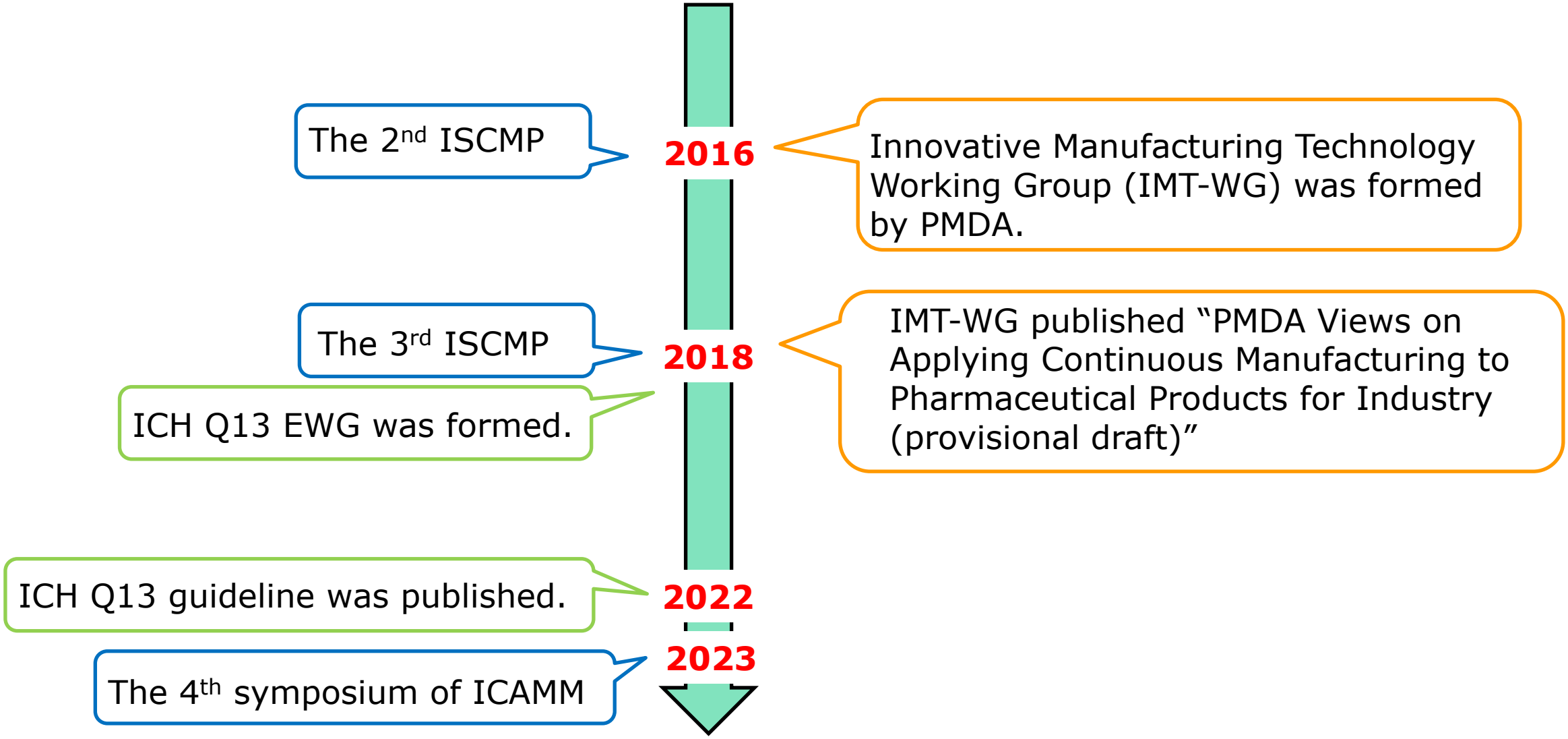
Regulators Perspective on Advanced Manufacturing - PMDA

Yoshihiro Matsuda, Ph.D.

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

Timeline


The 2nd ISCMP
2016
Innovative Manufacturing Technology Working Group (IMT-WG) was formed by PMDA.
The 3rd ISCMP
2018
IMT-WG published "PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft)"
ICH Q13 EWG was formed.
ICH Q13 guideline was published.
2022
2023
The 4th symposium of ICAMM

Innovative Manufacturing Technology Working Group (IMT-WG)

- The purpose of this WG is to discuss regulatory issues related to quality assessment and GMP inspection to facilitate the introduction of innovative manufacturing technology while ensuring appropriate quality.
- Established in July, 2016
- Members
  - Senior Scientist for Quality
  - Office of New Drug I-V (Quality)
  - Office of Cellular and Tissue-based Products
  - Office of Generic Drugs
  - Office of Manufacturing Quality for Drugs
  - Office of Review Management
  - Office of Research Promotion

Contributions and Related Activities

Industries

Scientific Advice

ICH

ICH Q13 Guideline

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA U.S. FOOD & DRUG ADMINISTRATION

Communication

IMT-WG

Presentations

Conferences

Assessment support

Product Evaluation Offices

Research

Including
・Academia
・Industries

AMED

Japan Agency for Medical Research and Development

Specialized teams for Advanced Manufacturing

- EMA
  - Quality Innovation Group (QIG)
- US FDA
  - Emerging Technology Team (ETT)
- PMDA
  - Innovative Manufacturing Technology Working Group (IMT-WG)

Communication with international authorities

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 outcomes

- 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 manufacturing

  Chemical and Pharmaceutical Bulletin 69(2), 211-217, 2021

- Control strategy and methods for continuous direct compression processes

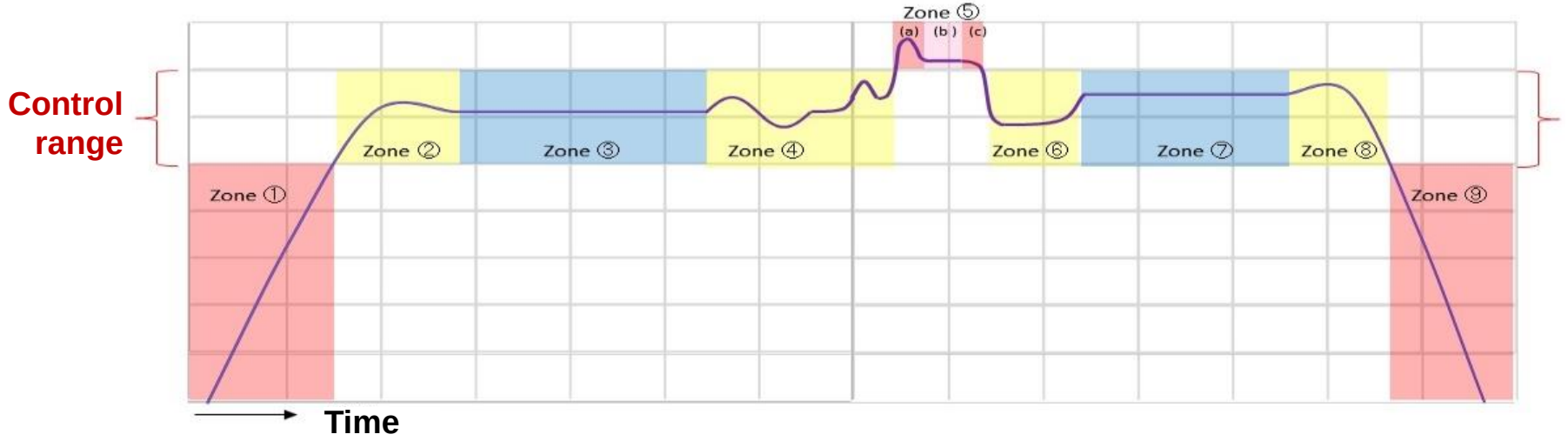
  Asian Journal of Pharmaceutical Sciences 16, 253-262, 2021

- Points to Consider in Continuous Manufacturing of Biotechnological Products

  PDA Journal of GMP and Validation in Japan Vo. 23, No. 1, 2021

An Example of AMED Research Outcomes

Concept of the Relation between "Steady State" and "State of Control"



Zone	(1)	(2)	(3)	(4)	(5)			(6)	(7)	(8)	(9)
Description of state	Start-up (yet to reach control range)	Start-up (within control range but non-steady state)	Steady state	Disturbance has occurred but within control range	(a) Deviation from control range (b) Entered steady state but outside control range (c) Entered non-steady state and still outside control range			Returned within control range but non-steady state	Steady state with values different from those in Zone3	Shut-down procedure has started but still within control range	Shut-down (Deviated from control range)
					(a)	(b)	(c)				
Steady state	N	N	Y	N	N	Y	N	N	Y	N	N
State of control	N	Y	Y	Y	N	N	N	Y	Y	Y	N
Discharge outside the system	Y	Y/N	N	Y/N	Y	Y	Y	Y/N	N	Y/N	Y

(Y: Yes, N: No, Y/N: Yes or No)

Reference: http://www.nihs.go.jp/drug/section3/AMED_CM_CONTROLST.pdf

Examples of CM products approved in Japan

Product	MAH	New/Change	PMDA Review Report
Verzenio® Tablets (abemaciclib) 50mg, 100g, and 150mg	Eli Lilly	New Drug	https://www.pmda.go.jp/drugs/2018/P20181004001/530471000_23000AMX00808_A100_1.pdf
Tramcet® Combination Tablets (tramadol hydrochloride, acetaminophen)	Janssen Pharmaceutical K.K.	From BM to CM	— (not subject to public disclosure)
Duvroq® Tablets (daprodustat) 1mg, 2mg, 4mg, 6mg	GSK	New Drug	https://www.pmda.go.jp/drugs/2020/P20200619003/340278000_30200AMX00505_A100_1.pdf
Tazverik® Tablets (tazemetostat) 200mg	Eisai	New Drug	https://www.pmda.go.jp/drugs/2021/P20210708001/170033000_30300AMX00278_A100_1.pdf
Xofluza® Tablets (baloxavir marboxil) 10mg, 20mg	Shionogi	From BM to CM	— (not subject to public disclosure)
Cibinqo ® Tablets (abrocitinib) 50mg, 100mg, 200mg	Pfizer	New Drug	https://www.pmda.go.jp/drugs/2021/P20211011001/672212000_30300AMX00443_A100_1.pdf

PMDA's new approach to Advanced Manufacturing

- Consultation of innovative manufacturing technology in relation to drugs
  - A new consultation service started in 2020 as a pilot program.
  - We currently accept one consultation every six months.
  - The unique aspect of this consultation is that assessors and GMP inspectors can visit the production/research site together to advise them.

Is "developing guidelines" for Advanced Manufacturing enough?

- It is necessary for pharmaceutical industries to make similar regulatory decisions globally.

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- The ICH is one of the most effective ways of harmonizing regulatory decisions. → ICH Q13

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- Are the ICH guidelines (ICH Q13) enough to harmonize properly?

↓

- In addition, we also need to consider regulatory convergence.

What is regulatory convergence?

A process whereby the regulatory requirements across countries or regions become more similar or "aligned" over time as a result of the gradual adoption of internationally recognized technical guidance documents, standards and scientific principles, common or similar practices and procedures, or adoption of regulatory mechanisms that might be specific to a local legal context but that align with shared principles to achieve a common public health goal.

How do we speed up the process?

Reference: https://www.fda.gov/vaccines-blood-biologics/international-activities/regulatory-harmonization-and-convergencenvergence

Ideal methods to speed up regulatory convergence

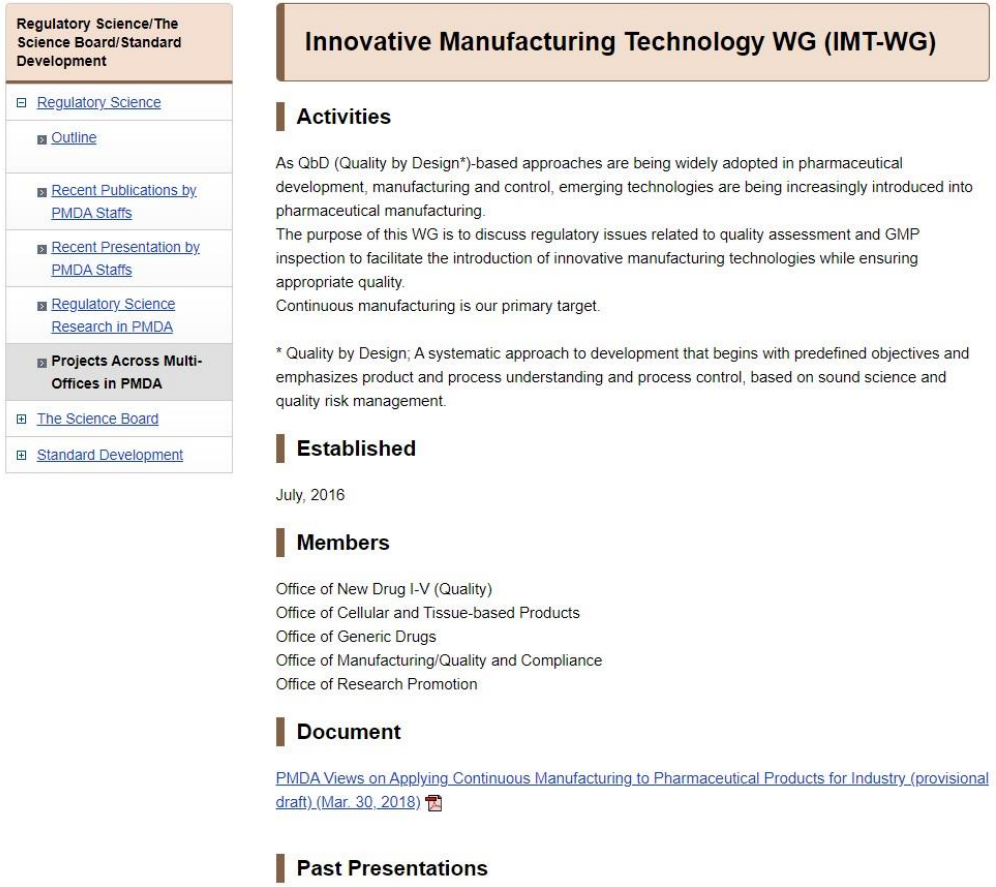
- Symposiums
  - For example, this ICAMM (ISCMP) symposium has become one of the most informative gatherings to discuss new technology and regulation.
- Training
  - For example, ICH Q13 IWG is developing training materials for continuous manufacturing for not only industries, but also regulators.
- Collaborative Pilot Programs
  - For example, the International Coalition of Medicines Regulatory Authorities (ICMRA) has started a pharmaceutical quality knowledge management system (PQKMS) collaborative pilot program.

Expectations in the future

- For example, CM could potentially be a standard of drug manufacturing in the pharmaceutical industry.
  - Many regulatory agencies, including the EMA, PMDA and US FDA, strongly support the implementation of CM technology.
  - CM is the necessary technology to make Industry 4.0（a concept given to the current trend of automation and data exchange in manufacturing technology) a reality.
  - CM can innovate the manufacturing and distribution of pharmaceuticals.

Advanced manufacturing will be a benefit to 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 advanced manufacturing including:

- Presentation files
- Regulatory documents, etc.

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

Thank you for your time