of Cleaning

Strongly Recommend to have PMDA consultations prior to submission!

Potential Regulatory Benefits for Industries

- Benefits
  - To communicate with PMDA IMT-WG
  - To gain PMDA's confidence
- Expectations for industries
  - What can industries commit to?
    - Continuous verification for CM
    - To return profits to patients?

Thank you for your attention