The Landscape of Continuous Manufacturing in Japan

Pharmaceuticals and Medical Devices Agency
Office of Cellular and Tissue-based Products

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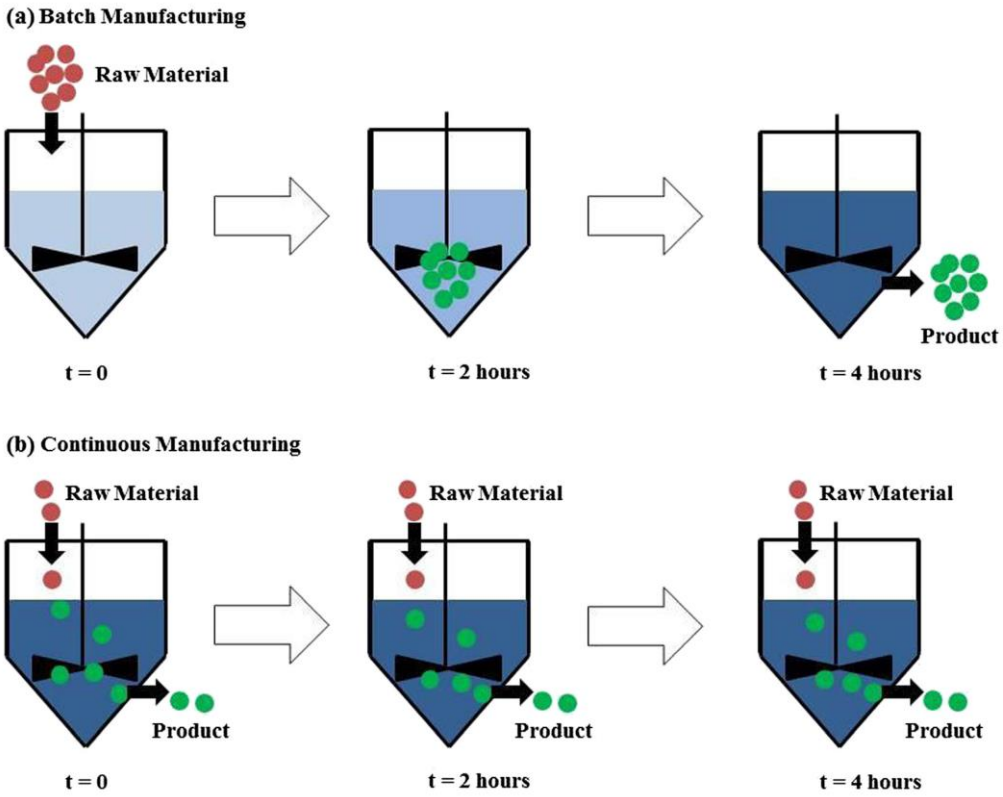
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Outline

1. What is the Continuous Manufacturing (CM)?
2. New ICH topics - CM
3. Innovative Manufacturing Technology Working Group
4. AMED study group

What is the CM?

- A harmonized definition of CM in pharmaceuticals area has not been provided yet.
- However, PMDA considers it as …

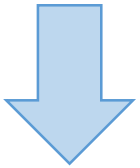


Lee S. and Woodcock J, et al., *J Pharma Innov* (2015)10; 191-9

CM 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.

Why is CM so focused?

- Does the batch manufacturing have some problems?



- No. The batch manufacturing is still working well in pharmaceutical area.
- However we expect the CM to bring us additional opportunities.

Opportunities by CM

- Realization of flexible manufacturing
  - Production in response to demand
- Detectability of poor quality product
  - Prevention of drug shortage problem
- Prevention of waste
  - Promotion of Green chemistry
  - Cost reduction

and so on

Expectation to bring innovation

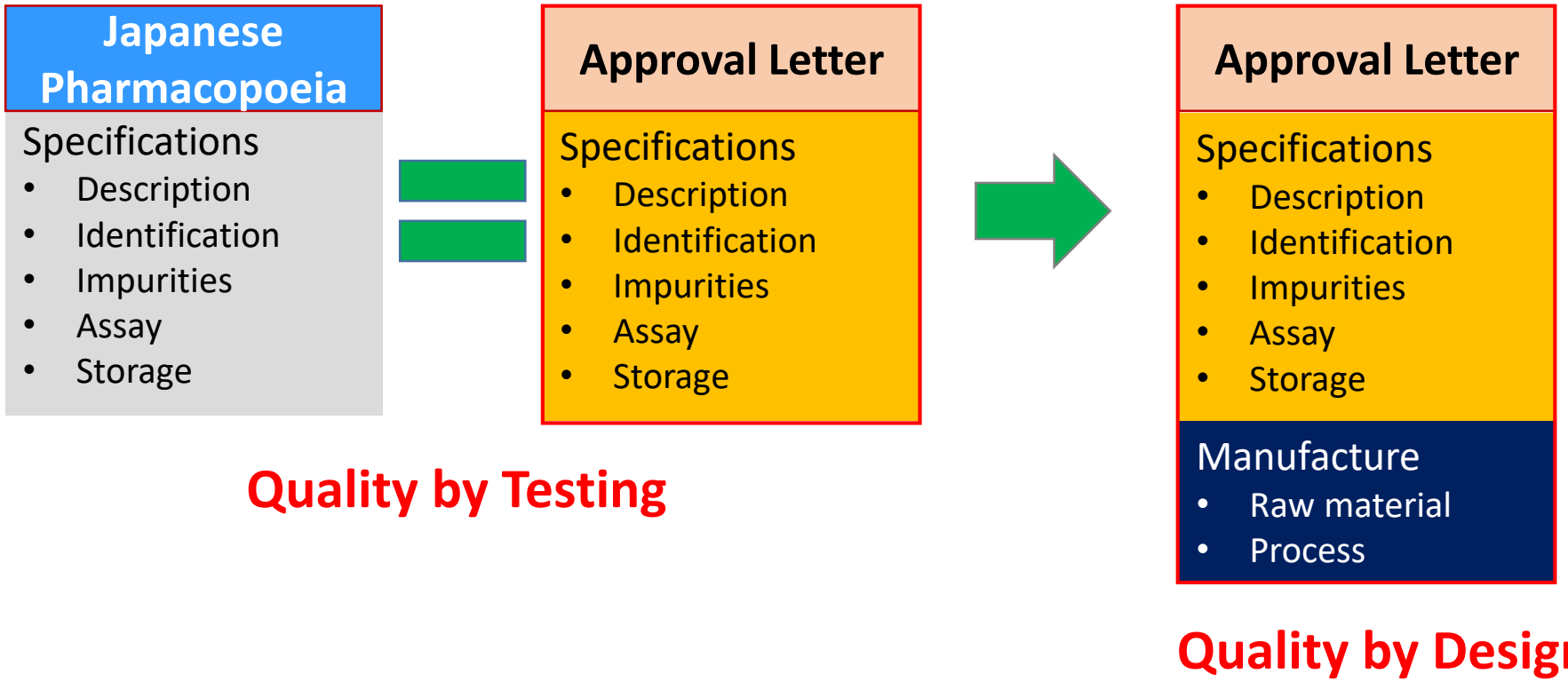
Why now?

- CM is not new technology in other area, such as petroleum refining, food processing, but in pharmaceutical area・・・

⇩ **New Paradigm**

- Now it is ready for new technologies by both regulators and pharmaceutical companies.

The Change of approved matters in Japan



Regulatory expectations for CM

- Our expectations for pharmaceutical quality are the same in between CM and Batch Manufacturing.
- However we expect that CM is a key enabler for modernization of pharmaceutical manufacturing to improve
  - Agility
  - Flexibility
  - Robustness

  in the manufacture of pharmaceuticals

A new ICH guidelines: ICH-Q13 on CM

- One of the new ICH Topics proposed by FDA.
- ICH Assembly agreed to begin work on Q13 at the Kobe meeting.

- Problem Statement
  - There are perceived challenges to implement CM 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.

A new ICH guidelines: ICH-Q13 on CM

- ICH-Q13 WG had first face to face meeting in Charlotte, NC, USA on 12-15 Nov 2018.
  - Rapporteur; Dr. Sau Lee (FDA, United States)
  - Regulatory Chair; Dr. Yoshihiro Matsuda (MHLW/PMDA, Japan)
  - Approximately 35 experts

- Progress at the meeting
  - Endorsement of Q13 Concept Paper and Business Plan by ICH Management Committee
  - Establishment of formal ICH Expert Working Group

ICH-Q13; Continuous Manufacturing of Drug Substances and Drug Products

- Objectives: The new ICH guideline document on CM will
  - Capture key technical and regulatory considerations that promote harmonization, including certain Current Good Manufacturing Practices (CGMP) elements specific to Continuous Manufacturing (CM),
  - Allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for the manufacture – drug substances and drug products – of small molecules and therapeutic proteins for new and existing products,
  - Provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies used in the manufacture of drug substances and drug products.

ICH-Q13; Continuous Manufacturing of Drug Substances and Drug Products

- This new guideline will
  - Harmonize CM-related definitions
  - Articulate key scientific approaches for CM
  - Harmonize regulatory concepts and expectations for CM across the regions

- Timing
  - The anticipated time to complete the guideline will be 3 years.
    - Step 2b: June 2020
    - Step 4: November 2021

CM in Japan

- Application approvals
  - Verzenio (abemaciclib) tablets [Eli Lilly Japan K.K.]
    - 1st NDA approval (September 2018)

- Number of industry meetings on CM
  - several chemical products (DS/DP) to date
    - Multiple meetings per product with industry have done
    - Including some products under review
    - No experience for biotechnological / biological products

Innovative manufacturing Technology Working Group (IMT-WG)

- Established in PMDA since July, 2016.
- Purpose
  - To establish PMDA's perspective on the latest technologies of pharmaceuticals 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, Cellular and Tissue-based products, Generic Drugs
  - From Office of Manufacturing / Quality and Compliance
  - From Office of Research Promotion

Innovative manufacturing Technology Working Group (IMT-WG)

- IMT-WG had F2F meetings with USFDA in 2016, 2018 and EMA in 2017
- IMT-WG visited CM sites of drug substance and drug product (chemical entities)
- IMT-WG joined some quality consultations regarding CM across multi-offices in PMDA.
- IWT-WG has good collaboration with national research projects on pharmaceuticals quality control.

http://www.pmda.go.jp/english/rs-sb-std/standards-development/cross-sectional-project/0012.html

AMED study group (Chemicals)

- Study on quality control techniques in a new development and manufacturing change of pharmaceuticals
  - It was started on Aug 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 (Reviewers, GMP inspectors)
    - National Institute of Health Science (researchers)
    - Universities
    - Industries

Research Outcome (Chemicals)

- Two documents were published
  - 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

- In the Points-to-consider document, the study group focused on 4 topics by following inputs from the Japan Pharmaceutical Manufacturers Association (JPMA) members.
  - Control Strategy
  - Batch Definition
  - Process Validation
  - Stability Testing

A provisional draft document for CM

- PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft) was published in March 30, 2018.
  - This provisional draft document was developed by Innovative Manufacturing Technology Working Group (IMT-WG) at PMDA, based on the point-to-consider document

https://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0018.html

AMED research group (Bio)

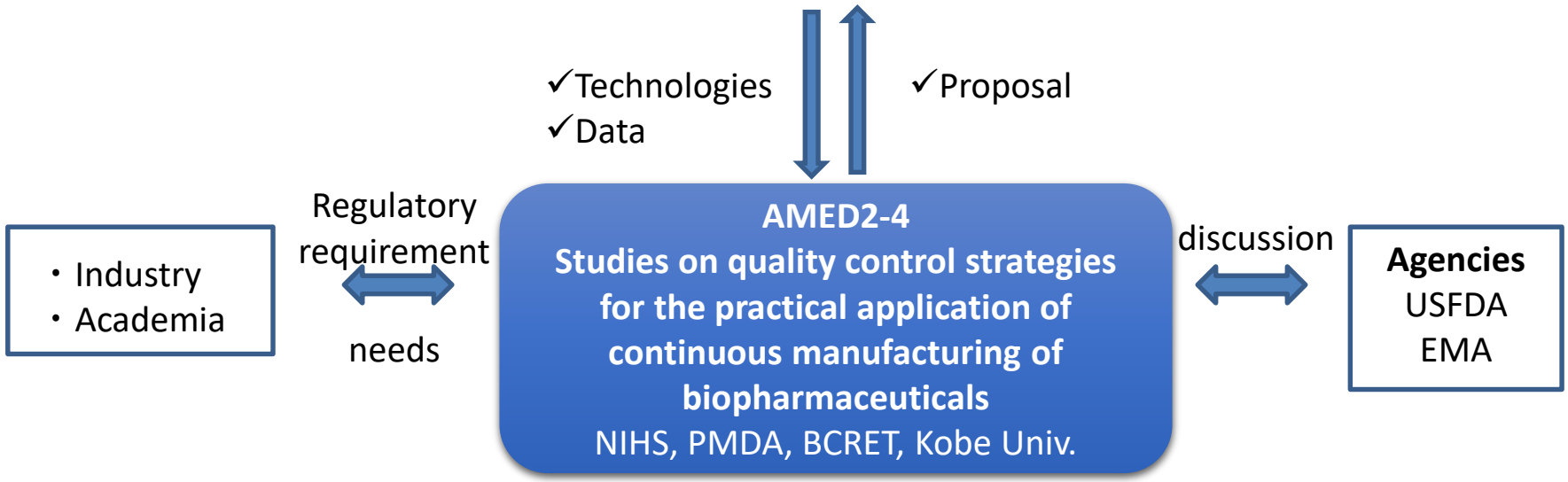
- Study on quality control strategies for the practical applicant of CM of biopharmaceuticals
  - It was started on May 21st, 2018 (3y).
  - Members
    - PMDA
    - NIHS (researchers)
    - Universities (Kobe Univ., Osaka Univ., Gifu Pharm. Univ.)
    - Industries
      - JPMA (Biopharmaceutical committee)
      - PDA Japan Chapter
        (API-GMP committee, Bio-virus safety committee)
      - Manufacturing Technology association of Biologics
  - Observers
    - AMED, MHLW, METI, BCRET

AMED Program: Project Focused on Developing Key Technology for Discovering and Manufacturing Drugs for Next-Generation Treatment and Diagnosis

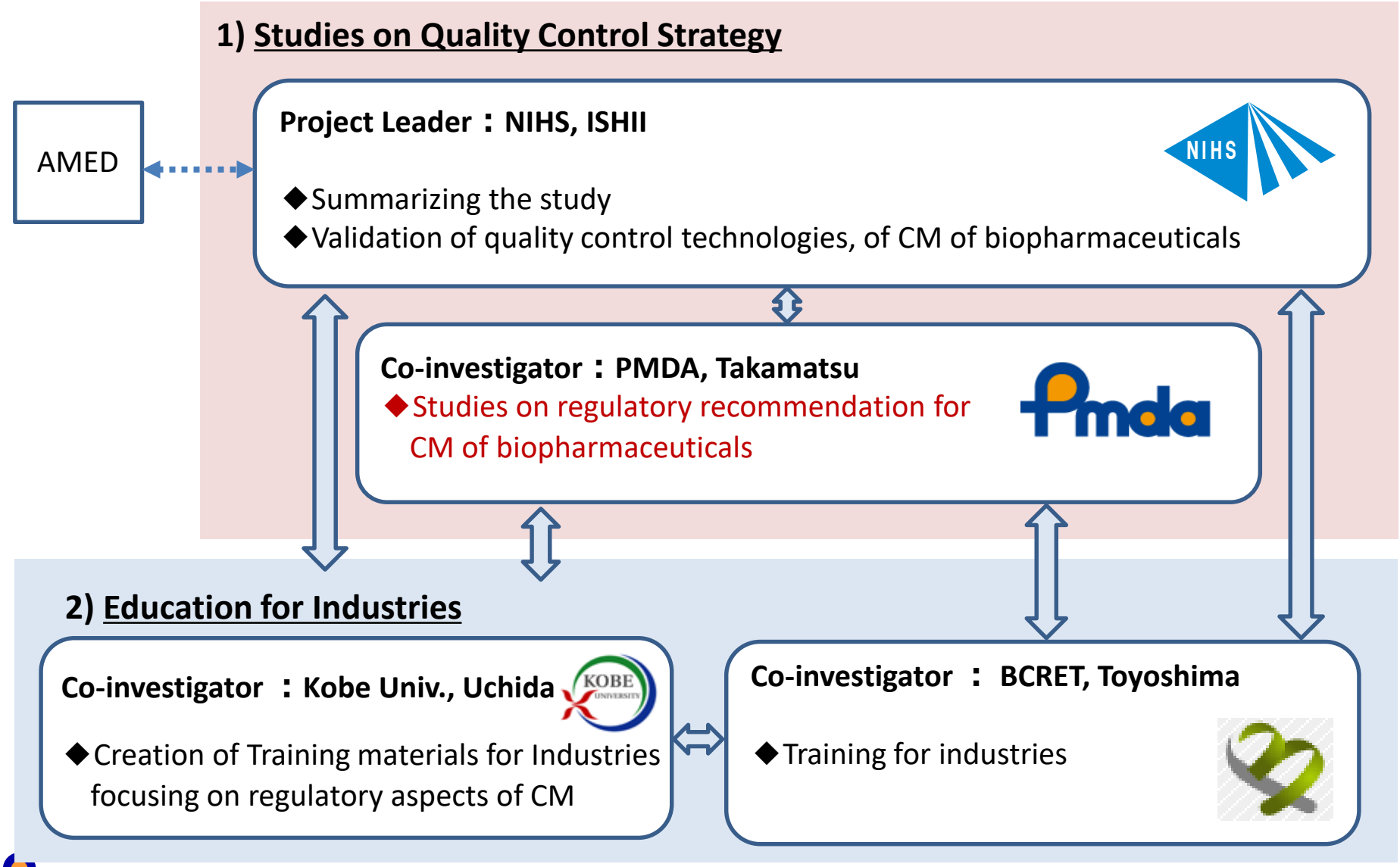
"Development of advanced manufacturing technology for biopharmaceuticals"

AMED project "Development of advanced manufacturing technology for biopharmaceuticals "

AMED2-1	Studies on construction of a high productive cell line
AMED2-2	Studies on development of basic technologies such as continuous production of biopharmaceuticals
AMED2-3	Studies on platform technologies on bioprocessing



Studies on quality control strategies for the practical application of continuous manufacturing of biopharmaceuticals



Points to Consider Regarding CM of Biopharmaceuticals

Table of contents (draft)

1. Introduction
2. Control Strategy (PAT, adventitious agents, Specification/RTR)
3. Process Validation
4. State of Control and Steady State
5. Stability (e.g., sampling points, lots)

Issues to be discussed (Bio)

- Control strategy
  - Control Strategy for Manufacturing Process
    - Risk assessment, Risk mitigation
    - Process dynamics
    - Raw materials
    - Performance-based approach
    - Fit for purpose
  - Monitoring
    - PAT
    - Continuous monitoring
    - Sampling point

Issues to be discussed (Bio)

- Control strategy
  - Adventitious agents
    - Risk mitigation for contamination
    - New method for virus and microbial control
  - Specification
    - Multi attribute method
    - RTRT
    - Control strategy

- Process Validation
  - Qualification of facility/equipment
  - Validation design
  - Definition of lot
  - Sampling points for process evaluation

Issues to be discussed (Bio)

- State of control and Steady State
  - State of Control / Steady State
  - Start-up /Shut-down
  - Deviation

- Stability
  - Selection of primary lot
  - Number of primary lot
  - Sampling points(spot, time etc.)
  - Stability monitoring

Prepare a consensus draft of the Points-to-Consider
by the end of 2019 and finalize it by March 2021

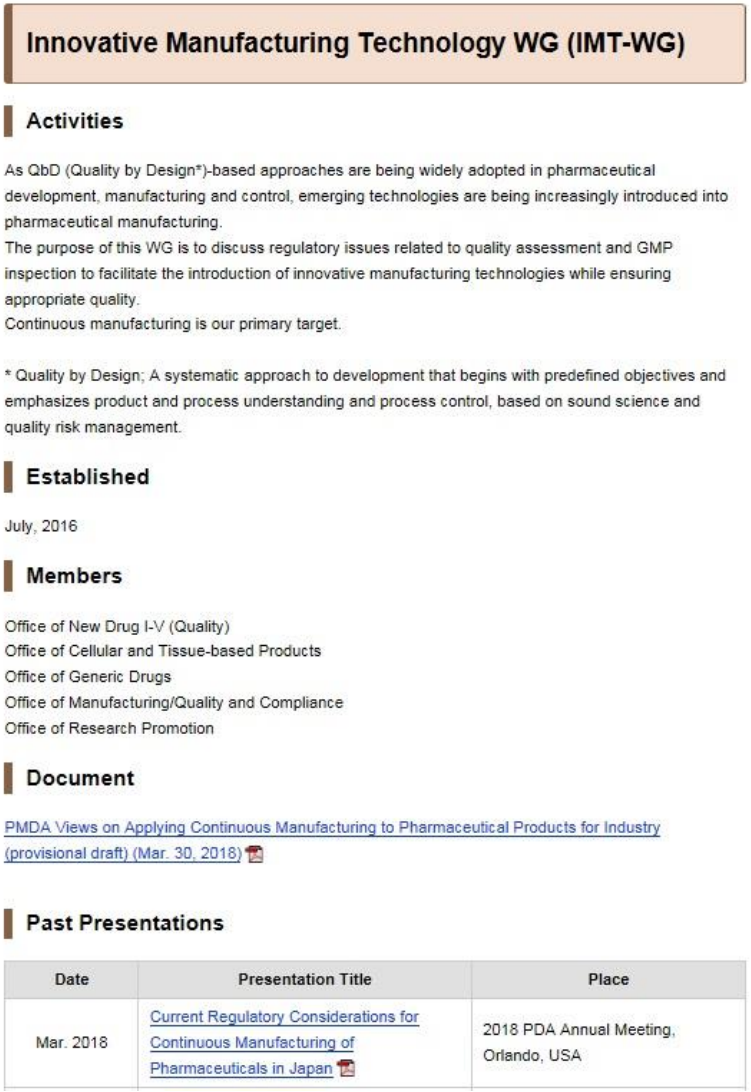
Summary and Conclusions

- PMDA is supportive of innovative pharmaceuticals manufacturing such as CM.
- PMDA believes that there are no regulatory hurdles for implementing CM in Japan.
- PMDA recommends industries to have early and frequent discussions with PMDA during CM development.

How to stay up to date with PMDA

- PMDA posts our presentation files and documents on our website.
- PMDA provides consultations.

http://www.pmda.go.jp/english/rs-sb-std/standards-development/cross-sectional-project/0012.html



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

Date	Presentation Title	Place
Mar. 2018	Current Regulatory Considerations for Continuous Manufacturing of Pharmaceuticals in Japan	2018 PDA Annual Meeting, Orlando, USA

Thank you for your attention!

Acknowledgements

- AMED * study group (*: Japan Agency for Medical Research and Development)
- PMDA Innovative Manufacturing Technology Working Group (IMT-WG)
- ICH Q13 Expert Working Group
- Colleagues in the Office of Cellular and Tissue-based Products