PMDA/JP Perspective on Continuous Manufacturing

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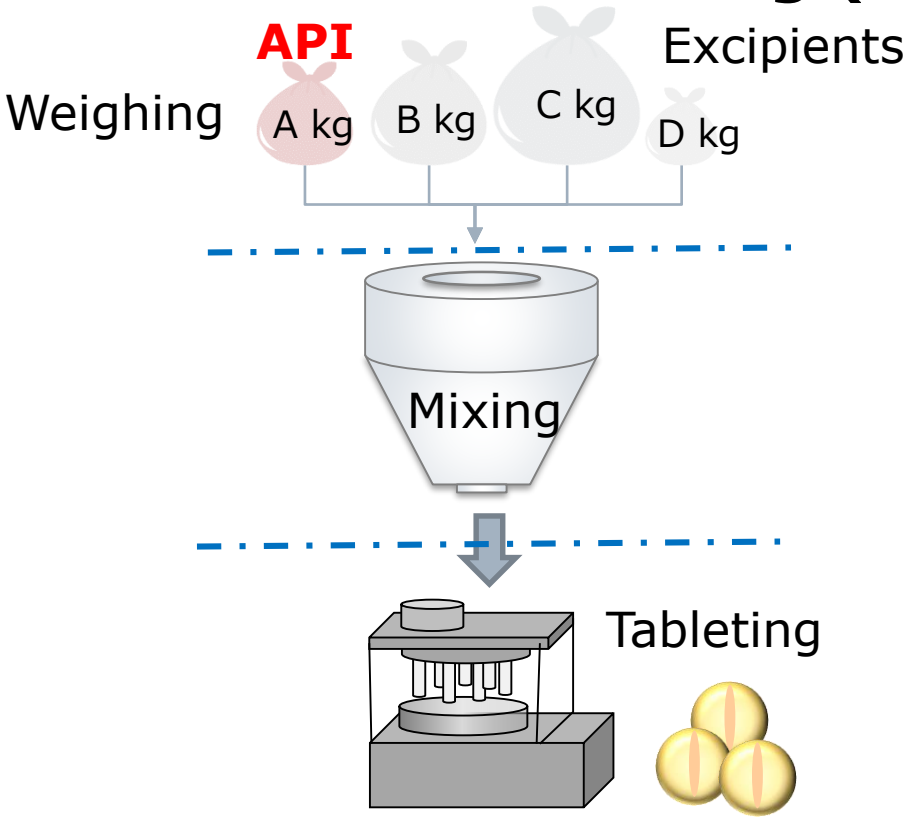
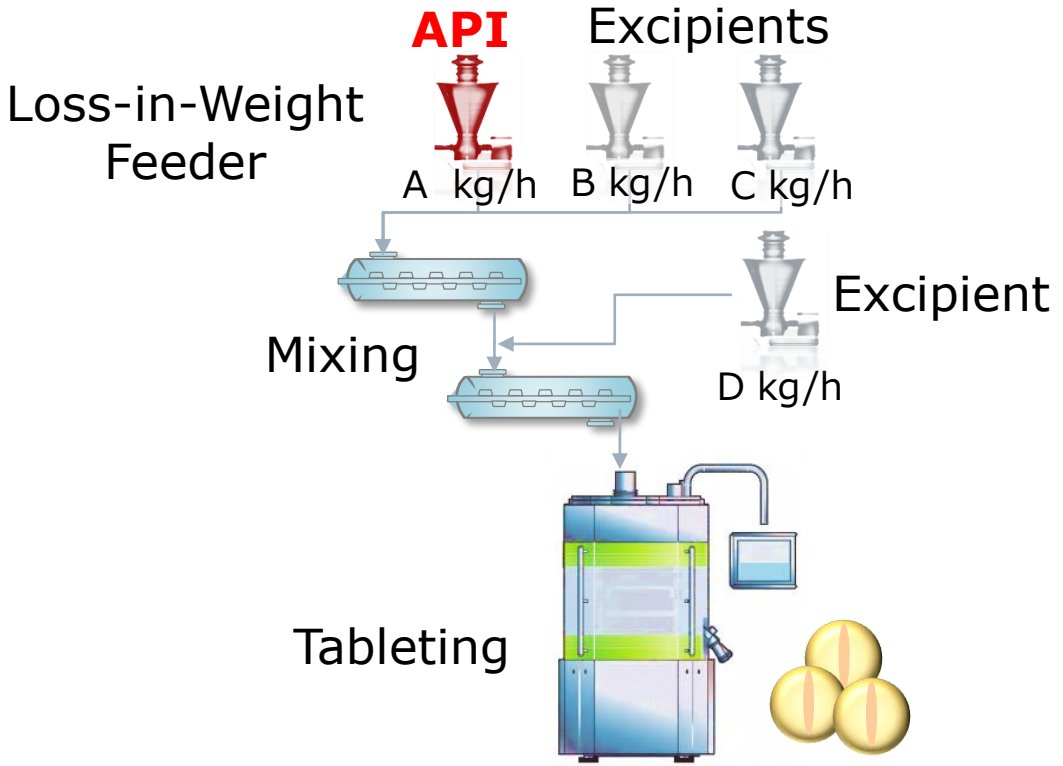
What is continuous manufacturing (CM)?

Batch Manufacturing (BM)

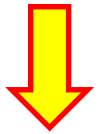


CM



Why is CM drawing attention?

- Are there any problems with conventional BM?

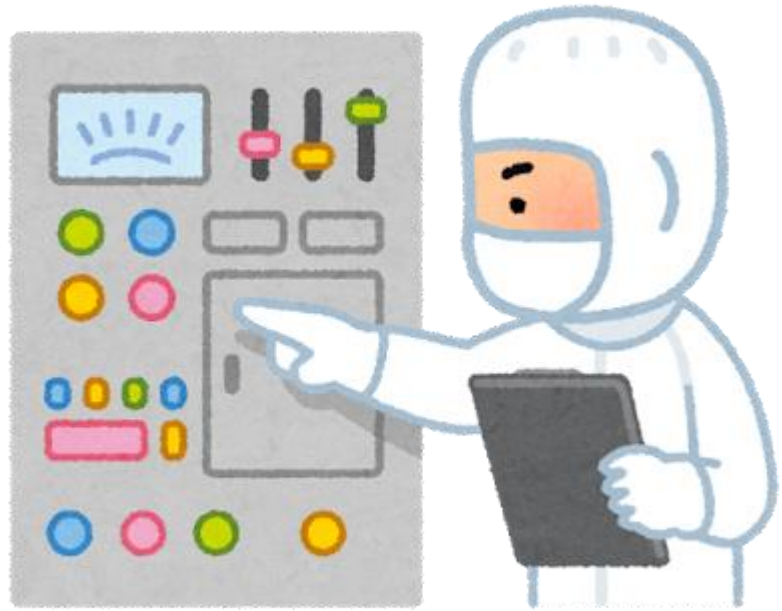


- There is nothing wrong with BM, which should remain one of the manufacturing methods to be used in the future.
- However, CM may offer us what is difficult to achieve with BM.

Expectations for CM

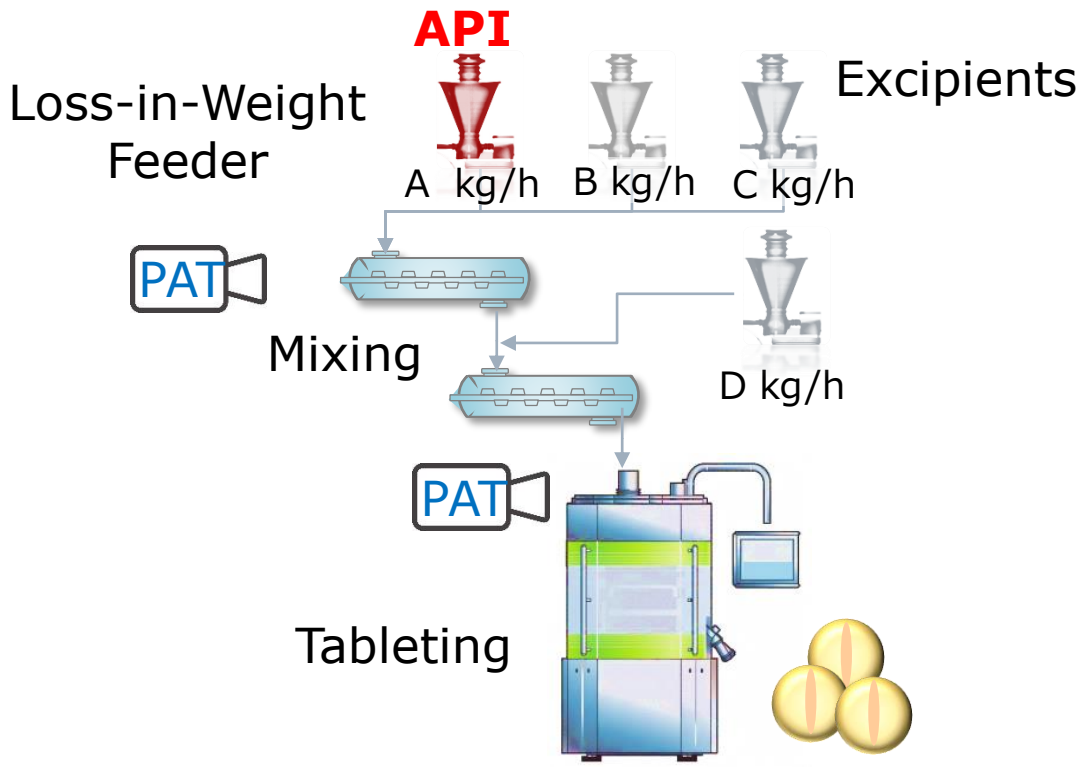
- Flexible manufacturing
  - Production in response to demand
- Detectability of poor quality products
  - Prevention of drug shortage problems
- Prevention of waste
  - Promotion of Green chemistry
  - Cost reduction

and so on



CM offers us a wider choice of manufacturing methods

What is the difference in control strategy between BM and CM?



In CM, fluctuations that occur in the upstream process directly affect the downstream process, so more integrated system management is required compared to conventional BM.

How to control CM specific matters?

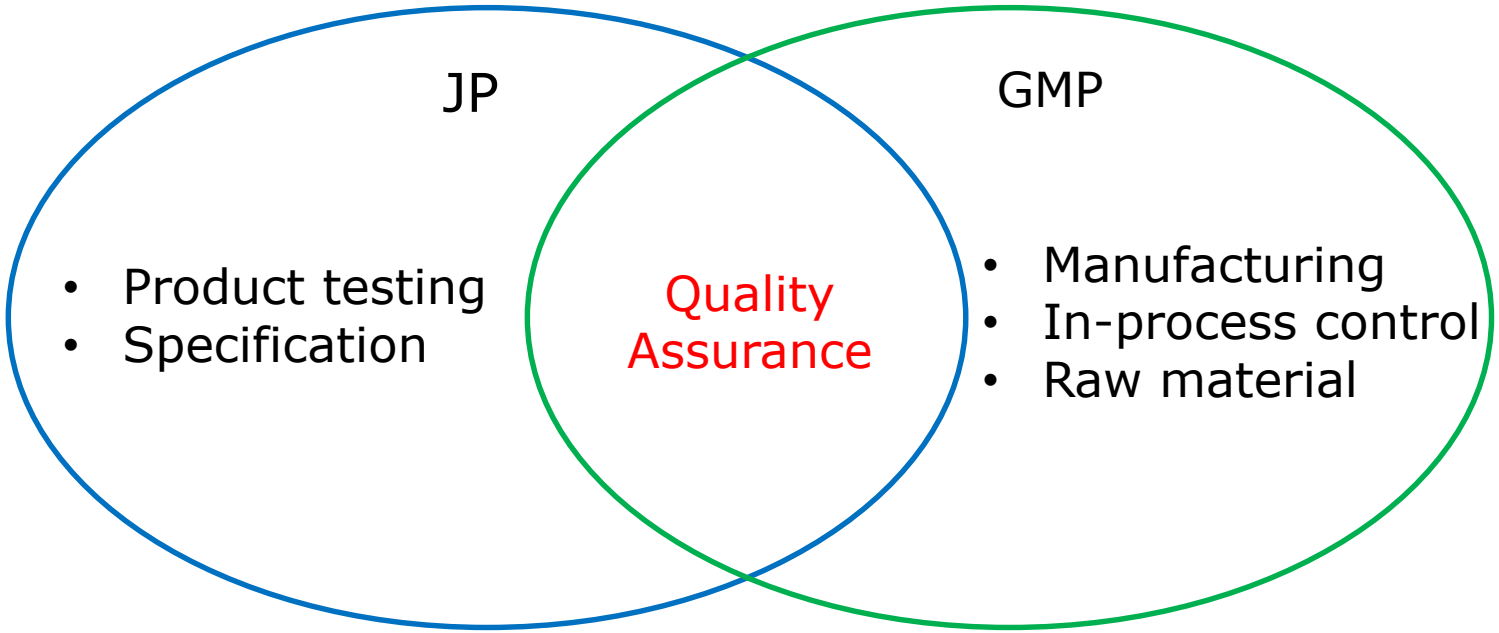
- CM specific matters
  - Equipment design and system integration
  - Material traceability
  - Process dynamics, etc.

- Controls
  - Traditional off-line testing
  - Models
    - NIRS (Chemometric models)
    - Process models (Mechanistic models)
    - Multivariate Statistical Process Control (MSPC), etc.

How can JP contribute to CM?

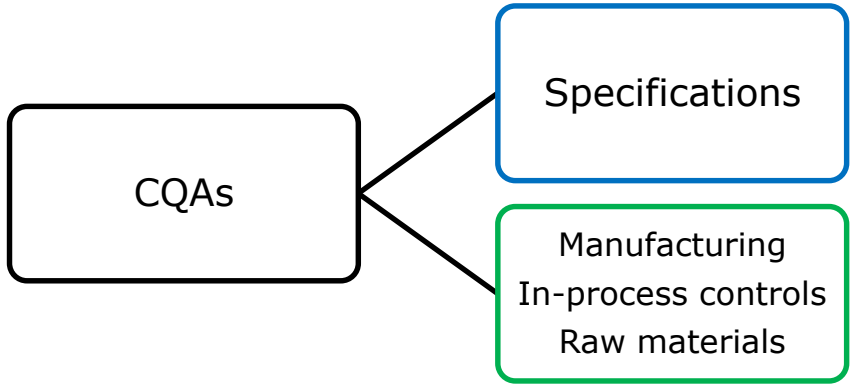
- General Tests, Processes and Apparatus
  - Raman Spectroscopy
- General Information
  - Basic Concepts for Quality Assurance of Drug Substances and Drug Products
  - Basic Concept of Quality Risk Management
  - Glossary for Quality by Design (QbD), Quality Risk Management (QRM), and Pharmaceutical Quality System (PQS)
  - Near Infrared Spectrometry
  - A Basic Concept of the Quality Assurance on Biotechnological Products (Biopharmaceuticals)
  - Criteria for Content Uniformity in Real Time Release Testing by Process Analytical Technology

Basic Concepts for Quality Assurance of Drug Substances and Drug Products



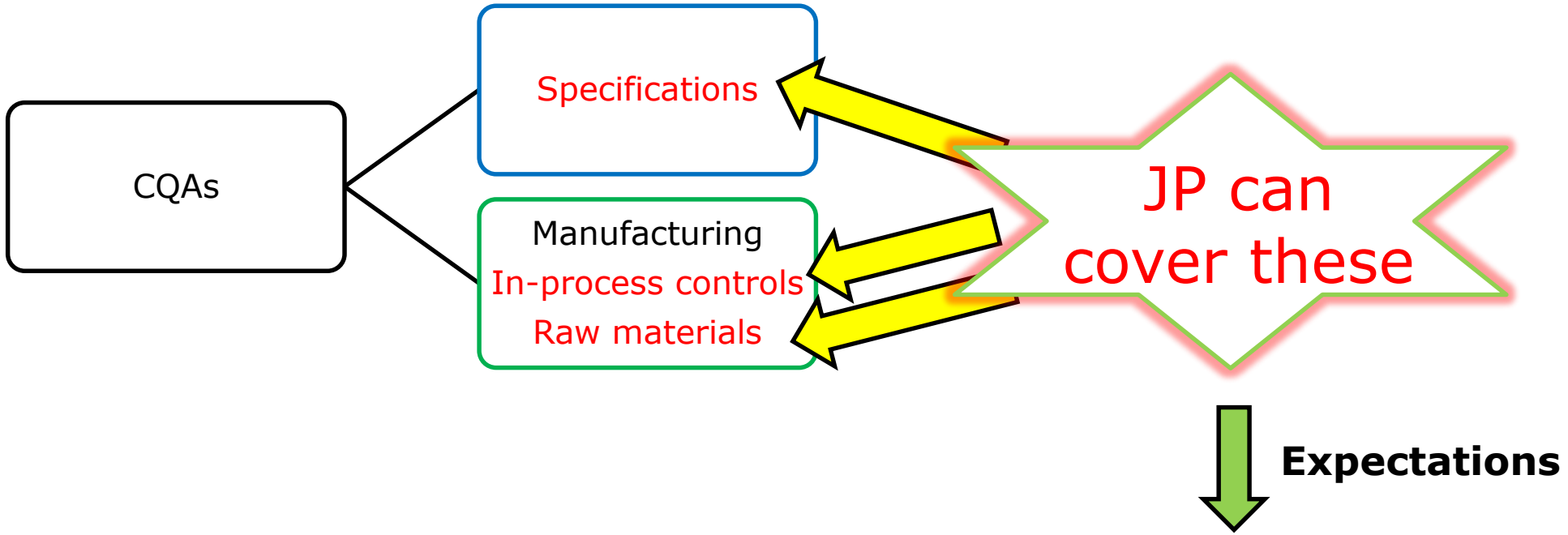
The concept for quality control

- Quality testing of final products (drug substances or drug products)
- Control of manufacturing processes, including management of raw material and other materials



CQA: Critical Quality Attribute

Expectations of JP



Models

- Process models (Mechanistic models)
- Multivariate Statistical Process Control, etc.

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 (IMT-WG)
  - AMED research group for small molecule
    - Study on quality assurance of pharmaceutical CM
  - AMED research group for large molecule
    - Study on quality control strategies for the practical application of CM of biopharmaceuticals
    - Communication between USP and PMDA

AMED: Japan Agency for Medical Research and Development

PMDA's Milestones

- PMDA 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
- AMED research group
  - Document: "Points to Consider Regarding Continuous Manufacturing"

    http://www.nihs.go.jp/drug/section3/AMED_CM_PtC.pdf
  - Document: "State of Control in Continuous Pharmaceutical Manufacturing"

    http://www.nihs.go.jp/drug/section3/AMED_CM_CONTROLST.pdf
  - Approach to establishment of control strategy for oral solid dosage forms using continuous

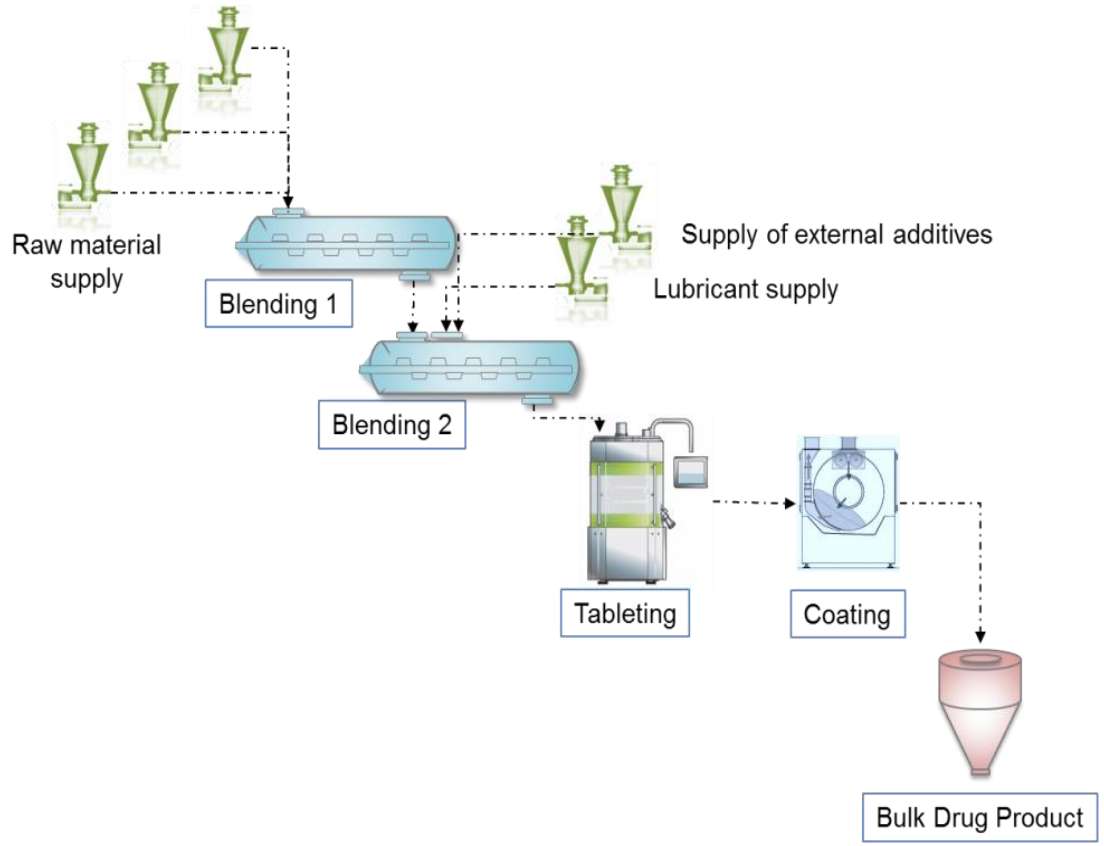
    Chemical and Pharmaceutical Bulletin 69(2), 211-217, 2021
  - Control strategy and methods for continuous direct compression processes

    Asian Journal of Pharmaceutical Sciences 16, 253-262, 2021

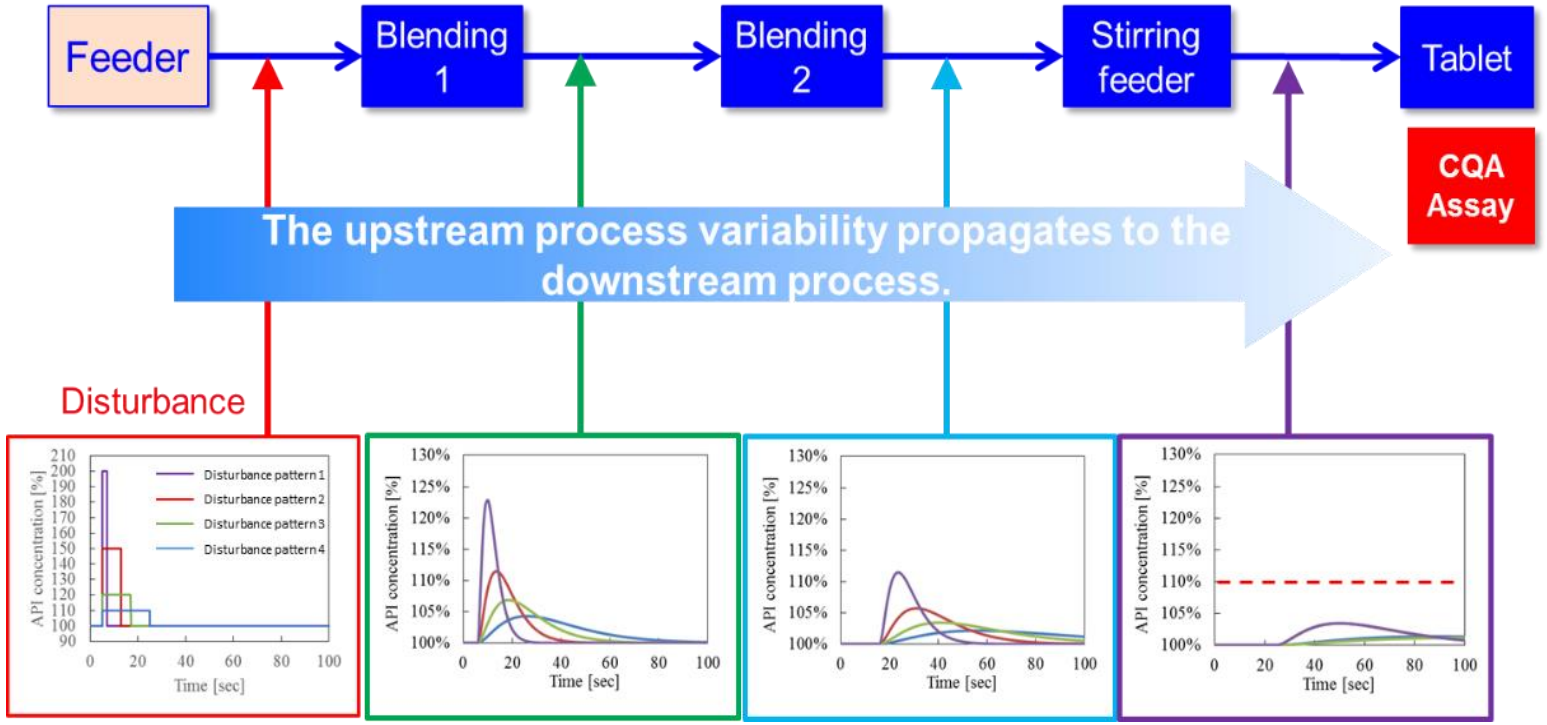
An Example of a Process Model: Residence Time Distribution (RTD) model

- The RTD model is a well-known theory in reaction engineering and can provide information about material flow and component concentration within the reactor.
- In the continuous direct compression process, the RTD model enhances the understanding of how the API and each excipient component flow in the blender and how they are blended.

Schematic diagram of the continuous direct compression process

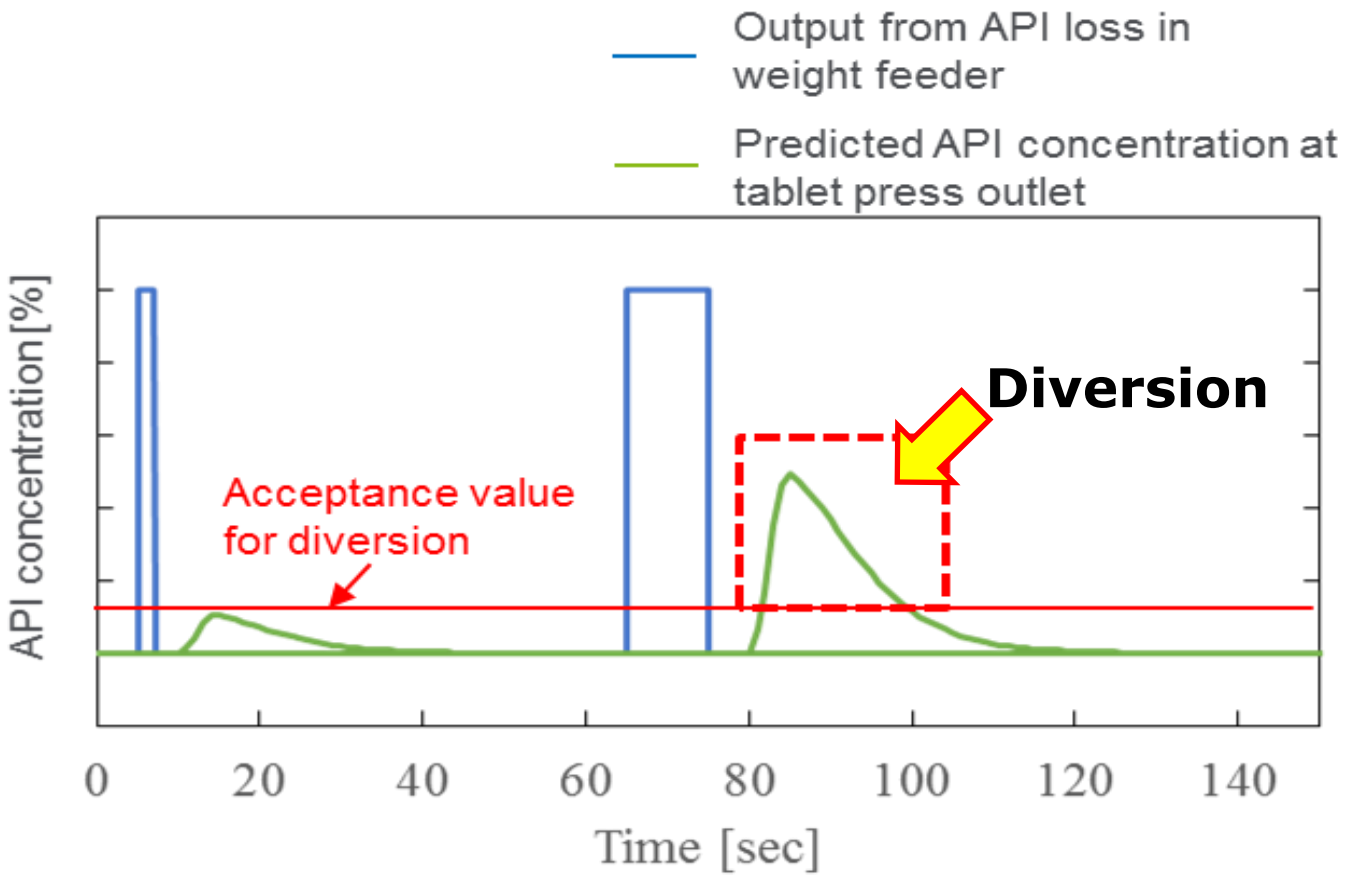


Variations of the Loss-In-Weight (LIW) feeder and an image of propagation to each process



It is possible to predict how the variation caused by the LIW feeder propagates in the process, how it affects the quality of the final drug product, and to set the acceptable range of variation of the LIW feeder.

A process control image based on the API concentration predicted by RTD



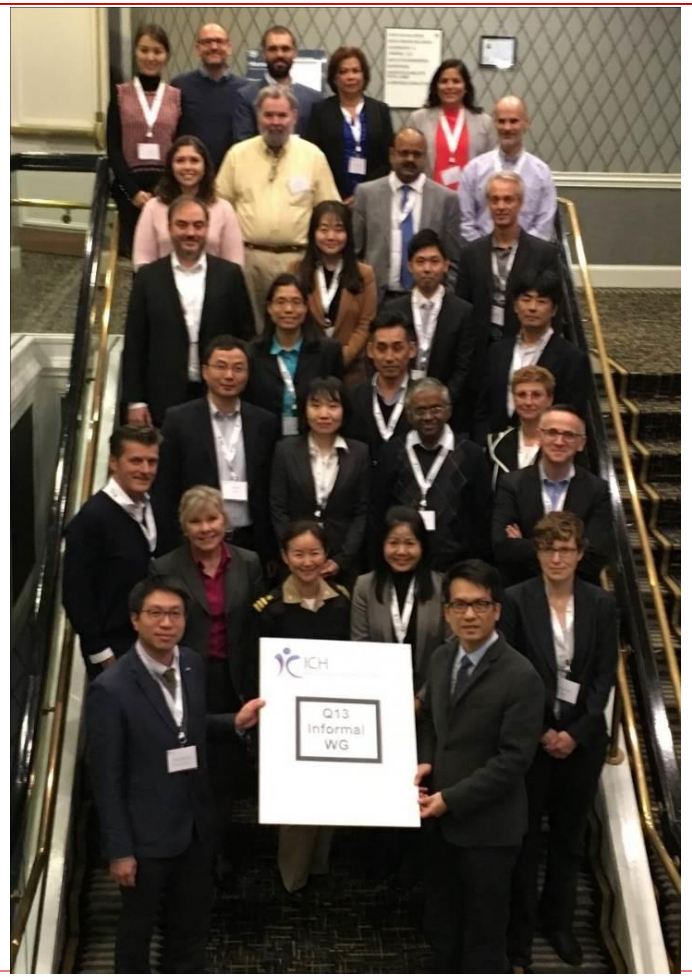
Using the RTD model, the magnitude and length of acceptable variation of the LIW feeder can be established from its impact on the CQA of Assay and can be incorporated into the control strategy of the continuous direct compression process.

Diversion Strategy

ICH Q13
Continuous Manufacturing of Drug Substances and Drug Products

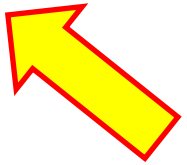
- Rapporteur: Dr. Sau (Larry) Lee (FDA, US)
- Regulatory Chair: Dr. Yoshihiro Matsuda (MHLW/PMDA)

- ANVISA, Brazil
- BIO
- EC, Europe
- EFPIA
- FDA, US
- Health Canada, Canada
- HSA, Singapore
- IGBA
- JPMA
- MFDS, Republic of Korea
- MHLW/PMDA, Japan
- NMPA, China
- PhRMA
- Swissmedic, Switzerland
- TFDA, Chinese Taipei
- IFPMA
- APIC
- IPEC
- National Center, Kazakhstan
- USP
- PIC/S
- EDQM



Concept Paper

- Definitions and regulatory concepts
  - Definition of CM, different modes of CM, state of control, etc.
- Scientific approaches
  - Concepts related to control strategy development, system dynamics, sampling, detection and removal of non-conforming material, material traceability, process models, etc.
- Regulatory expectations
  - Information to include in the dossier
  - Process validation and continuous process verification
  - Some aspects related to lifecycle management



An RTD model is one of key elements.

Current Status

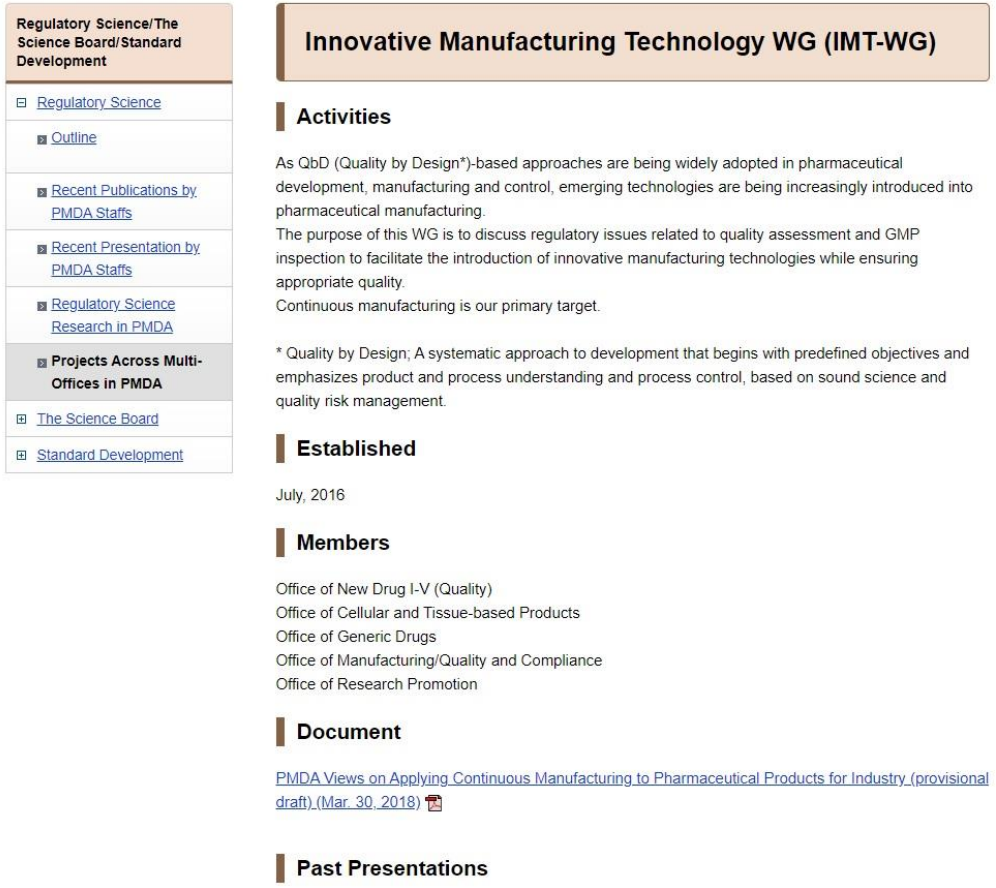
- June, 2021: Step1 sign-off & Step2a/2b endorsement
- June, 2021~: Regional Consultation
- November, 2022: Step4

Prospects for the future

- CM holds the potential to be a standard of drug manufacturing in the pharmaceutical industry.
  - Many regulatory agencies including PMDA and US FDA, supports the implementation of CM technology positively.
  - CM is a necessary technology to realize Industry 4.0（a concept given to the current trend of automation and data exchange in manufacturing technologies)
  - CM is a technology which can innovate manufacturing and distribution of pharmaceuticals.

This leads to the benefit of everyone.

How to stay up to date with PMDA



Regulatory Science/The Science Board/Standard Development

- ⊟ Regulatory Science
  - Outline
  - Recent Publications by PMDA Staffs
  - Recent Presentation by PMDA Staffs
  - Regulatory Science Research in PMDA
  - **Projects Across Multi-Offices in PMDA**
- ⊞ The Science Board
- ⊞ Standard Development

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

This website will provide compiled information on domestic regulations applicable to pharmaceutical CM including:

- Presentation files
- Regulatory documents, etc.

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

Thank you for your attention