# M12: Drug Interaction Studies

Step 4

## *Step 4* document – to be implemented

**Date: x March 2024**

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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# Background

- **This document has been signed off as a *Step 4* document (x March 2024) to be implemented by the ICH Regulatory Members**
- **The finalized *Step 4* document is anticipated to be implemented in the local regional regulatory system April/2024**
- **This document was developed based on a Concept Paper (18 November 2019) and a Business Plan (18 November 2019); *Step 2* document (24 May 2022) signed off by ICH Assembly for public consultation; *Step 3* public consultation comments (August-November 2022) and review of public consultation comments (January-December 2023)**

# Key Principles

- **The evaluation of the potential for an investigational drug to cause drug-drug interactions (DDIs) should be risk-based and proceed in a stepwise manner during the development**
- **Information about DDI potential should be gained as early in the drug development as practicably possible**
- **The timing and utility of different non-clinical studies, clinical studies, and predictive modelling is dependent on the context and type of the product**

# Key Principles (cont.)

- **The DDI potential of an investigational drug as an object (i.e., substrate) involves identification of the principal routes of the drug's elimination**
- **The DDI potential of an investigational drug as a precipitant (i.e., inhibitor/inducer) involves characterizing the effect of the drug on enzymes and transporters**
- **The approach for characterizing the DDI potential of metabolites with significant plasma exposure or pharmacological activity is similar to that considered for the parent drug**

# Key Principles (cont.)

- **If a drug is a substrate or inhibitor of a polymorphic enzyme, it is important to understand the impact of genotype on the pharmacokinetics to understand potential impact on DDI liability**
- **The risk of DDIs is generally lower for therapeutic proteins, so DDI assessment should consider the unique mechanism, pharmacology and clearance of moieties**
- **Interpretation and translation of the study results should be based on an understanding of variability of the drug exposures and exposure-response relationships for desirable and undesirable drug effects**

# Guideline Objectives

- **Main objectives and scope of the Guideline**
  - 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
  - Harmonize current regional guidances and facilitate drug development with the principles of 3Rs (Reduce, Refine, and Replace).
  - The Guideline is limited to pharmacokinetic interactions, with a focus on enzyme- and transporter-mediated interactions
  - Covers small molecules and biologics (monoclonal antibodies and antibody-drug conjugates). New modalities such as oligonucleotides are not included.

# Guideline Objectives

- Other key topics include metabolite-mediated interactions, role of endogenous biomarkers in the evaluation of DDI risk, predictive modeling (mechanistic static model and physiologically based pharmacokinetic (PBPK) modeling)
- Out of Scope: Pharmacodynamic interactions and other types of pharmacokinetic interactions due to gastric pH change, formation of complexes or chelates, food effects, etc.
- Implications and benefits of an internationally harmonized guidance:

- Reduced uncertainty for pharmaceutical industry to meet the requirement of multiple regulatory agencies, which may lead to more efficient utilization of resources

# 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 (cont.)

- **Reporting and Interpretation of Clinical DDI Study Results**
  - Pharmacokinetic data analysis; Reporting DDI results; Interpreting DDI study results
- **Risk Assessment and Management**
- **Appendices**
  - Glossary; Protein Binding; 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**

# Introduction

- **The Guideline harmonizes recommendations for designing, conducting and interpreting enzyme- or transporter-mediated in vitro and clinical DDI studies during the development of a therapeutic product**
- **The Guideline provides general expectations regarding**
  - **The nature of information that should be generated prior to conducting DDI studies**
    - Utility of clinical mass balance study in identifying and quantifying the contribution of elimination pathways
    - Utility of in vitro studies in identifying the main enzymes or transporter proteins involved and characterizing drug effects

# General Principles

- **Importance of early DDI evaluation to**
  - Assure safety of subjects in clinical studies
  - Avoid unnecessary restriction of concomitant medications or exclusion of subjects who require concomitant medications in clinical studies

- **A step-wise approach for DDI evaluation**
  - Often starts with in vitro experiments to elucidate potential mechanism
  - Based on the mechanistic knowledge clinical DDI studies are conducted to confirm the interaction

- **Timing of non-clinical and clinical studies is dependent on context and type of product**

# In Vitro Evaluation

- **Describes the importance of in vitro DDI evaluation and provides recommendations to predict whether the drug may be an *object* of clinical interactions related to:**
  - Cytochrome P450 (CYPs)
  - UDP-glucuronosyl transferases (UGTs)
  - Other enzymes
  - Transporters
- **Describes when to evaluate the in vitro DDI potential for *metabolite***
- **Provides recommendations when additional clinical characterization is needed**

# In Vitro Evaluation

- **Describes the importance of in vitro DDI evaluation and provides recommendations to anticipate clinical interaction and when to conduct clinical studies for drug as *precipitant***
  - Reversible inhibition of CYPs
  - Time-dependent inhibition (TDI) of CYPs
  - Induction of CYPs
  - Inhibition of UGTs
  - Inhibition of transporters

- **Describes when to evaluate the in vitro DDI potential for *metabolite* as *precipitant***

# In Vitro Evaluation

- **Describes the interpretation of in vitro DDI studies and indicates whether additional studies are expected or needed**
- **Describes when a measured fu,p (fraction unbound in plasma) can be used for all drugs, including highly protein bound drugs (i.e., >99% protein binding) for interpretation of results from the in vitro DDI studies**

# In Vitro Evaluation

## Interpretation of in vitro DDI: basic method reversible inhibition

| Enzyme / transporter | Calculation of precipitant cconcentrations | Target to *exclude* an interaction |
|---|---|---|
| *Gut*<br>CYP3A,<br>P-gp, BCRP | Dose/250 ml | $K_{i,u}$ >0.1 dose/250 ml<br>$IC_{50,u}$ >0.1 dose/250 ml |
| *Systemic*<br>CYPs,<br>MATEs, P-gp, BCRP,<br>OAT1/3, OCT2 | $f_{u,p} \times C_{max}$ | $K_{i,u}$> 50 $C_{max,u}$<br>$IC_{50,u}$> 50 $C_{max,u}$<br>$IC_{50,u}$> 10 $C_{max,u}$ |
| *Hepatic inlet*<br>OATP1B1/B3 | $C_{max,u,hep.inlet}$ =<br>$fu,p \times (Cmax + Fa \times Fg \times ka \times Dose/Qh/R_B)$ | $IC_{50,u}$> 10 $C_{max,u,hep.inlet}$ |

$K_{i,u}$ – inhibition constant; $IC_{50,u}$: unbound $IC_{50}$; $f_{u,p}$ – fraction unbound in plasma; $C_{max}$ – mean maximum concentration with the highest recommended dose at steady state; $C_{max,u}$ – mean maximum unbound concentration with the highest recommended dose at steadystate; $C_{max,u,hep.inlet}$ – mean maximum unbound concentration at the hepatic inlet with the highest recommended dose at steady state; Fa – fraction absorbed after oral dose; Fg – Fraction available after intestinal metabolism; ka – first order absorption rate constant; Qh – hepatic blood flow; $R_B$ – blood-to-plasma concentration ratio

# In Vitro Evaluation

## Interpretation in vitro DDI:

## basic method time dependent inhibition & induction

| | Calculation of Perpetrator concentrations | Target to *exclude* an interaction |
|---|---|---|
| *Time-dependent inhibition*<br>CYPs | [I] = 5×$C_{max,u}$ | ($k_{obs}$ + $k_{deg}$) / $k_{deg}$ < 1.25 $k_{obs} = \frac{(k_{inact} \times 5 \times C_{max,u})}{(K_{I,u} + 5 \times C_{max,u})}$ |
| *Induction*[&]<br>CYPs | [I] = **50**×$C_{max,u}$ | < 2-fold Induction at concentrations ≥ 50×$C_{max,u}$ |
| | [I] = 10×$C_{max,u}$ | R> 0.8 $R = \frac{1}{1 + d \times \frac{(E_{max} \times 10 \times C_{max,u})}{(EC_{50,u} + 10 \times C_{max,u})}}$ |

$C_{max,u}$ – mean maximal unbound plasma concentration of the inhibitor or inducer drug at steady state; $k_{obs}$ – apparent first-order inactivation rate constant of the affected enzyme; $k_{deg}$ – apparent first-order degradation rate constant of the affected enzyme; $k_{inact}$ – maximal inactivation rate constant; $K_{I,u}$ – unbound inhibitor concentration causing half- maximal inactivation

R – predicted AUC ratio of sensitive enzyme substrate with and without an inducer; $E_{max}$ – maximum induction effect; $EC_{50,u}$ – the unbound concentration causing half the maximal effect



[&] Another method for induction evaluation is correlation method. Refer to the Guideline for details.

# 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 ICH M12 Guideline:**

- Consistency among regional guidelines
- In vitro-in vivo analyses (literature; FDA, United States and EMA approved products)
- Impact of capping or not capping protein binding
- Likelihood of false negative prediction

# In Vitro Evaluation

## Provides general considerations to evaluate

### UDP-glucuronosyl transferases (UGT)-mediated DDIs

- A routine in vitro evaluation of investigational drugs to inhibit UGTs may not be warranted. Recommend evaluating UGT inhibition potential for drugs that are mainly metabolized by direct glucuronidation.
- Due to limited availability of data from clinical DDI studies that evaluate inhibition of UGT isoenzymes, cutoffs for determining DDI risk using basic models like those for CYP enzymes have not been established.

### Induction of UGT and transporters

- In vitro methods to evaluate induction of UGT and transporters are not well established. If an investigational drug has been observed to be an inducer of CYP enzymes via activation of nuclear receptors such as pregnane 360 X receptor (PXR) or constitutive androstane receptor (CAR), it is likely that UGTs and transporters regulated through these receptors will be induced.

# Clinical Evaluation

- **Describes the utility and considerations for clinical DDI studies such as**
  - Stand-alone and Nested DDI studies
  - Studies with index perpetrators and index substrates
  - Studies with expected concomitant use drugs
  - Cocktail studies
  - Endogenous biomarker studies
- **Describes study planning and design considerations for clinical DDI studies for inhibition and induction of CYPs, UGTs, and transporters**
- **Final guideline includes considerations for endogenous biomarker approach, including details regarding use of the approach to evaluate a drug as an inhibitor of hepatic OATP1B (Organic anion transporting polypeptide)**

# Other Topics

**Provides specific considerations for**

- **Utility of pharmacogenetic information in evaluating DDIs**
  - Prospective genotyping in clinical DDI studies is recommended
  - Exposure changes of the substrate in poor metabolizer phenotype is expected to approximate a strong inhibitor for that pathway
- **Evaluation of the DDI potential for therapeutic proteins with specific considerations for**
  - Proinflammatory cytokine-related mechanism
  - Antibody-Drug Conjugates

# Reporting and Interpreting Clinicial DDI Study Results

- **Lays out the expectations for reporting and data analysis**
- **Provides principles for data interpretation of object interaction and the determination of no-effect boundaries**
  - 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. *

* Sometimes a 90% confidence interval of 80-125% is proposed as a default no-effect boundary, this is however usually considered overly conservative.

# Reporting and Interpreting Clinicial DDI Study Results

- **Describes precipitant classification system (for CYPs)**
  - Currently, there are no classification systems for transporters or non-CYP enzymes. Specific substrates and inhibitors are lacking, and the interaction magnitude often has a more limited range compared to CYPs.
- **Elaborates on eextrapolation of study results to certain untested scenarios, including complex scenarios, e. g.**
  - Concurrent inhibition of an enzyme and a transporter or multiple transporters by a drug
  - Concurrent inhibition and induction of a drug's metabolic pathways
  - Use of inhibitors of more than one enzyme that metabolizes the drug
  - Inhibition of an enzyme other than the genetic polymorphic enzyme in poor metabolizers
  - Effect of enzyme/transporter inhibitors in subjects with varying degrees of impairment of drug eliminating organs (e.g., liver or kidney)
  - The two drugs affect one another's pharmacokinetics (both act as precipitant and object.

# Risk Assessment and Management

- **Provides general principles for risk assessment and management strategies**
- **In general, strategies should result in drug concentrations of the substrate drug falling within the no-effect boundaries.**
- **Risk assessment and development of risk minimization strategies should consider factors such as:**
  - The exposure-response relationships for safety and efficacy
  - The variability of observed DDI data, if available
  - The expected duration of concomitant drug use
  - The availability of monitoring parameters
- **DDI management strategies can include actions such as:**
  - Contraindicating or avoiding concomitant use
  - Temporarily discontinuing one of the interacting drugs
  - Modifying the dosing regimen of one of the drugs

# Appendices

- **Glossary** – provides definitions of key terms of interest
- **Protein Binding** – provides quality expectations for protein binding methods including bioanalytical assay and in-study performance and novel protein binding method validation
- **Provide eexperimental expectations for various in vitro studies**
- **Provides information on 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
- **Provides iillustrative lists of drugs that can be used in in vitro and clinical DDI studies for CYPs, UGTs and Transporters**

# Appendix 7.6

- **In consideration of regional guidelines and taking into account current scientific literature, lists of substrates and inhibitors for CYPs, UGTs, and transporters and also inducers for CYPs for in vitro experiments are provided.**
- **A list of the representative values of the turnover rate constant and half-life of major CYPs is provided.**
- **These tablets/lists are not comprehensive. Companies can use other drugs based on their experience and literature if those drugs are also suitable for the purposes.**

# Appendix 7.7

- In consideration of regional guidelines and taking into account current scientific literature, lists of index substrates and inhibitors for CYP enzymes that can be used in clinical studies are composed. Furthermore, a list of moderate and strong inducers is provided.
- Transporter substrates and inhibitors are generally less selective. In consideration of regional guidelines and taking into account current scientific literature, a selection of transporter substrates and inhibitors is provided.
- UGT substrates, inhibitors, and inducers are less established. Taking into consideration the current state of knowledge, UGT substrates and inhibitors/inducers that are useful for clinical DDI studies are listed.
- These tablets/lists are not comprehensive. Companies can use other drugs based on their experience and literature if those drugs are also suitable for the purposes.

# Conclusions

- **The harmonized Guideline promotes a risk-based approach to evaluating drug interactions mediated via metabolic enzymes and transporters**
- **Specific recommendations are provided for well-established topics while general considerations are provided for emerging areas, e.g., Protein Binding, Endogenous Biomarkers**
- **Utility and good practice considerations for predictive modeling approaches are described. This is an emerging area of high interest. Specific recommendations are beyond the scope of the Guideline**

# Considerations

- **Guidelines that should be read in conjunction**
  - Physiologically Based Pharmacokinetic Analyses- Format and Content Guidance for industry. US Department of Health and Human Services, FDA, United States. 2018
  - The Use of Physiologically Based Pharmacokinetic Analyses – Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls. Guidance for Industry. US Department of Health and Human Services FDA, United States. 2020
  - Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models. PSEHB/PED MHLW, Japan. 2020.
  - Reporting of physiologically based pharmacokinetic (PBPK) modeling and simulation. EMA/CHMP/458101/2016, Europe. 2018

# Considerations

- **Guidelines that should be read in conjunction**
  - OECD. Guidance document on the characterization, validation and reporting of Physiologically Based Kinetic (PBK) models for regulatory purposes. 2021
  - ICH M9 Biopharmaceutics Classification System-Based Biowaivers
  - ICH E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data, and Sample Coding Categories
  - ICH E18 Genomic Sampling and Management of Genomic Data
  - ICH M10 Bioanalytical Method Validation and Study Sample Analysis

# Additional Suggested Literature

## References of analyses providing support or relevant evidence to the criteria adopted by the guideline for CYP inhibition/induction or Transporter inhibition-mediated DDIs


Vieira ML , Kirby B, Ragueneau-Majlessi I, Galetin A, Chien JY, Einolf HJ, et al. Evaluation of various static in vitro-in vivo extrapolation models for risk assessment of the CYP3A inhibition potential of an investigational drug. Clin Pharmacol Ther. 2014;95(2):189-98.

Kenny JR, Ramsden D, Buckey DB, Dallas S, Fung C, Mohutsky M, et al. Considerations from the Innovation and Quality Induction Working Group in Response to Drug-Drug Interaction Guidances from Regulatory Agencies: Focus on CYP3A4 mRNA In Vitro Response Thresholds, Variability, and Clinical Relevance. Drug Metab Dispos. 2018 Sep;46(9):1285-1303.

Ramsden D, Fullenwider CL. Characterization of Correction Factors to Enable Assessment of Clinical Risk from In Vitro CYP3A4 Induction Data and Basic Drug-Drug Interaction Models. Eur J Drug Metab Pharmacokinet. 2022. Jul;47(4):467-482.

Zhou T,  Arya V, Zhang L. Comparing Various In Vitro Prediction Methods to Assess the Potential of a Drug to Inhibit P-glycoprotein (P-gp) Transporter In Vivo. J Clin Pharmacol. 2019;59(8):1049-60.

Vaidyanathan J, Yoshida K, Arya V, Zhang L. Comparing Various In Vitro Prediction Criteria to Assess the Potential of a New Molecular Entity to Inhibit Organic Anion Transporting Polypeptide 1B1. J Clin Pharmacol. 2016;56 Suppl 7:S59-72.

Lee SC, Arya V, Yang X, Volpe DA, Zhang L. Evaluation of transporters in drug development: Current status and contemporary issues. Adv Drug Deliv Rev. 2017;116:100-18.

# Additional Suggested Literature

**Reference providing examples of utility of endogenous biomarkers for evaluation of transporter inhibition potentials**

Rodrigues AD, Reimagining the Framework Supporting the Static Analysis of Transporter Drug Interaction Risk; Integrated Use of Biomarkers to Generate Pan-Transporter Inhibition Signatures. Clin Pharmacol Ther. 2023 May;113(5):986-1002. doi: 10.1002/cpt.2713. Epub 2022 Aug 10.

# Additional Suggested Literature

**References providing examples of Mechanistic static models for transporter inhibition-mediated DDIs**

Sane R, Cheung KWK, Kovács P, Farasyn T, Li R, Bui A, et al. Calibrating the In Vitro-In Vivo Correlation for OATP-Mediated Drug-Drug Interactions with Rosuvastatin Using Static and PBPK Models. Drug Metab Dispos. 2020;48(12):1264-70.

Chu X, Chan GH, Houle R, Lin M, Yabut J, Fandozzi C. In Vitro Assessment of Transporter Mediated Perpetrator DDIs for Several Hepatitis C Virus Direct-Acting Antiviral Drugs and Prediction of DDIs with Statins Using Static Models. AAPS J. 2022 Mar 21;24(3):45

Feng B, Hurst S, Lu Y, Varma MV, Rotter CJ, El-Kattan A, et al. Quantitative prediction of renal transporter-mediated clinical drug-drug interactions. Mol Pharm . 2013 Nov 4;10(11):4207-15.

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