Updates on ICH Efficacy Related Guidelines:

M12, Drug Interaction Studies

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Joint US FDA – Health Canada ICH Public Meeting
February 24, 2023

Outline

- Background
- Highlights of the draft guideline
- Public consultation and next steps

Background

- Drug-drug interactions (DDIs) can occur when patients take more than one drug
  - May impact safety or efficacy resulting in altered benefit/risk
- The potential for drug interaction for new medicinal products should be evaluated.
  - Impractical to evaluate every drug interaction in clinical trials during new drug development
- Systematic risk-based strategies are essential to characterize drug interaction potential
  - Regulatory agencies have developed region-specific guidelines to assist drug developers

Need for harmonized global guideline

As of 2018

In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies – Draft Guidance (2017)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Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications– Draft Guidance (2017)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)

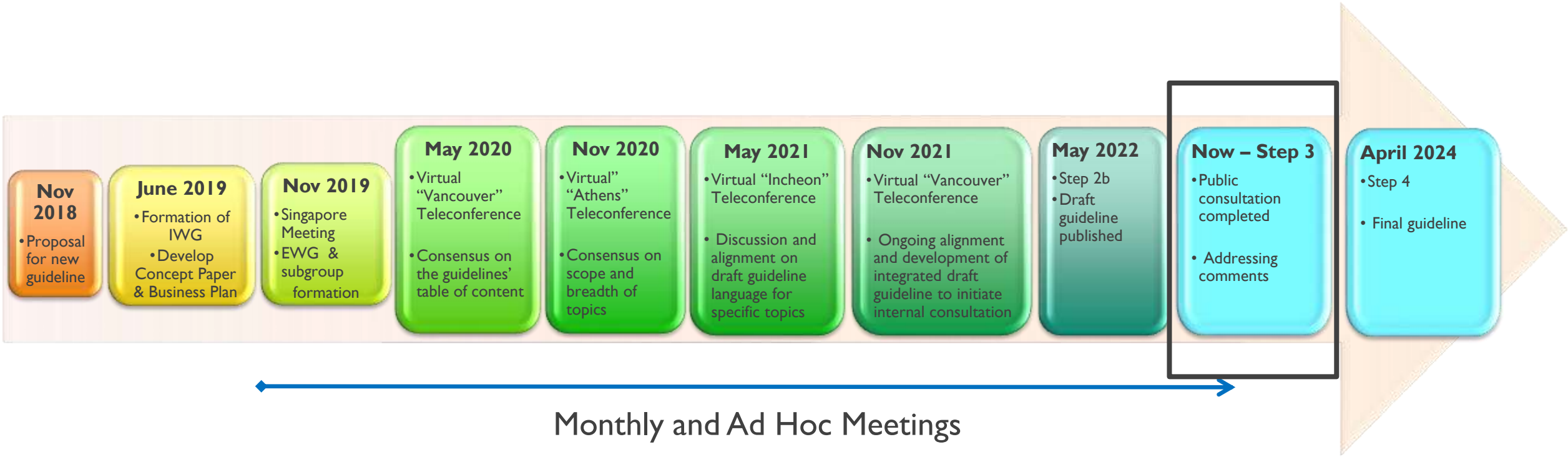
Guideline on the investigation of drug interactions – Revision 1(2012)
European Medicines Agency (EMA)

Concept paper on a revision (2017)

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

- 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

Formation and evolution of ICH M12



9 Regulatory Agencies

6 Industry Organizations

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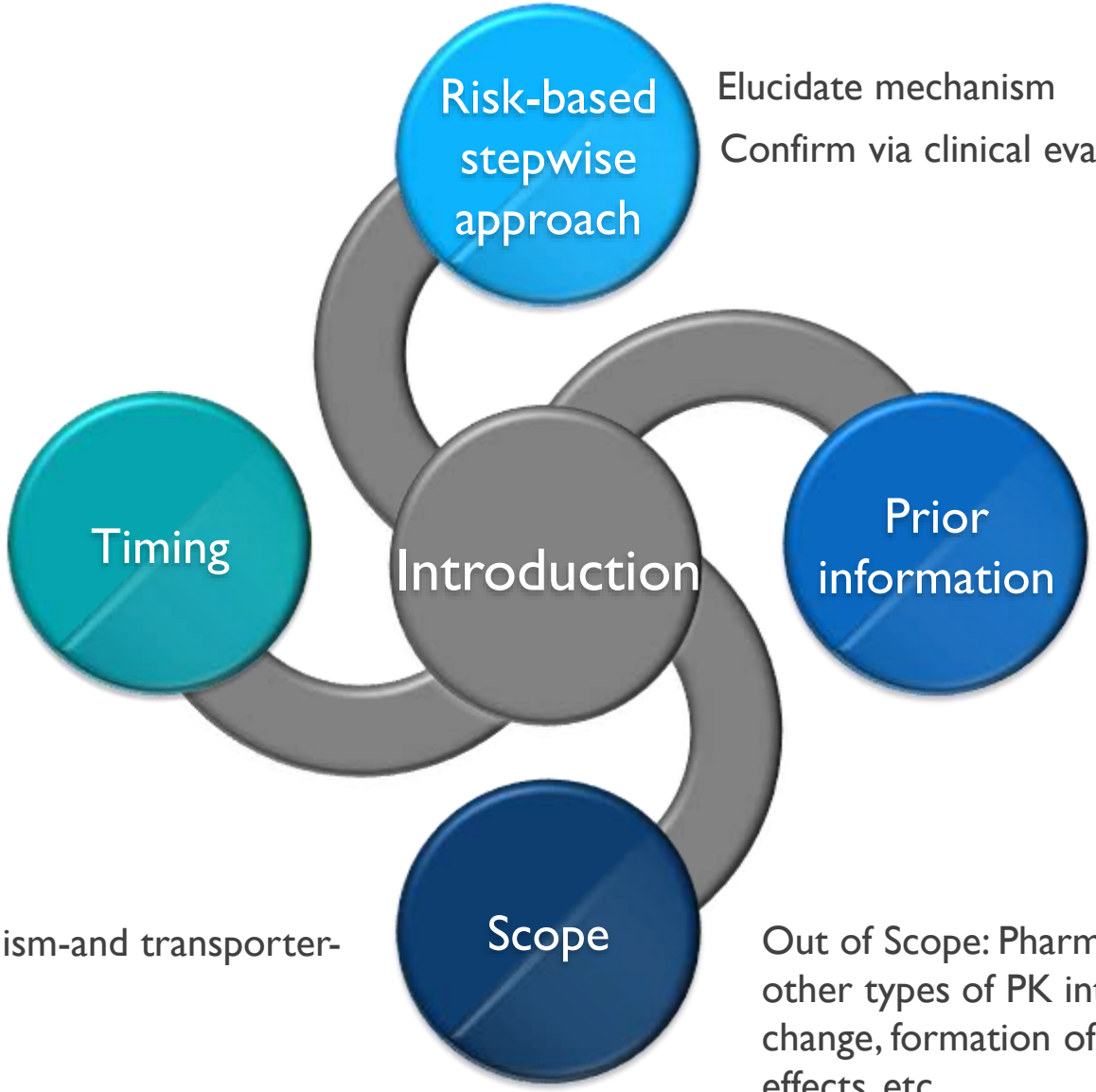
M12 – Objectives

- To develop recommendations that promote a consistent approach in designing, conducting, and interpreting in vitro and clinical DDI studies during the development of a therapeutic product
- To cover pharmacokinetic interactions, with a focus on enzyme- and transporter-mediated interactions
  - Small molecules and biologics (where enzyme- and transporter-mediated interactions may be anticipated),
  - Metabolite-mediated interactions,
  - Model-based data evaluation (mechanistic static model and physiologically based pharmacokinetic (PBPK) modeling) and DDI predictions

M12 – Table of Contents

- Introduction
  - Objective; Background; Scope; General principles
- In Vitro Evaluation
  - Metabolism-mediated interactions; Transporter-mediated interactions; DDI potential of metabolites
- Clinical Evaluation
  - Types of studies; Study planning and considerations
- Other Topics
  - Pharmacogenetics; Therapeutic protein DDIs
- Reporting and Interpretation of Clinical DDI Study Results
  - Pharmacokinetic data analysis; Reporting DDI results; Interpreting DDI study results
- Risk Assessment and Management
- Appendices
  - In vitro methodologies to evaluate metabolism- and transporter-based DDIs; Predictive modeling; Lists of drugs that can be used in in vitro and clinical studies
- References

M12 – Introduction



Elucidate mechanism

Confirm via clinical evaluation

Early evaluation

Avoid unnecessary restriction in later clinical studies

Utility of in vitro evaluation

Utility of clinical mass balance studies

In scope: Metabolism-and transporter-mediated DDIs

Out of Scope: Pharmacodynamic interactions and other types of PK interactions due to gastric pH change, formation of complexes or chelates, food effects, etc.

M12 – In vitro evaluation

- Metabolism-based
  - Substrate
  - Inhibition
  - Induction
  - Metabolite considerations

  (CYPs and UGTs)
- Data analysis and interpretation

  Inhibition:
  - Reversible inhibition
  - Intestinal inhibition
  - Time-dependent inhibition (TDI)

  Induction:
  - Basic mRNA fold-change method
  - Correlation methods
  - Basic kinetic model

- Transporter-based
  - Substrate
  - Inhibition
  - Induction
- Data analysis and interpretation
  - Efflux transporters (P-gp or BCRP)
  - Hepatic uptake transporters (OATP1B1/3)
  - Renal transporters (OAT1/3, OCT2, MATEs)

Protein binding considerations for highly bound drugs

UGT: Uridine 5'-diphospho264 glucuronosyltransferase; CYP: cytochrome P450; P-gp: P-glycoprotein; BCRP: breast cancer resistance protein; OATP: Organic anion transporting polypeptide; OAT: Organic anion transporter; OCT: Organic cation transporter; MATE: Multidrug and toxin extrusion protein

M12 – Clinical topics

- Type of clinical studies
  - Stand-alone studies
  - Nested studies
  - Studies with index substrates/perpetrators
  - Cocktail studies
- Study design and planning considerations
  - CYP
  - UGT
  - Transporters (Potential utility of endogenous markers)
- Other topics
  - Pharmacogenetic considerations
  - Considerations for therapeutic proteins
- Expectations for reporting and interpretation
  - Data analysis
  - No-effect boundaries
  - Considerations for extrapolation
- Risk assessment and management
  - General considerations

M12 – Appendices

- Experimental details for various in vitro studies
- Predictive modelling approaches - static mechanistic and dynamic mechanistic (PBPK)
  - Potential applications
    - Characterize potential for DDIs
    - Indicate whether a clinical DDI study is needed
    - Support some clinical recommendations in the absence of a clinical DDI study
  - Best practice considerations when applying such approaches
- Illustrative lists of drugs that can be used in in vitro and clinical DDI studies for CYPs, UGTs and Transporters

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Public Consultation

- Public comment period closed on 11/30/2022

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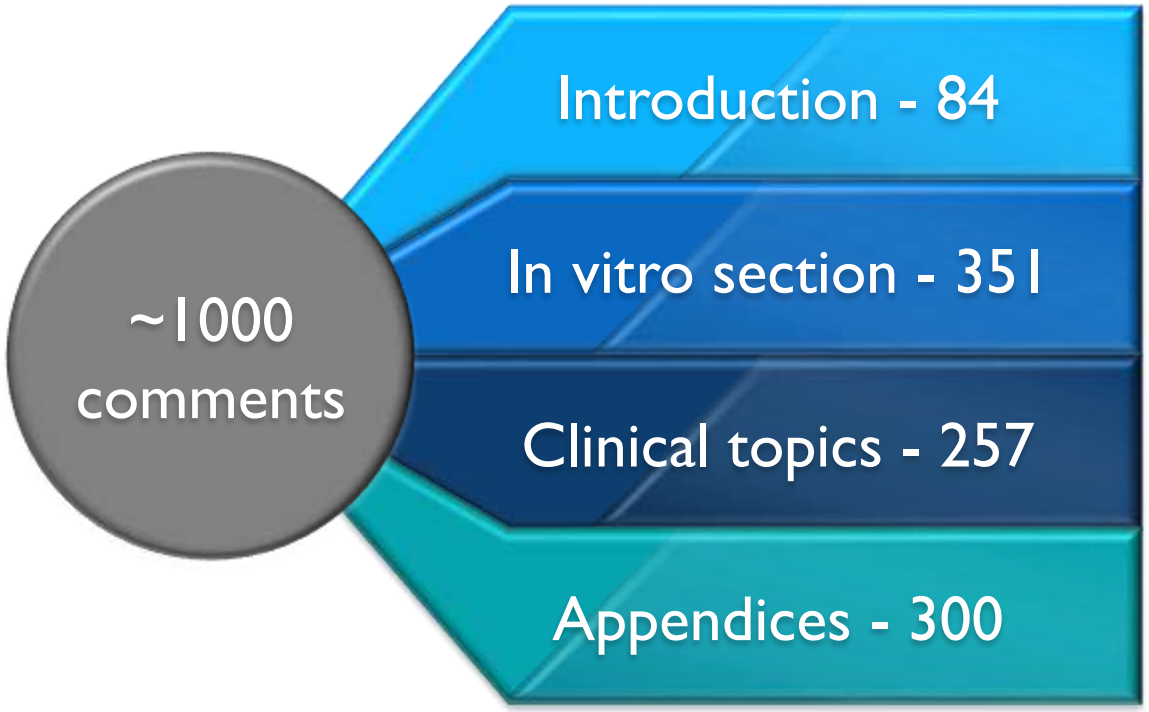
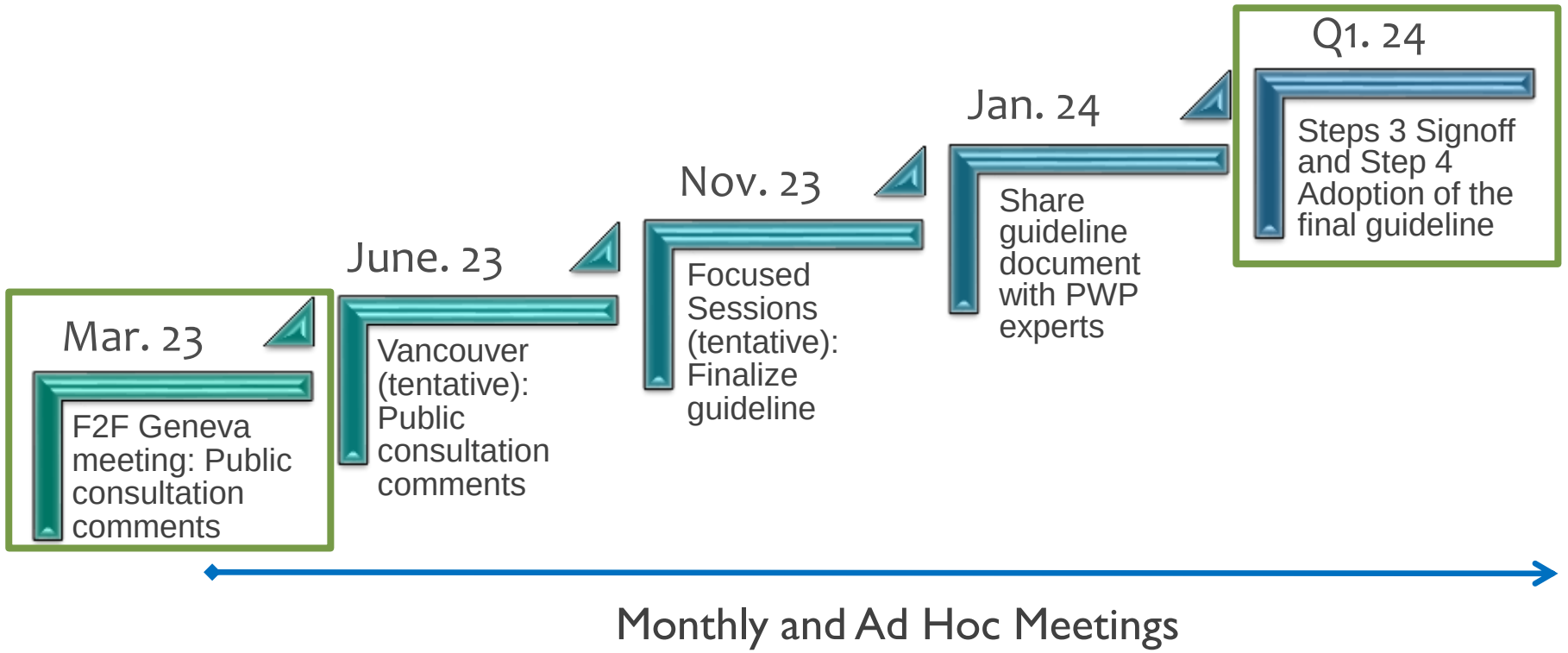
Stakeholders

20 Pharmaceutical Companies
4 Consortia/Associations
1 Academia



Next Steps


Mar. 23
F2F Geneva meeting: Public consultation comments
June. 23
Vancouver (tentative): Public consultation comments
Nov. 23
Focused Sessions (tentative): Finalize guideline
Jan. 24
Share guideline document with PWP experts
Q1. 24
Steps 3 Signoff and Step 4 Adoption of the final guideline
Monthly and Ad Hoc Meetings

Acknowledgements

DELEGATIONS	REPRESENTATIVES
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IFPMA-Switzerland (International Federation of Pharmaceutical Manufacturers & Associations)	Ms. Xiaolu Tao (Standing Observer)
MFDS- Republic of Korea (Ministry of Food and Drug Safety)	Ms. Ji Sun Kim (Topic Leader)
IGBA-World (International Generic and Biosimilar Medicines Associations)	Dr. Michael Forstner (Topic Leader)
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ICH Secretariat	Secretariat Working Group


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