CMC Strategy Forum Japan 2023, 4-5 December, 2023, Tokyo Marriot Hotel, Tokyo, Japan

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Regulatory Updates and a Perspective on Biopharmaceuticals in Japan

KISHIOKA Yasuhiro, Ph.D.
Review Director
Office of Cellular and Tissue-based Products
Pharmaceuticals and Medical Devices Agency (PMDA)

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.

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

“Continual improvement is an unending journey”

(Lloyd Dobyns)

Outline

- Regulatory Updates in Japan
- International Activities (ICMRA PQKMS, ICH Q12, ICH M4Q(R2))
- Product-related Topics (Biosimilars, Microbiome, Exosomes)

Recent MHLW's Initiatives

(MHLW; Minister of Health Labour and Welfare)

10. Jul, 2023～

Review Committee on Pharmaceutical Regulation for Strengthening Drug Discovery Capabilities and Securing Stable Supply

https://www.mhlw.go.jp/stf/shingi/other-iyaku_128701_00006.html

9. Jun, 2023

Report of the Panel of Experts on Comprehensive Measures to Achieve Rapid and Stable Supply of Pharmaceuticals

https://www.mhlw.go.jp/stf/newpage_33548.html

- Ensure stable supply
- Strengthen drug discovery capabilities
- Resolve the issues of "drug lag/loss"
- Efforts toward appropriate distribution of pharmaceuticals

Review Committee on Pharmaceutical Regulation for Strengthening Drug Discovery Capabilities and Securing Stable Supply

- Summary of considerations
  - Promotion of pharmaceutical development
  - Clinical trials
  - Post-marketing safety measures
  - Dissemination of information
  - Quality

    Review the description of manufacturing process in Application Form and post-approval CMC changes, taking into account international consistency

Background: Post-Approval Change Reporting Categories

ICH Q12 Classification	Japan	US	EU
Prior Approval	PCA (Partial Change Application)	PAS (Prior Approval Supplement)	Type II Variation
Notification Moderate		CBE-30	Type IB Variation
Notification Low	MCN (Minor Change Notification)	CBE-0	Type IA_{IN} Variation
		Annual Report	Type IA Variation
Not Reported	Not Approved Matters		

4th Review Committee (13 Oct, 2023)

https://www.mhlw.go.jp/stf/newpage_35743.html

- Direction *(needs further discussion)*
  - Introduce “middle-category” (pilot program)
  - Introduce “annual report” (pilot program)
  - Review the description of Application Form
    - to achieve internationally harmonized & risk-based approach for post-approval CMC changes
    - discuss the need for the overhaul of “Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law in 2005”

https://www.pmda.go.jp/files/000153677.pdf (in English)

Outline

- Regulatory Updates in Japan
- International Activities (ICMRA PQKMS, ICH Q12, ICH M4Q(R2))
- Product-related Topics (Biosimilars, Microbiome, Exosomes)

ICMRA PQKMS (Pharmaceutical Quality Knowledge Management System)

Pharmaceutical Quality Knowledge Management System (PQKMS) | International Coalition of Medicines Regulatory Authorities (ICMRA)

- **ICMRA Statement** on Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility (Jun 11, 2021)

  Global Pharmaceutical Quality Knowledge Management: Enhancing Regulatory Reliance and Agility | International Coalition of Medicines Regulatory Authorities (ICMRA)

- **ICMRA-ICH-PIC/S-IPRP Joint Reflection Paper**;
  A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines
  (Jul. 21, 2022)

  A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines | International Coalition of Medicines Regulatory Authorities (ICMRA)

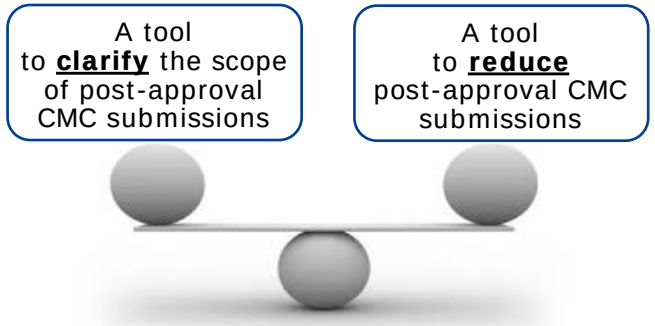
Major Challenges toward Successful/Harmonized Implementation of ICH Q12

- Effective Pharmaceutical Quality System (PQS) incl. Change Management
- Identification of Established Conditions (ECs) and Associated Reporting Categories (RCs)
  - Criticality assessment *vs.* Risk assessment
  - Risk Tolerance
  - Can PQS maturity reduce the details of ECs?
  - Feasibility of unified ECs/RCs across regions based on current RC systems in all regions
- Post-Approval Change Management Protocol (PACMP)
  - Need to accumulate experience for both regulators and the industry

Divergent Views / Expectations on ECs

ICH Q12

- The concept of ECs provides a clear understanding between the MAH and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed. *(Chapter 1.3)*
- ECs are legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority. *(Chapter 3.2.1)*

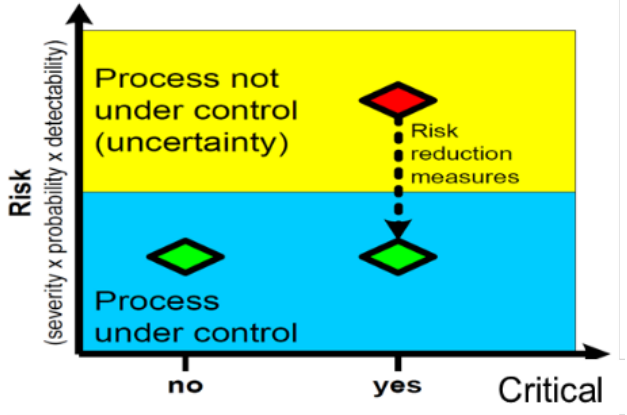


To what extent can enhanced understanding of product and process reduce ECs?

ECs for manufacturing process parameters

- ICH Q12 Chapter 3.2.3.1

Process parameters that need to be controlled to ensure that a product of required quality will be produced should be considered ECs. These ECs are identified through an initial risk assessment and application of knowledge gained from executed studies, prior knowledge, and a criticality assessment that determines the level of impact that a process parameter could have on product quality. The criticality assessment should account for severity of harm and whether the ranges studied sufficiently account for the expected variability in the EC. CPPs and other process parameters where an impact on product quality cannot be reasonably excluded should be identified as ECs.



ICH Q-IWG Discussion (2013)

ICH M4Q(R2): Revision of M4Q (R1) (1)

https://www.ich.org/page/ctd

The M4Q(R2) EWG is focusing on the revision of CTD Quality sections in Modules 2 and 3 to capture quality information for the registration and lifecycle management of pharmaceuticals for human use.
The main issues to be resolved during this revision include:

- Expanding the scope of M4Q(R1) guideline. This M4Q(R2) guideline applies to all pharmaceutical drug substances and products (both chemical and biological) that require a marketing authorization.
- Establishing the role of M4Q(R2) as the main source of the structure and location of regulatory quality information.
- Organizing product and manufacturing information in a suitable format for easy access, analysis, and knowledge management.

ICH M4Q(R2): Revision of M4Q (R1) (2)

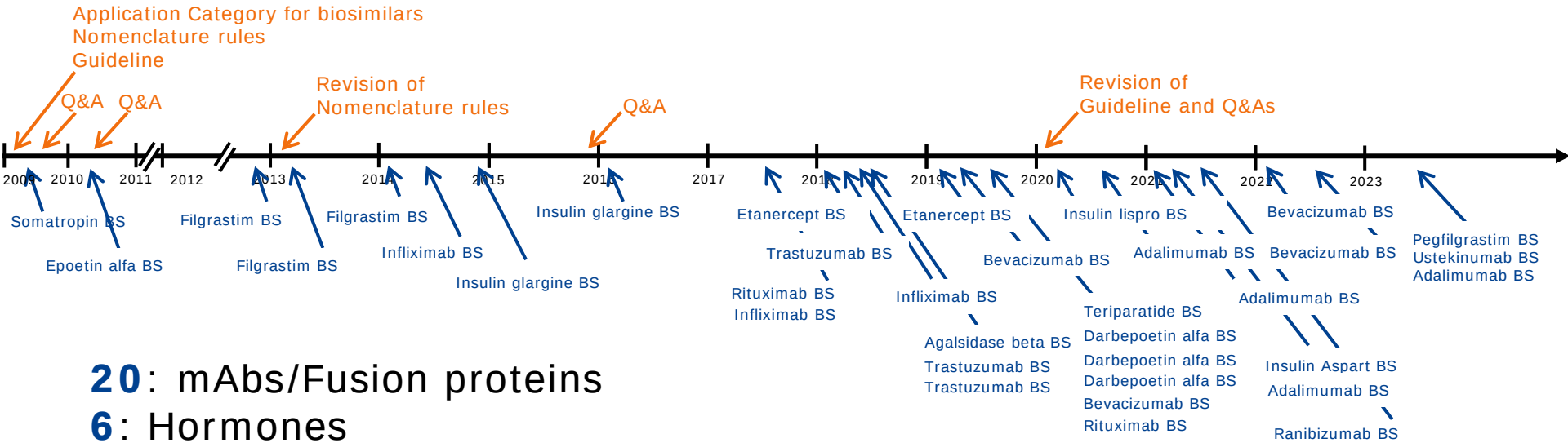
https://www.ich.org/page/ctd

- Incorporating concepts and data expectations presented in ICH Quality guidelines and aligning with currently recognized international standards and guidelines.
- Better capturing the pharmaceutical development and the proposed overall control strategy, which should be the backbone of the revised M4Q structure. This should address key elements of the proposed pharmaceutical product, including the Quality Target Product Profile (QTPP), manufacturing process, and overall control strategy.
- Enhancing the Quality Module 2 to facilitate the efficiency and effectiveness of regulatory submissions and assessments.

Outline

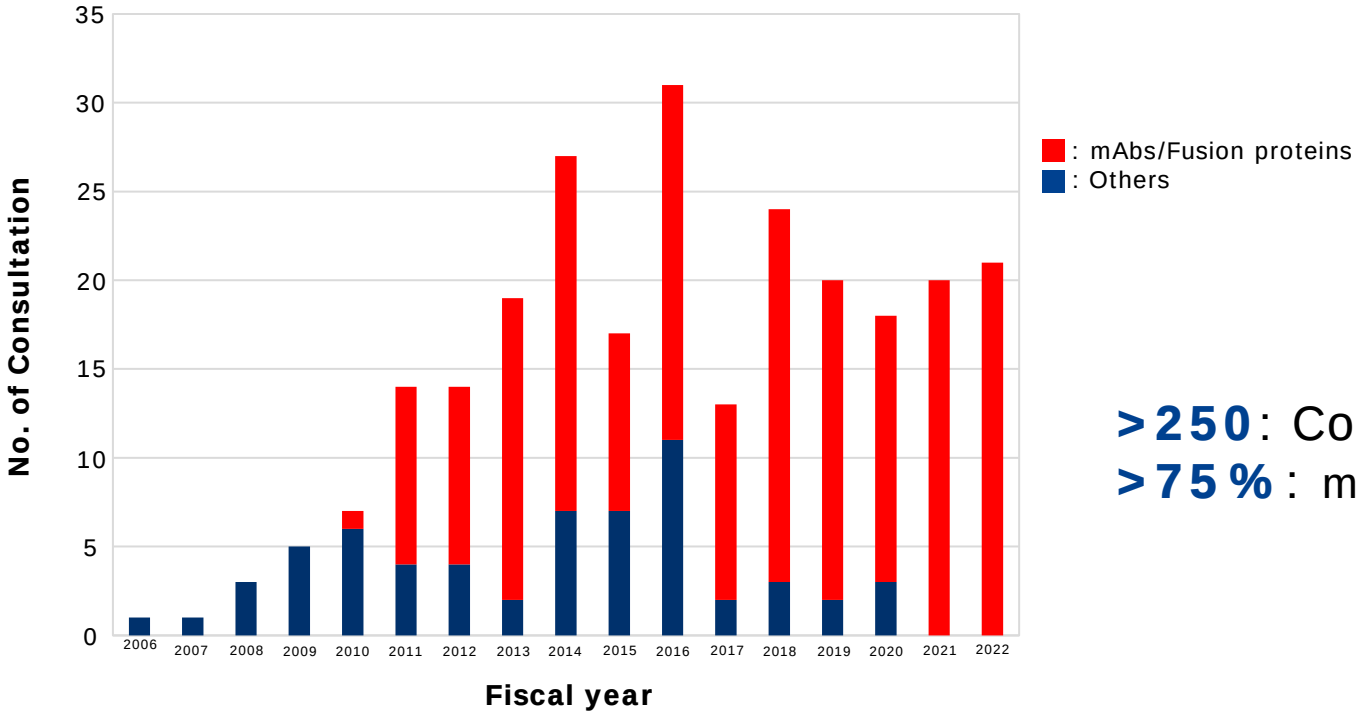
- Regulatory Updates in Japan
- International Activities (ICMRA PQKMS, ICH Q12, ICH M4Q(R2))
- Product-related Topics (Biosimilars, Microbiome, Exosomes)

Regulatory History and Status of Biosimilars as of December 2023



20: mAbs/Fusion proteins
6: Hormones
4: EPOs
4: Cytokines
1: Enzymes

Consultation for Biosimilars



>250: Consultations

>75%: mAbs/Fusion proteins

IPRP Biosimilars WG Workshop (Sep. 2023)

IPRP International Pharmaceutical Regulators Programme

IPRP Biosimilars Working Group Workshop: "Increasing the Efficiency of Biosimilar Development Programs-Re-evaluating the Need for Comparative Clinical Efficacy Studies (CES)"

- Goal: Increase efficiency in biosimilar development programs
- How: Re-evaluate the need for comparative clinical efficacy studies in biosimilar development programs based on the experience accrued from international experts and external subject matter experts

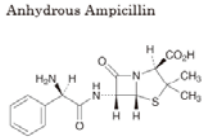
Presentation is available at FDA website; https://www.fda.gov/media/172198/download

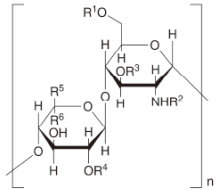
Approach to Development of Follow-on products

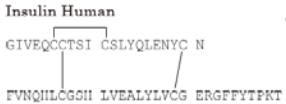
depends on;

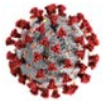
- Analytical techniques
- Understanding of quality attributes relevant to efficacy and safety
- Residual uncertainty
- Experience/Knowledge (Regulatory confidence/relief)

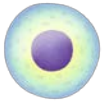
Small molecules | Sugar | Nucleic acid | Peptide | Protein | Virus | Cell | Tissue











small & simple

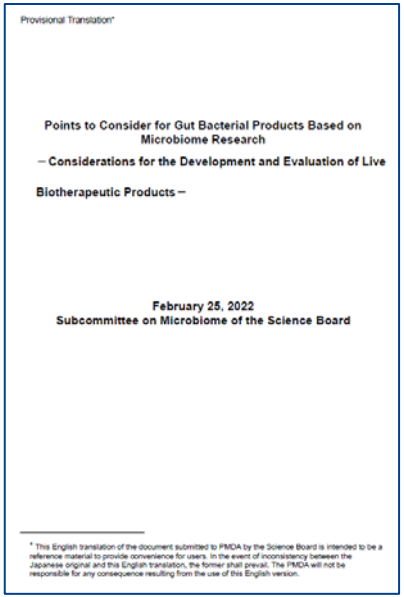
large & complex

From Dr. Kameda, PMDA

Microbiome

PMDA Science Board;
https://www.pmda.go.jp/english/rs-sb-std/sb/science-committee/0010.html

Report from PMDA Science Board (25 Feb, 2022)



Provisional Translation*

Points to Consider for Gut Bacterial Products Based on Microbiome Research

–Considerations for the Development and Evaluation of Live Biotherapeutic Products–

February 25, 2022
Subcommittee on Microbiome of the Science Board

* This English translation of the document submitted to PMDA by the Science Board is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Table of Content

https://www.pmda.go.jp/files/000249812.pdf (in English)

FMT; Fecal Microbiota Transplantation
LBPs; Live Biotherapeutic Products

Extracellular Vesicles (EVs) incl. Exosomes

- Report from PMDA Science Board (17 Jan, 2023)

エクソソームを含む細胞外小胞(EV)を利用した治療用製剤に関する報告書

目次

Table of Content

https://www.pmda.go.jp/files/000249829.pdf (in Japanese)

"Continual improvement is an unending journey"

(Lloyd Dobyns)

Thank you for your attention!

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