# PERSPECTIVES FROM JAPAN

## *SECURING QUALITY ACCORDING TO RECENT ICH GUIDELINES*

**JUNE 18TH 2021**

**CHINA AND JAPAN REGIONAL JOINT PUBLIC MEETING ON ICH**

Japan Pharmaceutical Manufacturing Association
ICH Project *Quality topics*
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# JAPAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION(JPMA)

**JPMA (74 research-oriented pharmaceutical companies** (as of April, 2021).

**C**ontributing to advancing global healthcare

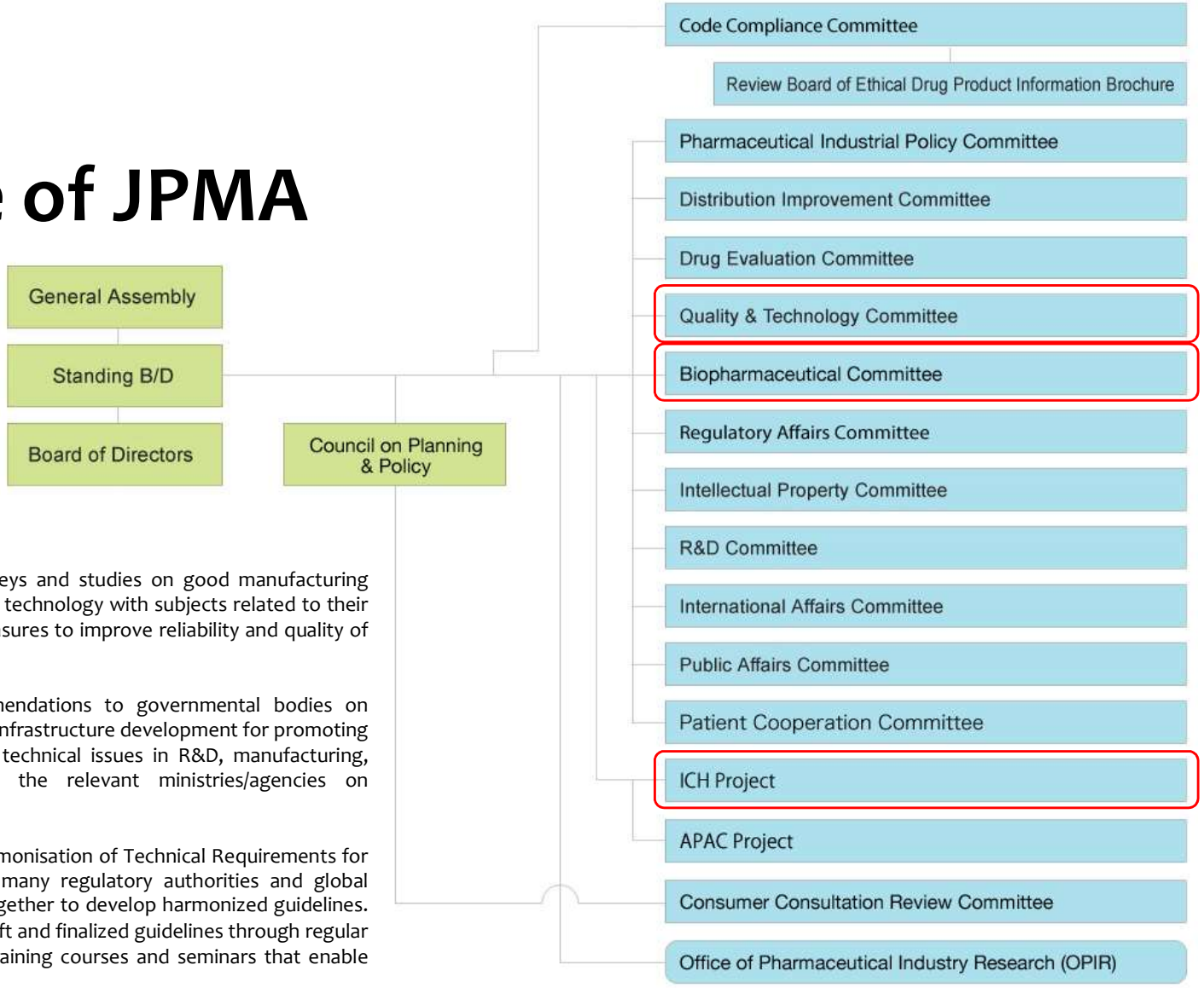
- Development of innovative ethical drugs
- Facilitating sound development of the pharmaceutical industry
- Establishing policies and recommendations in response to globalization and enhancing public understanding of pharmaceuticals.

**E**ngaged with various global issues in the pharmaceutical and healthcare sector, including countermeasures against emerging disease across the globe and infectious disease in developing countries, drug access problems, intellectual property rights and threat of counterfeit drugs.

**W**orking collaboratively with **PhRMA**, **EFPIA**, and taking active roles at **ICH**, which aims at international harmonization of pharmaceutical regulations.

JPMA continues to act globally for the advancement of medical treatments for patients worldwide

# Structure of JPMA




**Quality & Technology Committee** Conducts surveys and studies on good manufacturing practice(GMP), and pharmaceutical manufacturing technology with subjects related to their physical properties. Establishes and promotes measures to improve reliability and quality of pharmaceutical products.

**Biopharmaceutical Committee** Presents recommendations to governmental bodies on biopharmaceutical-related policies concerning the infrastructure development for promoting R&D of biotechnology-based drugs. Investigates technical issues in R&D, manufacturing, post-marketing surveillance, and recommends the relevant ministries/agencies on improvements.

**ICH Project** Joins the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),in which many regulatory authorities and global organization of pharmaceutical industries bring together to develop harmonized guidelines. The Project promotes better understanding of draft and finalized guidelines through regular capacity building activities, such as workshops, training courses and seminars that enable people to improve their skills and knowledge.

# ICH QUALITY GUIDELINES


Q1A - Q1F Stability


Q2 Analytical Validation


Q3A – Q3E Impurities


Q4A- Q4B Pharmacopoeias


Q5A – Q5E Quality of Biotechnological Products


Q6A – Q6B Specifications

Q7 Good Manufacturing Practice


Q8 Pharmaceutical Development


Q9 Quality Risk Management


Q10 Pharmaceutical Quality System


Q11 Development and Manufacture of Drug Substances


Q12 Lifecycle Management

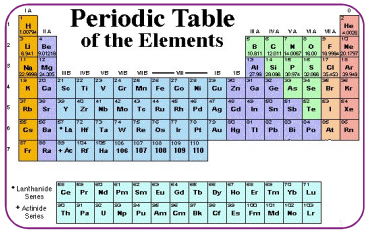
- Focus on technical approach for the quality
- Re-visit updates to the guidelines
- Provide guidance of desired quality to the global
- Have direct impact to the dossier submission to ICH countries

- Focused on development of the product based on science and risk base approach
- Quality approach based on technical approach of the product development
- Considers knowledge, risk, and science based development for innovative drug produce development

# REVISION OF ICH Q3/M7 GUIDELINES

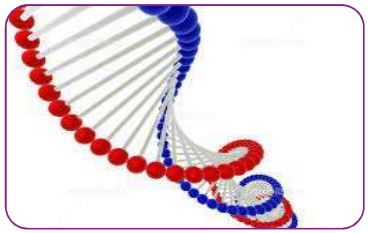
## ICH Q3C residual solvent guideline maintenance

- Apr. 2021 (R8) re-visitation of solvent PDE (2-Me-THF, CPME, tButyl alcohol)
- Oct 2018 (R7) correction for PDE and concentration limit for ethyleneglycol
- Nov. 2016(R6) PDE for Trimethylamine
- Feb. 2011 (R5) revision based PDE




## ICH Q3D elemental analysis

- Nov. 2011 (R2) PDE for Eis established for skins and its appendages
- June 2020 (R1) establishes Permitted Daily Exposures (PDEs) for 24 Elemental Impurities
- Sept 2015 control of elemental impurities in the new drug products



## ICH M7 mutagenic impurities

- June 2010 Guideline on the analysis of Structure Activity Relationships (SAR) for genotoxicity
- June 2017 (R1) Incorporate acceptable limits (Acceptable Intakes (AIs) or Permitted Daily Exposures (PDEs)) for new DNA reactive (mutagenic)

# ABOUT PERMITTED DAILY EXPOSURE (PDE)

Permitted Daily Exposure (PDE): The maximum acceptable intake per day of residual solvent in pharmaceutical products (μg/day)

$$PDE = \frac{NOAEL \times \text{Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

ICH Q3C Guideline

F1 = A factor to account for extrapolation between species
F2 = A factor of 10 to account for variability between individuals
F3 = A variable factor to account for toxicity studies of short-term exposure
F4 = A factor that may be applied in cases of severe toxicity
F5 = A variable factor that may be applied if the no-effect level was not established

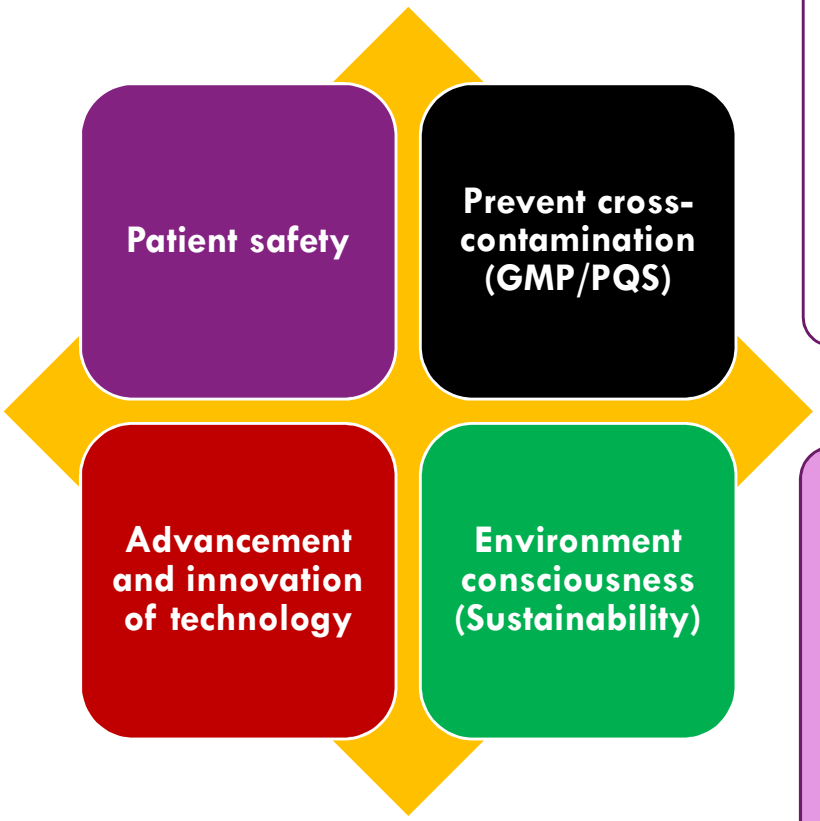
ICH Q3C: NOEL
ICH Q3D: NO(A)EL
EMA, PIC/S: NOAEL
→PoD

PDE value is used to determine the cleanliness of the equipment and to determine the open exposure control of the impurities to prevent cross-contamination as well

NOAEL is determined from non-clinical and clinical data

Particularly for EU and PIC/S participating countries, it is necessary that these values are established and reported by the SMEs

# INTENT OF ICH QUALITY GUIDELINES, SAFETY AND QUALITY




- Put Patient's safety and maximize the efficacy of the new drug products and provide innovative drug products, fast
- Ensure the quality of the product with more insight look at the operation, building/equipment, testing and results
- Better understanding of the product and its better processes, this will lead guide the company to contribute the sustainability of the environment and employees

- Key learnings
  - Need for Pharmaceutical Quality System (PQS, ICH Q10)
    - Achieve Product Realization
    - Establish and Maintain a State of Control
    - Facilitate Continual Improvement
  - Maximize the knowledge and risk management of the product (KM, QRM, ICH Q8, Q11, and ICH Q9)
  - Pharmaceutical Lifecycle Management (established condition, ICH Q12)

# SECURE PHARMACEUTICAL SUPPLY CHAIN

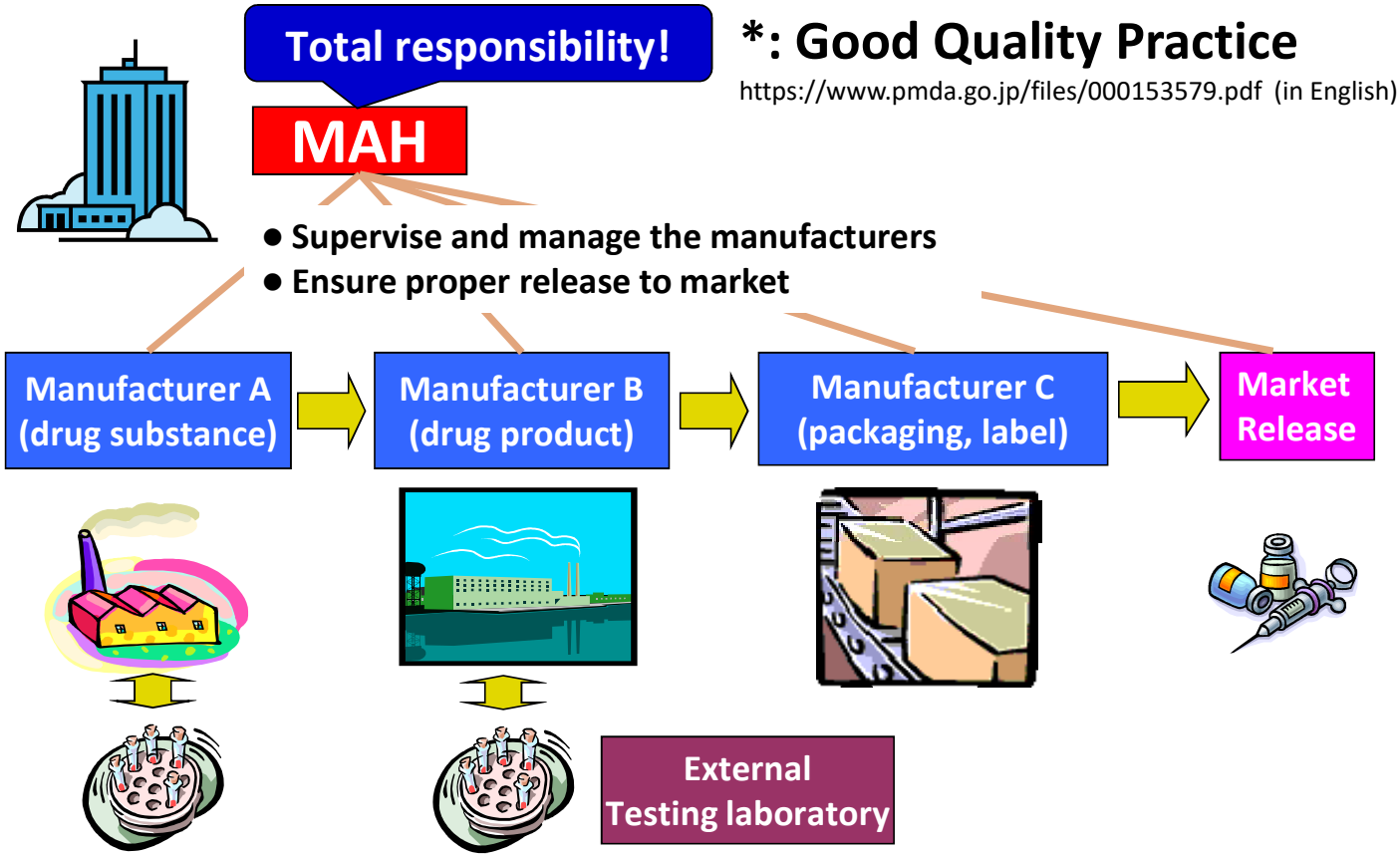
To ensure the traceability of Pharmaceutical product, clarify the responsibility in complex supply chain.

The risk assessment is extended to the supply chain of not only Drug Product but APIs or excipients and other product related stakeholders.

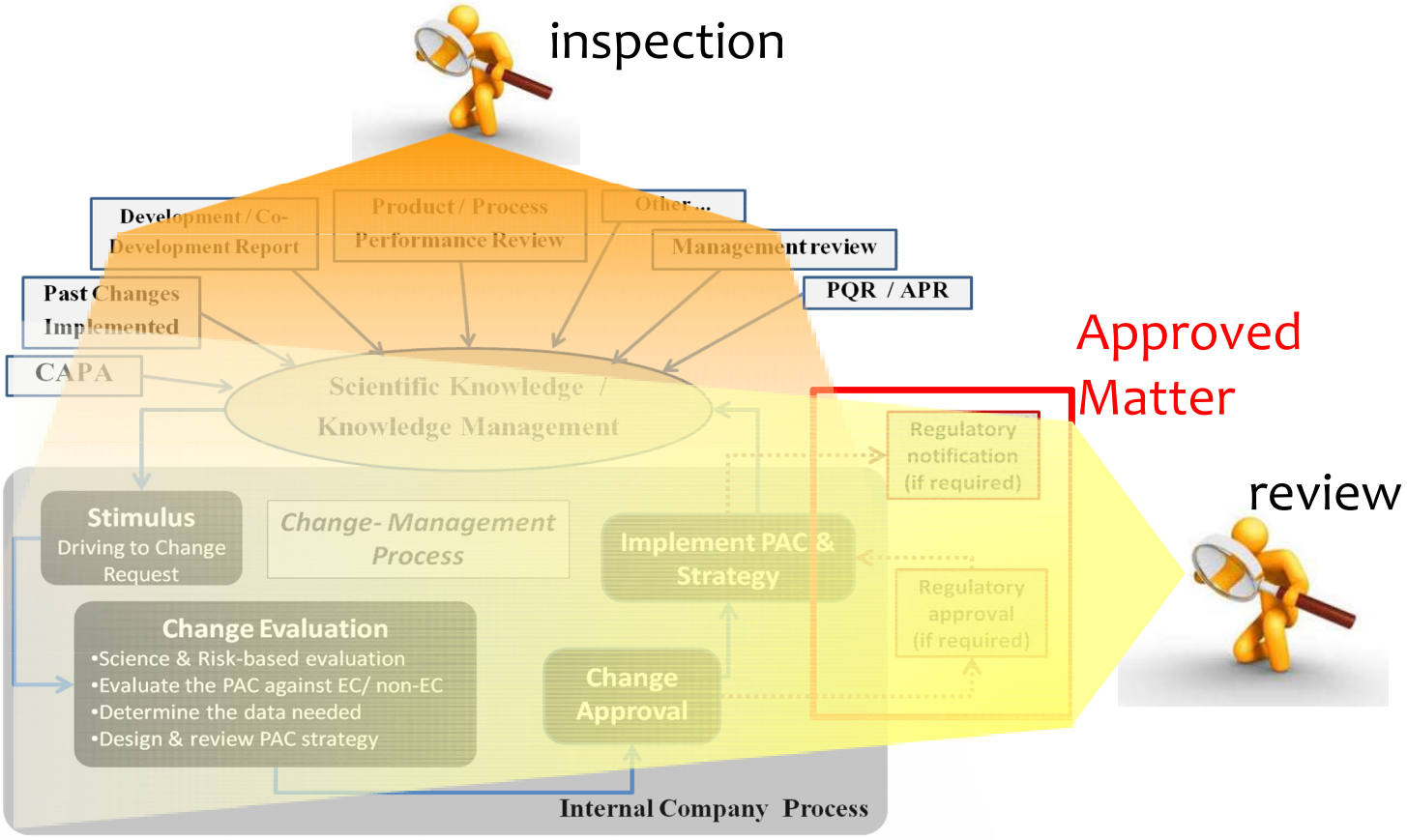
# PERCEIVED PROBLEM

- Pharmaceutical companies have responsibility to supply same quality of drug products to the patients in the global. Better understanding of the science and advancement in the technology, and use of knowledge and quality risk management led to higher degree of product quality
- Now Pharmaceutical companies rely on C(D)MO for the development of the products as well as to supply the drug products
- The responsibility of the pharmaceutical companies includes activities from the upstream to the down stream of the supply chain, and any change in the approved matter need to be notified by the stakeholders of the product manufacturing

# RESPONSIBILITY OF MAH BASED ON GQP* IN JAPAN



# REVIEW AND INSPECTION



# FROM SUPPLY CHAIN TO QUALITY VALUE CHAIN

- ICH guidelines are subject to revision to meet the demand for quality. As there is more demand for high level of product quality, there is better control over the product impurities
  - Genotoxicity impurities (ICH M7(R1))
  - Residual solvent (ICH Q3C)
  - Elemental analysis (ICH Q3D)
  - Extractable and leachable (ICH Q3E series)
- Use of database, digital technologies in development, processing, control and monitoring the products is becoming more important. These data are highly important to assure the quality as well as conveyed as a part of knowledge guiding to next new products
  - Pharmaceutical Quality System (ICH Q10)
  - Quality Risk Management (ICH Q9)
  - Product Lifecycle Management (ICH Q8, Q11, Q12)
- The relationship among pharmaceutical company and its service providers are **no longer a part of the supply chain, but as a value chain supplier to focusing on the quality of the product through communication, exchange new findings, and manage consistent production and control of the product**

# THANK YOU FOR LISTENING

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