



Drug Interaction Studies M12: An Overview

Step 2

Step 2 document – to be released for comments

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Background

- This document has been signed off as a ***Step 2*** document (24 May 2022) to be issued by the ICH Regulatory Members for public consultation
- This document was developed based on a **Concept Paper** (18 November 2019) and a **Business Plan** (18 November 2019)
- Anticipating finalization as a ***Step 4*** document to be implemented in the local regional regulatory system: **April/2024**

Key Principles

- **The potential for an investigational drug to cause drug-drug interactions (DDIs) should be risk-based and investigated 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

- **The DDI potential of an investigational drug as a victim involves identification of the principal routes of the drug's elimination**
- **The DDI potential of an investigational drug as a perpetrator involves characterizing the effect of the drug on enzymes and transporters**
- **The DDI potential of metabolites with significant plasma exposure or pharmacological activity is similar to that of the parent drug**

Key Principles

- **If a drug is a substrate or inhibitor of a polymorphic enzyme, it is important to understand the impact of genotype on the pharmacokinetics**
- **The risk of DDIs is generally lower for therapeutic proteins and 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
 - 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)

Guideline Objectives

- Covers metabolite-mediated interactions, model-based data evaluation (mechanistic static model and physiologically based pharmacokinetic (PBPK) modeling) and DDI predictions
- 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 harmonised guidance**
 - Reduced uncertainty for pharmaceutical industry to meet the requirement of multiple regulatory agencies and 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
- **Other Topics**
 - Pharmacogenetics; Therapeutic protein DDIs

Table of Contents

- **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**

Summary of Guideline Content

- **The Guideline harmonises 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

Summary of Guideline Content

- The timing of non-clinical and clinical studies
 - 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
- General principles and scope of the current Guideline

Summary of Guideline Content

- **Describes the importance of in vitro DDI evaluation and provides recommendations to anticipate clinical interaction and when to conduct clinical studies for**
 - Reversible inhibition of CYPs
 - Intestinal inhibition of CYPs
 - Time-dependent inhibition (TDI) of CYPs
 - Induction of CYPs
 - P-gp or BCRP inhibition
 - Inhibition of hepatic uptake transporters OATP1B1/3
 - Inhibition of renal transporters (OAT1/3, OCT2, MATEs)
 - Metabolite as inhibitor or inducer

Summary of Guideline Content

- **Describes the interpretation of in vitro DDI**
 - Basic Methods
 - Predictive Modeling
 - Clinical DDI Studies

Summary of Guideline Content

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

Target	Calculation of Perpetrator Concentrations	Target to exclude an interaction
Enzyme / transporter		
Gut	Dose/250 ml	
CYP3A4, P-gp, BCRP		$K_i > 0.1 \text{ dose}/250$
Systemic	$f_{u,p} \times C_{max}$	
CYPs,		$K_i > 50 C_{max,u}$
MATEs, P-gp, BCRP,		$K_i > 50 C_{max,u}$
OAT1/3, OCT2		$K_i > 10 C_{max,u}$
Hepatic inlet	$C_{max,u,hep.inlet} = f_{u,p} \times (C_{max} + F_a \times F_g \times k_a$	$K_i > 10 C_{max,u,hep.inlet}$
OATP1B1/B3	$\times \text{Dose}/Q_h/R_B)$	

K_i – inhibition constant; $f_{u,p}$ – fraction unbound in plasma; C_{max} – average maximum concentration with the highest recommended dose at steady state; $C_{max,u}$ – average maximum unbound concentration with the highest recommended dose at steady state; $C_{max,u,hep.inlet}$ – average maximum unbound concentration at the hepatic inlet with the highest recommended dose at steady state; F_a – fraction absorbed after oral dose; F_g – Fraction available after intestinal metabolism; k_a – first order absorption rate constant; Q_h – hepatic blood flow; R_B – blood-to-plasma concentration ratio

* Metabolite: $AUC_{metabolite} \geq 25\%$ of AUC_{parent} and also account for at least 10% of drug-related material in circulation (i.e., considered as major metabolite). Not all metabolites are relevant for inhibition of intestinal CYPs or transporters.

Summary of Guideline Content

Interpretation in vitro DDI – basic method time dependent inhibition & induction[#]

	Calculation of Perpetrator concentrations	Target to exclude an interaction
Time-dependent inhibition CYPs	$[I] = 5 \times C_{\max,u}$	$(k_{\text{obs}} + k_{\text{deg}}) / k_{\text{deg}} < 1.25$ $k_{\text{obs}} = \frac{(k_{\text{inact}} \times 5 \times C_{\max,u})}{(K_{I,u} + 5 \times C_{\max,u})}$
Induction CYPs ^{&}	$[I] = 15 \times C_{\max,u}$	< 2-fold Induction at $15 \times C_{\max,u}$ or higher concentrations
	$[I] = 10 \times C_{\max,u}$	$R > 0.8$ $R = \frac{1}{1 + d \times \frac{(E_{\max} \times 10 \times C_{\max,u})}{(EC_{50} + 10 \times C_{\max,u})}}$

$C_{\max,u}$ – maximal unbound plasma concentration of the inhibitor 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} – the concentration causing half the maximal effect

[#] Metabolite: $AUC_{\text{metabolite}} \geq 25\%$ of AUC_{parent} and also account for at least 10% of drug-related material in circulation (i.e., considered as major metabolite). For induction only when the parent drug is a prodrug or metabolite is mainly formed extra-hepatically.

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

Summary of Guideline Content

- **Provides general considerations to evaluate**
 - UDP-glucuronosyl transferases (UGT)-mediated DDIs
 - Induction of transporters

Summary of Guideline Content

- **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
- **Describes study planning and design considerations for clinical DDI studies for inhibition and induction of CYPs, UGTs, and transporters**
- **Mentions potential utility of endogenous substrates for inhibition of transporters**

Summary of Guideline Content

- **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

Summary of Guideline Content

- **Lays out the expectations for reporting and interpretation of clinical DDI results with focus on**
 - Data analysis
 - Determination of No-Effect boundaries
 - Emphasis on use of exposure-response information to determine no-effect boundaries for the drug as a victim
 - Perpetrator Classification System (for CYPs)
 - Extrapolation of study results to certain untested scenarios, including complex scenarios
- **Provides general principles for risk assessment and management strategies**

Summary of Guideline Content

- **Appendices describe/provide**
 - 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

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. EC, Europe. 2018

Considerations

- **Guidelines that should be read in conjunction**
 - OECD. Guidance document on the characterisation, 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

Conclusions

- **The harmonized Guideline promotes a risk-based approach to evaluating drug interactions mediated via enzymes and transporters**
- **Specific recommendations are provided for well-established topics while general considerations are provided for emerging areas**
- **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**

Contact

- **For any questions please contact the ICH Secretariat:**

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