Updates on ICH Efficacy Related Guidelines:

M12, Drug Interaction Studies

Kellie Schoolar Reynolds, Pharm.D.
Director, Division of Infectious Disease Pharmacology
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Joint US FDA – Health Canada ICH Public Meeting
February 22, 2024

Outline

- Background (general principles, objectives and scope, timeline)
- Table of contents
- Five selected topics
  - In vitro cut-off values
  - Drugs with high protein binding
  - Endogenous biomarkers
  - Studies with concomitant medications
  - Interpretation of study results

General principles

- Drug-drug interactions (DDIs) can occur when patients take more than one drug
  - May impact safety or efficacy, resulting in altered benefit/risk

- Evaluation of DDI potential
  - Risk based
  - Stepwise (in vitro to clinical, often includes predictive modeling)
  - As early in drug development as practicably possible

General principles

- Timing and utility of non-clinical studies, clinical studies, predictive modeling
  - Dependent on clinical context and type of product

- Interpretation and translation of DDI study results should be based on an understanding of the variability of the drug exposures and the exposure-response relationships for desirable and undesirable drug effects

Objectives of M12 Guideline

- Develop recommendations that promote a consistent approach in designing, conducting, and interpreting in vitro and clinical DDI studies during development of a therapeutic product

- Reduce uncertainty for the pharmaceutical industry to meet the expectations of multiple regulatory agencies, which may lead to more efficient use of resources

Scope of M12 Guideline

- Scope includes:
  - Pharmacokinetic interactions, with a focus on enzyme- and transporter-mediated interactions
  - Small molecules and biologic products (monoclonal antibodies and antibody-drug conjugates)

- Out of scope:
  - Pharmacodynamic interactions; pharmacokinetic interactions due to gastric pH change, formation of complexes or chelates, food effect
  - New modalities, such as oligonucleotides

The Journey

Nov 2018
Proposal for new guideline

June 2019
Formation of IWG
Develop Concept Paper & Business Plan

Nov 2019
Singapore Meeting
EWG & subgroup formation

May 2020
- Virtual "Vancouver" Teleconference
- Consensus on the guidelines' table of content

Nov 2020
- Virtual" "Athens" Teleconference
- Consensus on scope and breadth of topics

May 2021
- Virtual "Incheon" Teleconference
- Discussion and alignment on draft guideline language for specific topics

Nov 2021
- Virtual "Vancouver" Teleconference
- Ongoing alignment and development of integrated draft guideline to initiate internal consultation

May 2022
- Step 2b
- Draft guideline published

Nov 2022
- Public consultation completed
- Compiling comments

March 2023
Geneva Interim Meeting
- Strategy
- Begin Addressing comments

Oct - Nov 2023
Prague Meeting
- Finalize guideline
- Initiate Clearance

March 2024
Step 4
Adoption of ICH M12

Public Consultation

- Public comment period closed on 11/30/2022

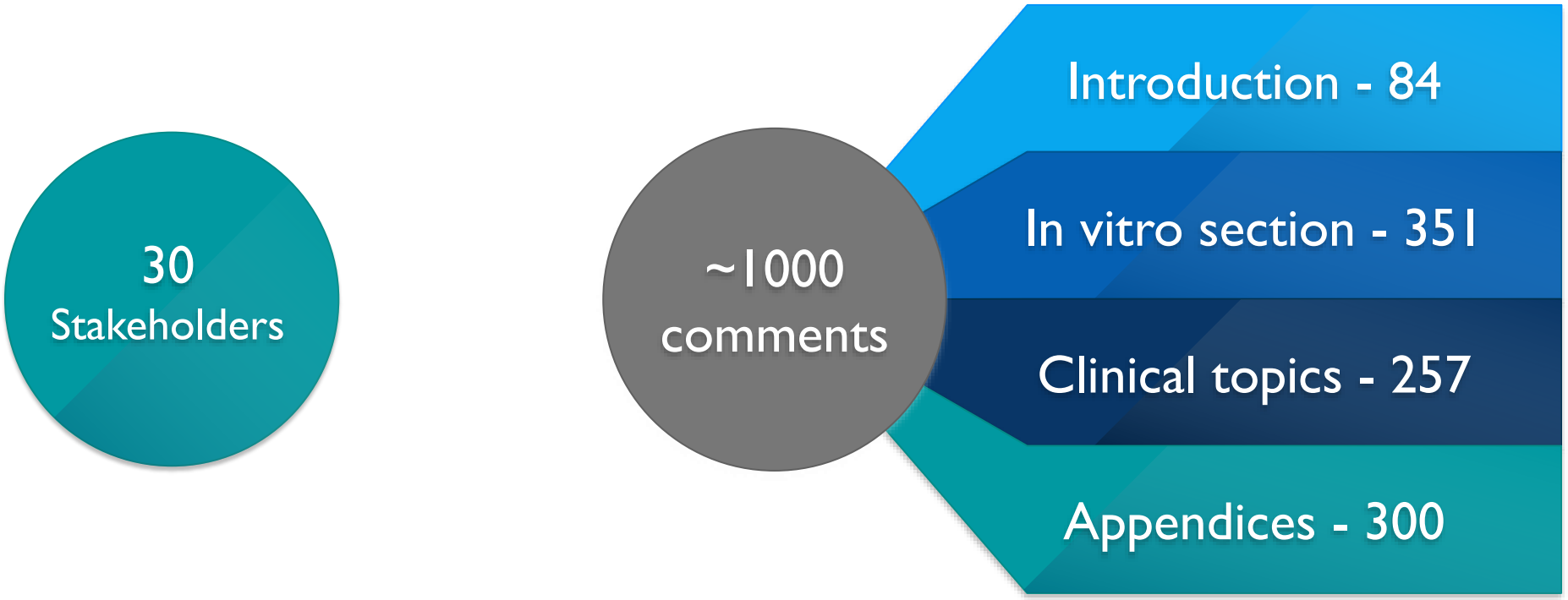
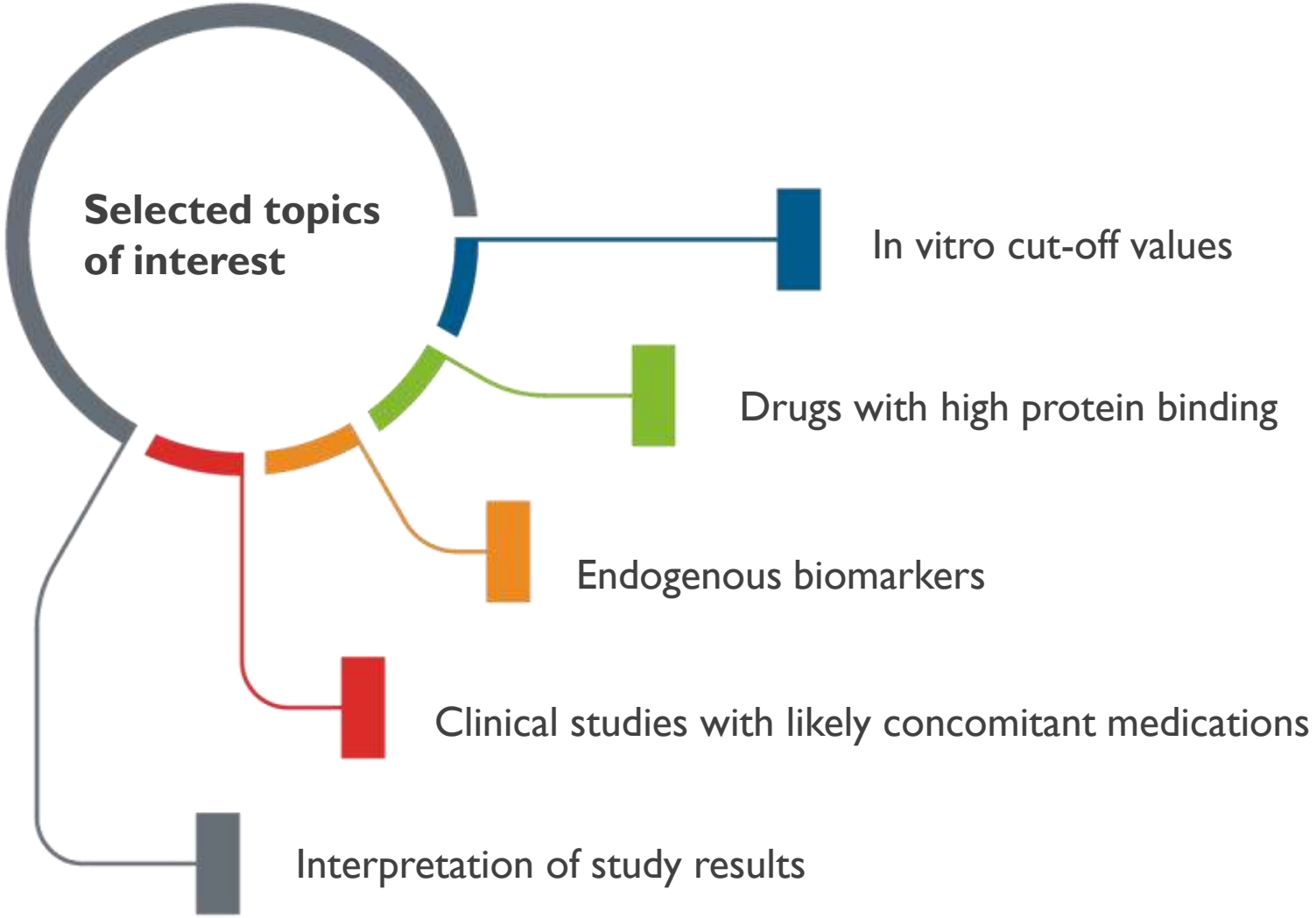


Table of Contents

- 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; **Endogenous Biomarkers**
- Other Topics
  - Pharmacogenetics; Therapeutic protein DDIs

Table of Contents

M12 – Topics to discuss today



In vitro cut-off values

- Cut-off values compare an in vitro measure of inhibition or induction with an estimated clinical exposure, to determine whether a clinical DDI study is recommended
- Factors considered when selecting cut-off values for M12 guideline
  - Consistency among regional guidelines
  - In vitro-in vivo analyses (literature; FDA and EMA approved products)
  - Impact of capping protein binding
  - Likelihood of false negative prediction

Drugs with high protein binding

- The Draft Guideline (2022) indicated the following regarding protein binding measurements
  - The are uncertainties in accuracy of protein binding measurements for highly bound drugs (i.e. >99% protein binding)
  - Due to uncertainties, fraction unbound in plasma should be capped at 0.01 (1%)
  - However, there have been advances in the methodology and this is an active area of research
  - In some situations, measure fraction unbound less than 0.01 can be used in the accuracy and precision of measurement is demonstrated (validation data, including bioanalytical method, appropriate positive controls)

Drugs with high protein binding

- Based on comments received, the working group discussed the need for additional clarity regarding expectations
  - Bioanalytical methods
  - When positive controls are needed
  - Whether multiple protein binding experimental approaches are needed
- External experts (industry) presented evaluation results
- Literature review
- Revise the guideline
  - Clarity throughout the document
  - Added an appendix that describes considerations for protein binding measurements for highly bound drugs

Endogenous Biomarkers

- The Draft Guideline (2022) indicated the following regarding the use of endogenous biomarkers
  - Recent literature: potential utility of endogenous substrates for some drug transporters
  - Evaluation of change in exposure of the endogenous substrate in the presence of investigational drug may provide information about the drug's potential as a transporter inhibitor

Endogenous Biomarkers

- Based on comments received and continued advancements in this emerging area, the working group discussed the need for additional information in the guideline
- External experts (industry) presented evaluation results
- Literature review
- Revise guideline to clarify how this emerging area can contribute to drug interaction evaluation

Clinical studies with likely concomitant medications

Draft Guideline (2022) indicated

- Drugs with well-understood and predictable pharmacokinetic and DDI properties regarding level of inhibition, induction, or metabolic pathway are known as "index drugs"

- Studies with likely concomitant medications often follow index studies
  - consider the mechanistic understanding of the potential for DDIs and the relative frequency of co-administration
  - often informative to patients and medical professionals, but the results may be difficult to extrapolate to other drugs

- Lack of index drugs for transporters and UGT enzymes
  - DDI studies for these pathways often include concomitant medications

Clinical studies with likely concomitant medications

- Based on comments requesting more clarity on specific studies with concomitant medications, working group further discussed the topic
- In general, selection of potential concomitant mediations for DDI studies is case-by-case, depending on therapeutic area, intended population, and the safety and efficacy properties of the drugs
- Consulted with external expert to refine the lists of UGT substrates and inhibitors included in the guideline appendix
- Conducted literature and database research to refine the lists of transporter and UGT substrates and inhibitors included in the guideline appendix

Interpreting Results

- While writing the draft guideline and addressing comments, the interpretation of results was a topic of high interest
- Overall principle- Emphasis on use of exposure-response information to determine no-effect boundaries for the drug as an object
  - No effect-boundaries represent the interval within which a change in systemic exposure measure is considered not significant enough to warrant clinical action (e.g., avoiding coadministration, dose or schedule adjustment, or additional therapeutic monitoring)
  - The point estimate of the ratio (with/without precipitant) is normally evaluated in relation to the no-effect boundary. Variability should also be taken into consideration
  - Consider all available evidence when interpreting the results

Acknowledgements

DELEGATIONS	REPRESENTATIVES
EC-Europe (European Commission)	Dr. Carolien Versantvoort (Topic Leader) Dr. Elin Lindhagen (Deputy topic Leader)
FDA-US (Food and Drug Administration)	Dr. Rajanikanth Madabushi (Rapporteur) Dr. Kellie Reynolds (Topic Leader) Dr. Xinning Yang (Deputy Topic Leader) Ms. Helen Heymann (Rapporteur Supporter, Content Manager)
MHLW/PMDA- Japan (Pharmaceuticals and Medical Devices Agency)	Dr. Akihiro Ishiguro (Regulatory Chair) Dr. Motohiro Hoshino (Deputy Topic Leader)
EFPIA- Europe (European Federation of Pharmaceutical Industries and Associations)	Dr. Sheila-Annie Peters (Topic leader) Dr. Venkatesh Pilla Reddy (Deputy topic leader)
JPMA- Japan (Japan Pharmaceutical Manufacturers Association)	Dr. Sou Miyoshi (Topic Leader) Mr. Ryota Shigemy (Deputy Topic Leader)
PhRMA-US (Pharmaceutical Research and Manufacturers of America)	Dr. Vikram Sinha (Topic Leader) Dr. Heidi Einolf (Deputy Topic Leader)
Swissmedic- Switzerland	Dr. Matthias Roost (Topic Leader) Dr. Arno Nolting (Alternate)

DELEGATIONS	REPRESENTATIVES
NMPA-China (National Medical Product Administration)	Ms. Li Li (Topic Leader) Ms. Shujun Fu (Deputy Topic Leader)
IFPMA-Switzerland (International Federation of Pharmaceutical Manufacturers & Associations)	Ms. Tao Xiaolu (Standing Observer) Ms. Sylvia Zhao (Alternate)
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)
ANVISA- Brazil (Agência Nacional de Vigilância Sanitária)	Ms. Luiza Borges (Topic Leader) Ms. Mayara Chaves Faria Brina (Alternate)
TFDA- Chinese Tapei (Taiwan Food and Drug Administration)	Dr. Meng-Syuan Yang (Topic Leader)
CIOMS-World (Council for International Organizations of Medical Sciences)	Dr. Hervé Le Louet (Observer Expert)
TGA, Australia (Therapeutic Goods Administration)	Dr. Irene Horne (Observer Expert)
ICH Secretariat	Secretariat Working Group