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

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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.

Wisdom

(Explicit) Knowledge

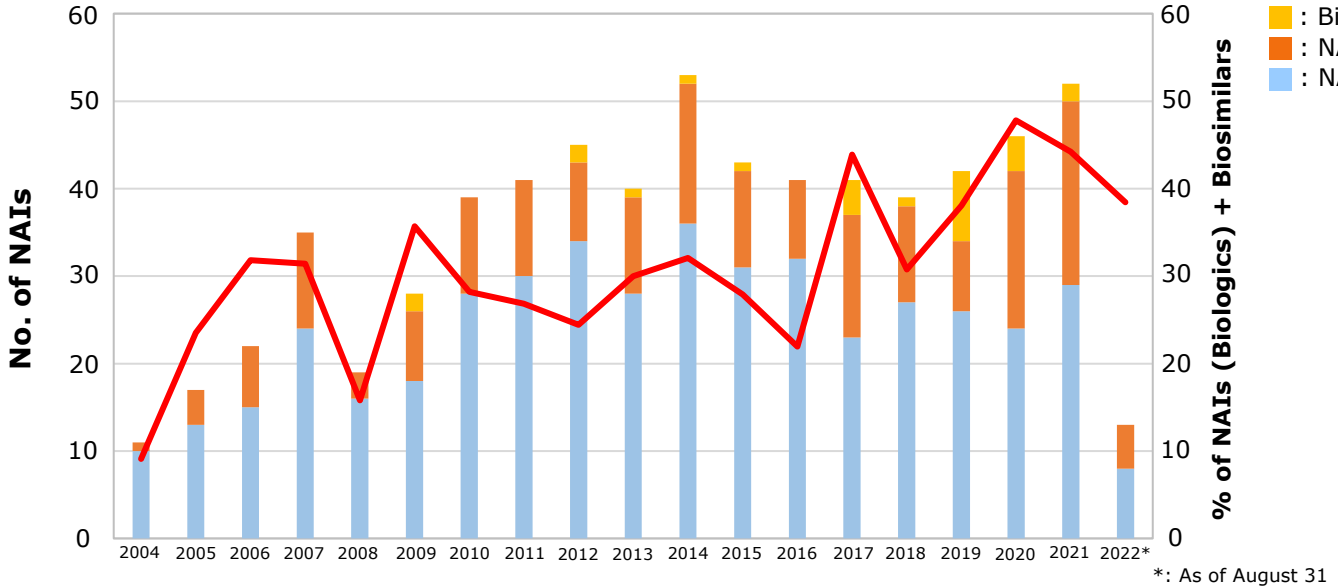
"Ba"

Nonaka & Konno (1998)

Outline

- Recent trends of Biopharmaceuticals in Japan
- On-going ICH-Quality Topics
- Lessons Learned from COVID-19 Pandemic

Trend of New Active Ingredients (NAIs) and Biosimilars



List of Approved Products | Pharmaceuticals and Medical Devices Agency (pmda.go.jp)

Trend of Biopharmaceuticals

- mAbs are predominant among therapeutic proteins (e.g., mAbs, Fusion proteins, EPOs, Enzymes, Hormones, Interferons, Coagulation factors).
  - A mock example of CTD Module 2.3 (2.3.S.2.2, 2.3.S.2.3 and 2.3.S.2.4) and Application Form (Module 1.2) of mAb developed by AMED* Research group (Oct. 2022)

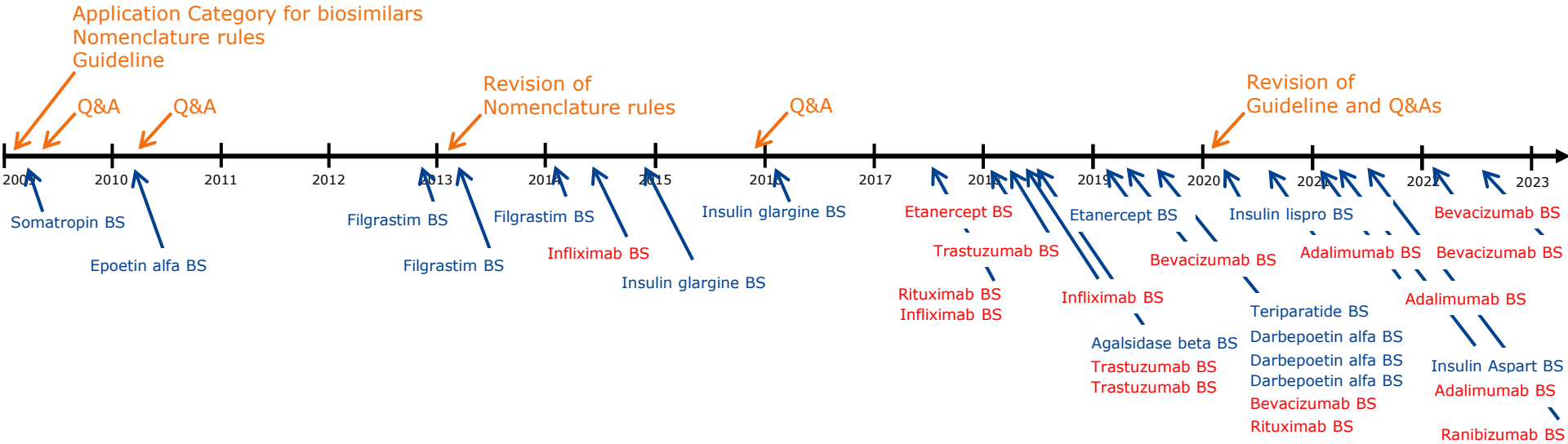
    *: Japan Agency for Medical Research and Development

    BIO_mockup.pdf (nihs.go.jp)

    Note: The mock example should not be used as a template or the sole basis for a regulatory submission

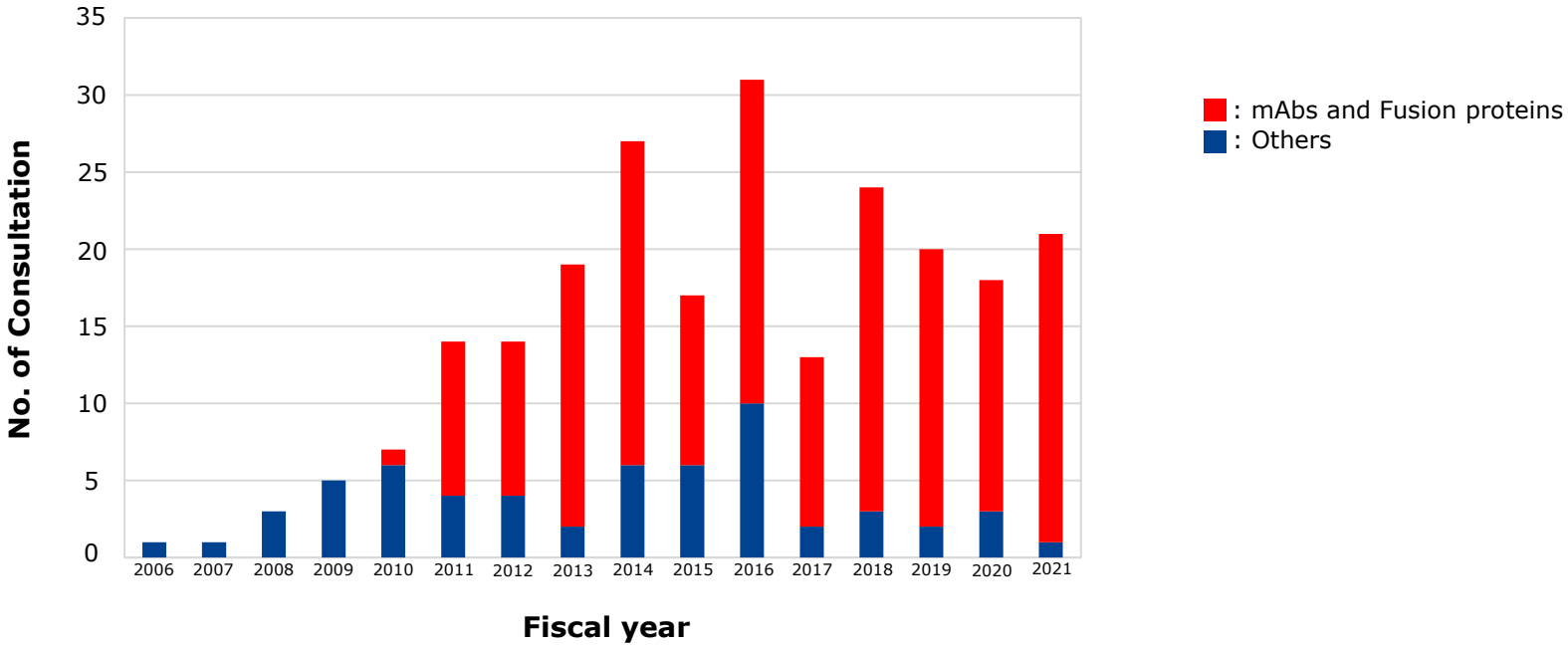
- Various types of mAbs (conjugate (radioisotopes, drug, near infrared dye), bispecific, nanobody)

Regulatory History and Status of Biosimilars



Red: mAbs and Fusion proteins
Blue: Others

Consultation for Biosimilars



Question to be addressed

- To what extent can analytical (incl. *in vitro assay*) similarity ensure equivalent efficacy and similar safety profile to/as the reference product?

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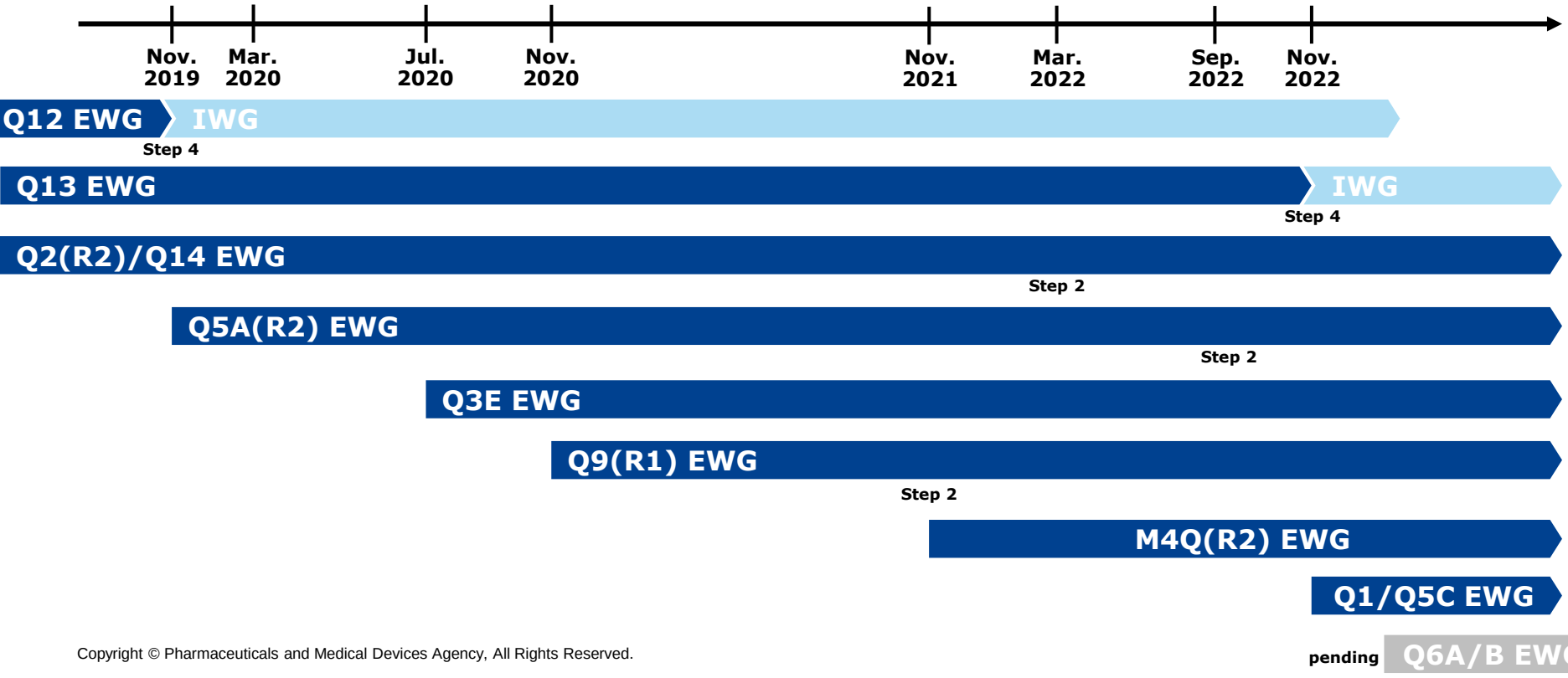
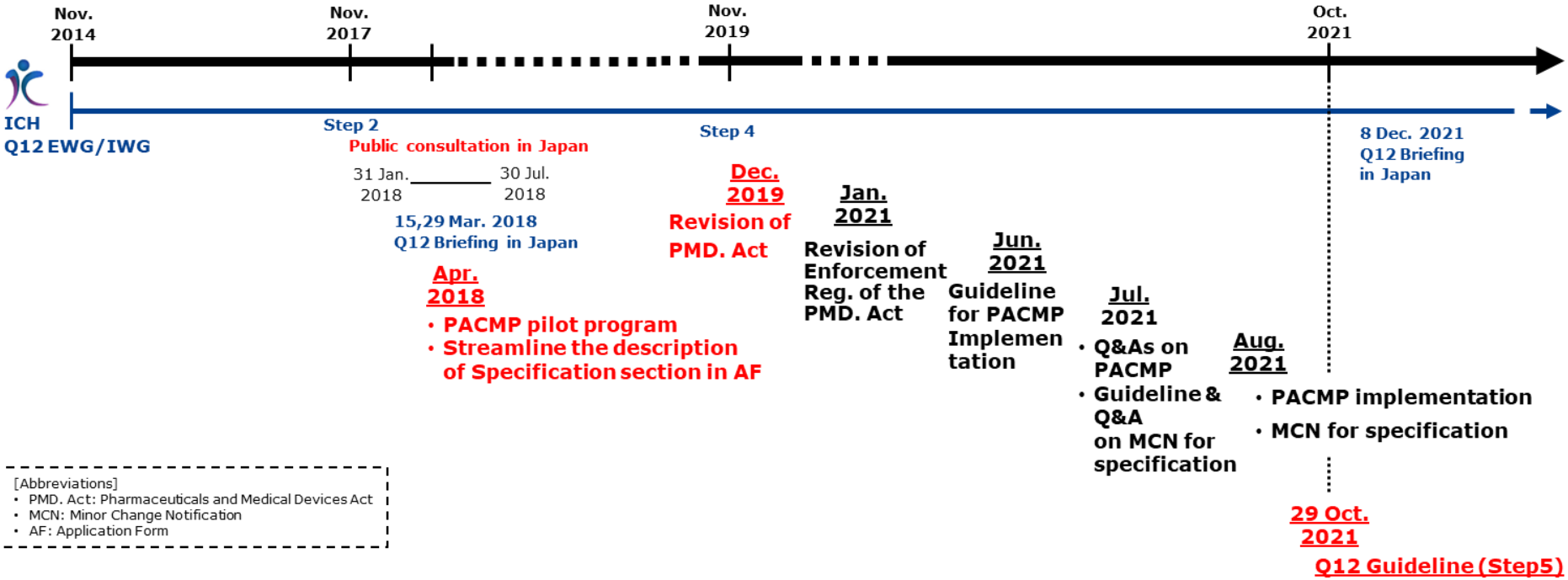
On-going ICH-Quality Topics

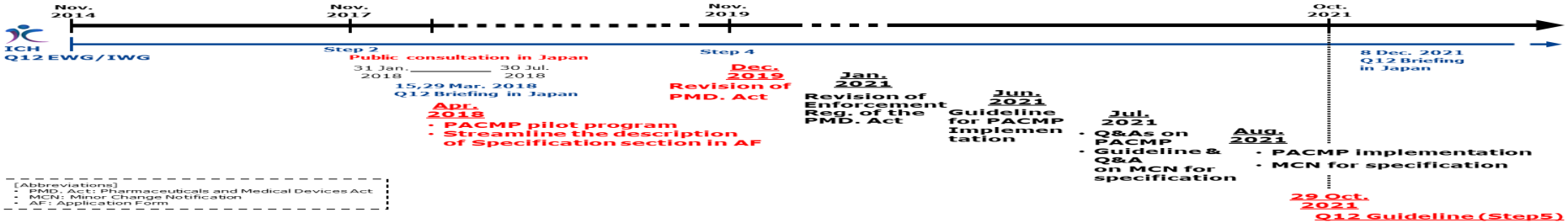


ICH Q12 Implementation in Japan



[Abbreviations]
- PMD. Act: Pharmaceuticals and Medical Devices Act
- MCN: Minor Change Notification
- AF: Application Form

Behind-the-scenes preparations



May 2015

PMDA ICH Q12 WG

- Member: Sr. Mgmt., Reviewers (chemicals, biologicals, generics), GMP inspectors
- Discuss regulatory, technical and practical issues within PMDA

Dec. 2014

AMED Research Group

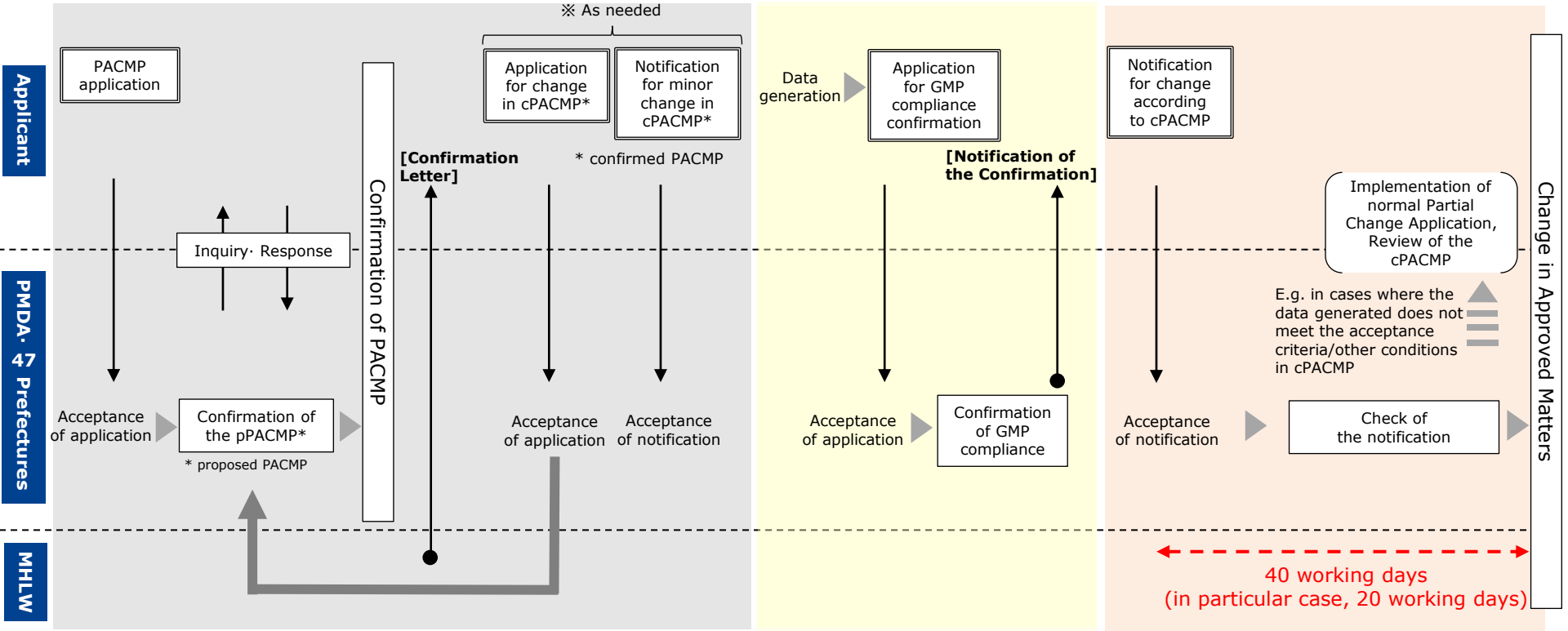
- Member: Academia, Industry, PMDA
- Discuss technical and practical issues, Report the outcome and proposal to the MHLW

Sep. 2016

MHLW/PMDA-FPMAJ Task Force

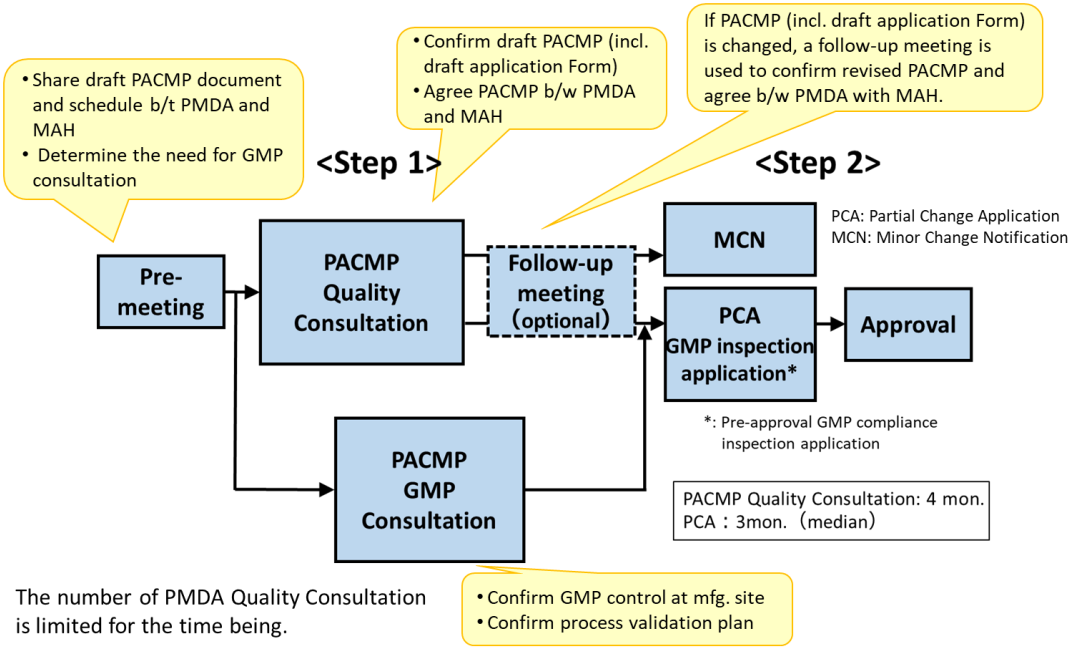
- Members: MHLW, PMDA, FPMAJ (The Federation of Pharmaceutical Manufacturers' Associations of JAPAN)
- Driven by "domestic problems" (not by ICH Q12)
- Streamline the regulatory procedures for post-approval CMC changes

PACMP: Guideline (MHLW PSEHB/ELD Notification 0616-14, 16 Jun. 2021)



https://www.mhlw.go.jp/hourei/doc/tsuchi/T210618I0010.pdf (in Japanese)

PACMP Pilot Program (Apr. 2018 – Jul. 2021)



The number of PMDA Quality Consultation is limited for the time being.

Number of Consultations;

- PACMP Quality Consultation: 15
- PACMP GMP Consultation: 5

Products;

- Vast majority: therapeutic proteins
- Blood products, Chemicals

Scope;

- Addition of manufacture site with/ without Manufacturing process change
- Extension of shelf-life

Lessons learned from the Pilot Program and on-going pre-submission meetings

- Scope of one PACMP

  ***ICH Q12**: If the protocol describes several changes for a particular product, a justification should be added showing how the changes are related and that inclusion in a single protocol is appropriate.*

- Level of details of proposed changes/proposed acceptance criteria for each test/study at Step 1

  ***ICH Q12**: A detailed description of the proposed change(s), including a rationale. The differences before and after the proposed change(s) should be clearly highlighted (e.g., in a tabular format).*

- Practical procedures including administrative ones

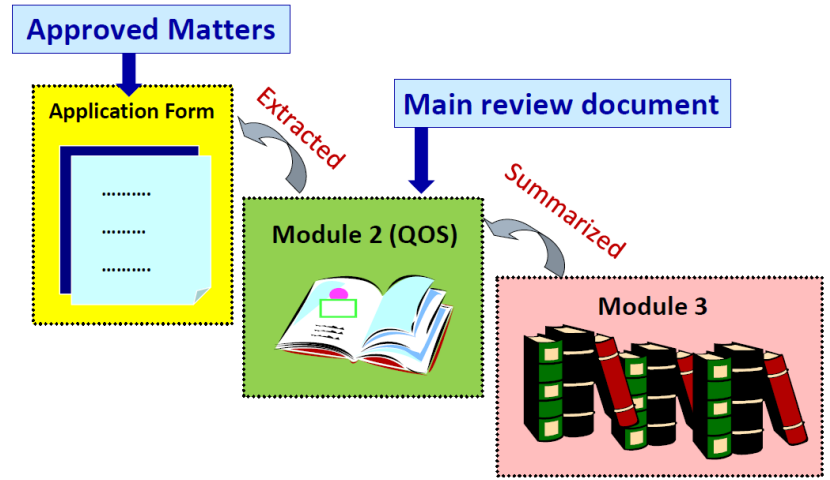
Major Challenges toward Successful/Harmonized Implementation

- 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
- PACMP
  - Need to accumulate experience for both regulators and the industry
- Product Lifecycle Management (PLCM) document
  - How a tabular format covers all elements of ECs?

Post-Approval CMC Changes in Japan

Where are we heading, in conjunction with ICH M4Q(R2) ?

Relationship between Application Form and ICH CTD



Post-Approval Change Reporting Categories

Impact on quality	Japan	US	EU
High	Partial change Application (prior approval for change)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	Minor change Notification (within 30 days after implementation or shipping)	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low	(Non-approved matters)	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

For more details about Post-Approval CMC Changes in Japan :
https://www.pmda.go.jp/files/000215714.pdf (presentation in English)

Outline

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COVID-19 Therapeutics and Vaccines in Japan

	Brand Name	Nonproprietary Name	Approval Date
Chemicals	Veklury	Remdesivir	May 7, 2020
	Lagevrio	Molnupiravir	December 24, 2021
	paxlovid	Nirmatrelvir/Ritonavir	February 10, 2022
Therapeutic proteins (mAbs)	Ronapreve	Casirivimab/Imdevimab	July 19, 2021
	Xevudy	Sotrovimab	September 27, 2021
	Evusheld	Tixagevimab/Cilgavimab	August 30, 2022
Vaccines	Comirnaty	Tozinameran	Feb 14, 2021
	Spikevax	Elasomeran	May 21, 2021
	Vaxzevria	COVID-19 (SARS-CoV-2) vaccine(recombinant chimpanzee adenovirus vector)	May 21, 2021
	Nuvaxovid	Recombinant coronavirus (SARS-CoV-2) vaccine	April 19, 2022
	Jcovden	COVID-19 (SARS-CoV-2) vaccine(recombinant chimpanzee adenovirus vector)	June 20, 2022

Information about extension of indication and adapted vaccines are not included.

Regulatory Flexibilities for COVID-19 mAbs

- All products
  - Early/frequent communication with applicants
  - Rolling review
  - Special Approval for Emergency (SAE)
- Ronapreve (Casirivimab/Imdevimab)
  - Number of model virus in viral clearance studies
  - Bioassay of DS/DP specification
  - Acceptance criteria of DS/DP specification
  - Shelf-life of DS/DP
- Xevudy (Sotrovimab)
  - Bioassay of DS/DP specification
  - Acceptance criteria of DS/DP specification
  - Storage condition and Shelf-life of DS/DP
- Evusheld (Tixagevimab/Cilgavimab)
  - Bioassay of DS/DP specification
  - Acceptance criteria of DS/DP specification
  - DP shelf-life extension of specific lots already released

Note: Based only on publicly available information (e.g., Review Reports: Drugs | Pharmaceuticals and Medical Devices Agency (pmda.go.jp) in English/Japanese)

ICMRA (International Coalition of Medicines Regulatory Authorities)

- **A voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities** that work together to
  - address current and emerging human medicine regulatory and safety challenges globally, strategically and in an on-going, transparent, authoritative and institutional manner
  - provide direction for areas and activities common to many regulatory authorities' missions
  - identify areas for potential synergies
  - wherever possible, leverage existing initiatives/enablers and resources
- Provide a global architecture to support enhanced communication, information sharing, crisis response and address regulatory science issues

International Coalition of Medicines Regulatory Authorities (ICMRA) | International Coalition of Medicines Regulatory Authorities (ICMRA)

ICMRA-Industry Virtual Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic (Jul. 7-8, 2021) (1)

- The overall aims were;
  - **enhance Regulators' understanding of specific challenges** faced by manufacturers seeking to increase manufacturing capacity for COVID-19 therapeutics and vaccines
  - **improve Industry's awareness of current regulatory approaches** that have been used to enable the rapid increase of manufacturing capacity for the production of COVID-19 therapeutics and vaccines
  - **identify opportunities for further collaboration, alignment, and/or harmonization** to enable more efficient and effective global regulatory response to the current and future public health emergencies
- Video recording, presentation, transcript and workshop report are available at ICMRA website

ICMRA workshop on enabling manufacturing capacity in the COVID-19 pandemic | International Coalition of Medicines Regulatory Authorities (ICMRA)

ICMRA-Industry Virtual Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic (Jul. 7-8, 2021) (2)

- the most effective regulatory flexibilities were identified as the following;

Regulator Position	Industry Position
• Use of PACMPs, or similar, to expedite PACs • Remote inspections • Rolling review • Expedited timelines to meet public need • Labelling flexibilities • Conditional marketing authorisation /emergency use authorisation / or similar regulatory mechanism to meet urgent public health need • Use of risk-based, post-authorization obligations to collate CMC-data (e.g., what is the most/least critical data required for approval)	• Establishment of quick, frequent, and continuous communications/ engagement with regulators • Specific reliance practices: Full or partial reliance on assessment reports of regulatory authorities from other regions • Process Qualification/Validation Data: leveraging of platform data and prior knowledge, concurrent validation, decoupling DS and DP validation, and/or continuous process verification • Approval of PACs in the 'absence of full data' (with certain data provided at a later date)

ICMRA Statement on Pre-Requisites for Regulatory Flexibility in Pharmaceutical Manufacturing Change Management (Oct. 12, 2021)

ICMRA Statement on Pre-Requisites for Regulatory Flexibility in Pharmaceutical Manufacturing Change Management | International Coalition of Medicines Regulatory Authorities (ICMRA)

As regulatory authorities work to extend regulatory reliance and collaborative assessment and refine their tools and approaches to expedite availability of safe and effective medicines and vaccines worldwide, ***ICMRA calls on pharmaceutical companies and manufacturers to continually demonstrate their commitment to quality, including striving for better product and process knowledge, ensuring GMP compliance, and implementing an effective PQS.*** *These collectively enable regulatory authorities to grant suitable flexibilities that can facilitate post-approval change management, enabling industry to expand their manufacturing capacities of essential vaccines and therapeutics to meet critical and global needs created by pandemics like COVID-19.*

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)

ICMRA Pilot Programs

Pharmaceutical Quality – Regulatory Collaboration Pilots: Call for Industry Applications | International Coalition of Medicines Regulatory Authorities (ICMRA)

- Collaborative Assessment Pilot
- Collaborative Hybrid Inspection Pilot
- Aims;
  - Develop an initial common framework for collaborative assessment and hybrid inspections
  - Deliver a single list of questions to the sponsor or manufacturer wherever possible, and identify any misalignments, differences, and potential areas for alignment or harmonization across participating regulators' regions
  - Share application sponsors' or manufacturer responses between the participating quality assessors/inspectors who will work towards a common approach to assessment and decision making
  - **Identify best practices and standards** in the quality assessment of CMC post-approval changes and collaborative hybrid inspections to inform relevant quality assessments
  - Identify the conditions (products/ cases) where cross-regional collaboration efforts in the collaborative assessment and hybrid inspection pilots should focus and make recommendations to ICMRA for a future cross-regional pathway(s)

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Thank you for your attention!

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