Global Regulatory Harmonization

Xinning Yang, Ph.D.
Policy Lead, Guidance & Policy Team
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER | FDA

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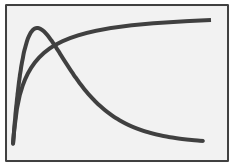
Clinical Pharmacology in Drug Development and Regulatory Review

Comprehensive Clinical Pharmacology Review Questions



To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

ACCESS

USE

Good Review Practices: Clinical Pharmacology Review of New Molecular Entity (NME) New Drug Applications (NDAs) and Original Biologics License Applications (BLAs). https://www.fda.gov/media/71709/download

International Regulatory Harmonization: Some Avenues for Discussions & Engagements

Regulatory Clusters

Global Bioequivalence Harmonisation Initiative (GBHI)

International Council for Harmonisation (ICH)

https://www.ema.europa.eu/en/partners-networks/international-activities/cluster-activities

https://pqri.org/gbhi-2024/

https://www.ich.org/page/ich-guidelines

ICH Guidelines related to Clinical Pharmacology

- Dose-Response Studies (E4) [1994]
- Ethnic Factors (E5(R1) /Q&As) [1998 / 2006]
- Clinical Trials in Geriatric Population (E7/Q&As) [1993 / 2010]
- Clinical Trials in Pediatric Population (E11(R1) /E11A) [2017 / ongoing]
- Clinical Evaluation of QT (E14/S7B Q&As) [2022]
- Definitions in Pharmacogenetics /Pharmacogenomics (E15) [2007]
- Qualification of Genomic Biomarkers (E16) [2010]
- Multi-Regional Clinical Trials (E17) [2017]
- Genomic Sampling (E18) [2017]
- Inclusion of Pregnant and Breastfeeding Individuals in Clinical (E21) [2022]

https://www.ich.org/page/efficacy-guidelines

Clinical Pharmacology Engagement in Recent ICH Guideline Development

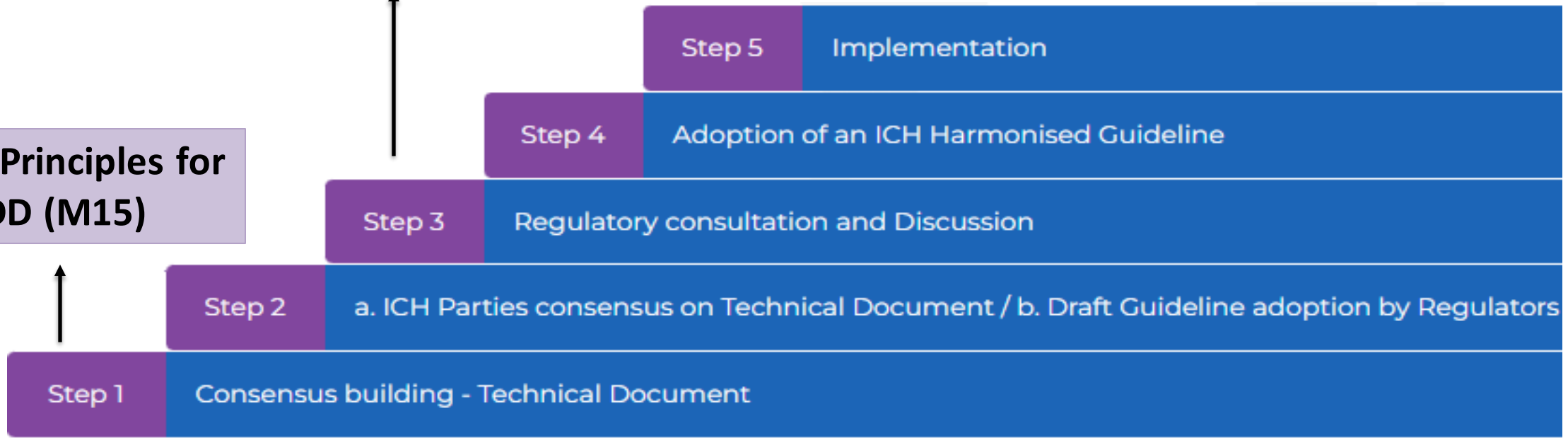
Biopharmaceutics Classification System-based Biowaivers (M9)

Analytical Method Validation and Study Sample Analysis (M10)

Clinical Evaluation of QT (E14/S7B Q&A)

Drug Interactions (M12)
BE for IR Solid Oral Dosage Forms (M13A) (OGD led)
Pediatrics (E11A) (OND led)

General Principles for MIDD (M15)



Need for Harmonized Global Guideline

- Motivation for Developing M12 Drug Interaction Guideline

In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies – Draft Guidance (2017)
US Food and Drug Administration (FDA)

Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications– Draft Guidance (2017)
US Food and Drug Administration (FDA)

Guideline on the investigation of drug interactions – Revision 1(2013)
European Medicines Agency (EMA)

Guideline on drug interaction for drug development and appropriate provision of Information (2018)
Pharmaceuticals and Medical Devices Agency (PMDA)

Review > Drug Metab Pharmacokinet. 2020 Feb;35(1):71-75. doi: 10.1016/j.dmpk.2019.10.006. Epub 2019 Oct 22.

Evaluation of drug–drug interactions in drug metabolism: Differences and harmonization in guidance/guidelines

Takafumi Iwatsubo [1]

Comparative Study > Curr Drug Metab. 2020;21(6):403-426. doi: 10.2174/1389200221666200620210522.

2020 FDA Drug–drug Interaction Guidance: A Comparison Analysis and Action Plan by Pharmaceutical Industrial Scientists

Sirimas Sudsakorn [1], Praveen Bahadduri [1], Jennifer Fretland [1], Chuang Lu [1]

A comparison of FDA, EMA & PMDA regulatory guidance for in vitro drug–drug interaction (DDI) assessments

by **Labcorp Drug Development** updated on **Wednesday, July 7, 2021**

- Some differences exist among the regulatory guidelines
  - Heterogenous expectations
  - Non-harmonious interpretation and translation
- Potentially increased drug development cost, delayed patient access and heterogenous recommendations

Adapted from: Dr. Raj Madabushi, ASCPT Satellite DDI Workshop 2022

ICH M12 EWG
- Leverage Expertise from Multiple Stakeholders

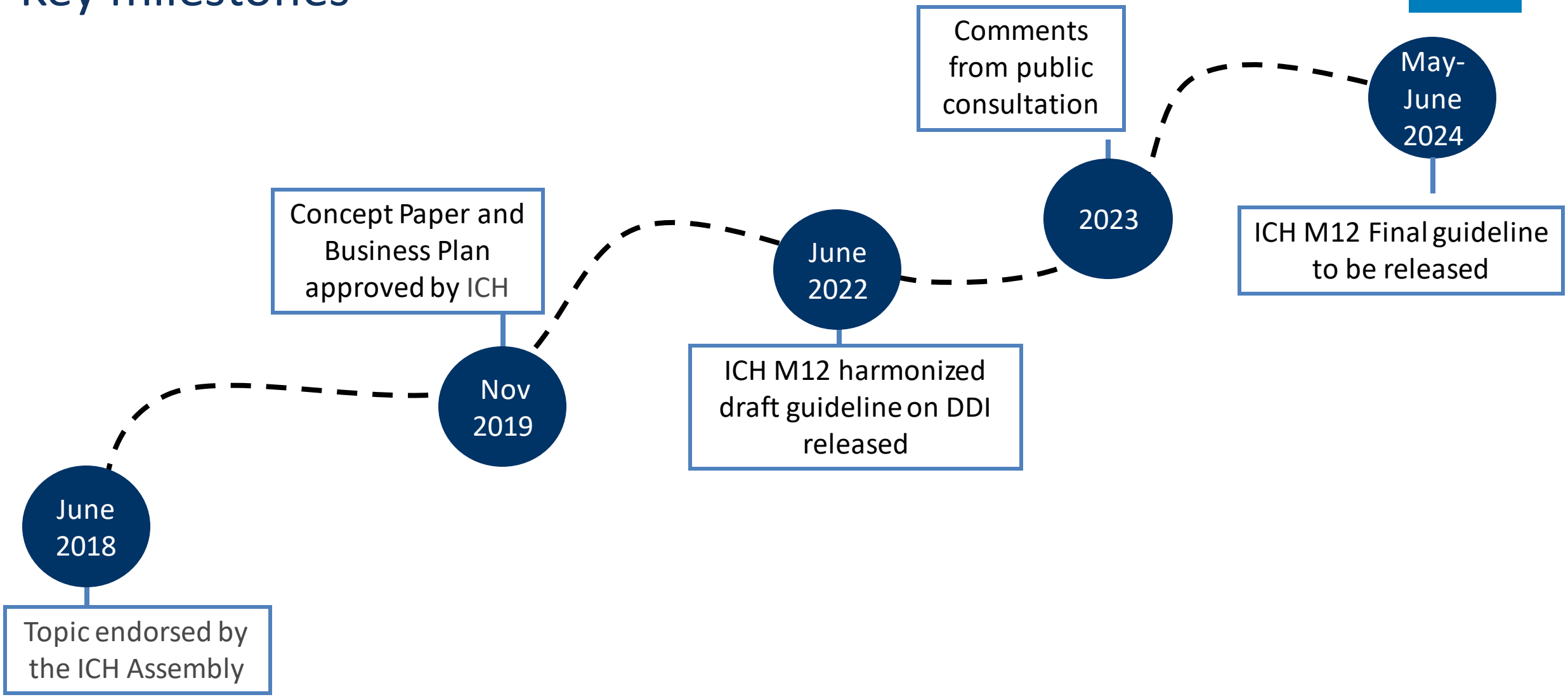
Regulatory agencies

Industry consortiums

Internal SMEs
Industry groups (e.g.,IQ)
Academia

ICH M12 Guideline

Key milestones



Modified from slide of Dr. Sheila Annie Peters (part of ICH M12 working group), DMDG meeting, 2022

What are the Future Opportunities for Harmonization?

Patients with **Organ Impairments** (e.g., Renal Function, Hepatic Function)

New therapeutic Modalities (e.g., ADC, Peptide, Oligos)

Pediatric and Maternal Health (e.g., Neonatal, Lactation Studies)

Impact of Factors Affecting Bioavailability (e.g., Food Effect)

Other Drug-Drug Inteaction Mechanisms (e.g., gastric pH change, therapeutic proteins, oral contraceptives)

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https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Acknowledgement

- ICH M12 EWG
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- OCP internal SMEs on DDIs