PMDA's Perspectives on Continuous Manufacturing

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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 encourage 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 Industries who are studying CM.
- 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.
- 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 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

CM Sites Visit

- 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.
- We will visit a Drug Substance CM site in March, 2017.

It's not PMDA activity. These site visits are parts of AMED sponsored Study Group activities

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/Lot Definition
  - Process Validation
  - Stability Test

Control Strategy (draft)

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

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Performance based Approach

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

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

Batch/Lot Definition (draft)

- The definition of Batch/Lot is same between CM and BM.
- How to set the Batch/Lot size can be different.
  - A production run time and speed
  - An amount of incoming raw material

The Batch/Lot size can be changed for each production. However the maximum size should be defined in advance.

Process Validation (draft) (1)

- The purpose of PV is same between CM and BM. Specifically for CM;
  - To ensure 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/lots, but also in a batch/lot.
- The number of PV batches/lots
  - Basically three PV batches/lots are required as same as batch manufacturing in Japan.
  - It would be able to use manufacturing batches/lots during development as PV batches/lots by redefining it on PV implementation plan.

Process Validation (draft) (2)

- Scale for PV batches/lots
  - Fundamentally the maximum size(run time and speed) is not needed for all of three PV batches/lots because it should be ensured that the CM is under "the state of control". However at least one batch/lot should be the maximum size.
- Change the maximum size after a PV study
  - At least one PV(prospective process validation or concurrent process validation) batch/lot data should be required.

Stability Test (draft)

- Batch/Lot size
  - It would be possible to consider the batch/lot which was manufactured by different batch/lot size to be the primary batch/lot of the drug substance/product.
  - Even if it is under the state of control, it would be important to understand potential risks of batch/lot size differences and to explain that it exhibits the same property between the primary batch/lot and the commercial scale batch/lot.
- The number of the primary batches/lots
  - Data from formal stability studies should be provided on at least three primary batches/lots as ICH Q1A(R2) described.
  - Because the batch/lot sizes are different, the information of sampling points should be recorded.

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