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Drug Interaction Studies M12: An Overview

Step 2 document – to be released for comments

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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 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**

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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**

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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

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

Cytochrome P450 – CYP ; P-glycoprotein – P-gp ; Breast cancer resistance protein – BCRP ;
Organic anion transporting polypeptide – OATP ; Organic anion transporter – OAT ;
Organic cation transporter – OCT ; Multidrug and toxin extrusion protein – MATE

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

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

* Metabolite: $AUC_{metabolite}$ ≥ 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×$C_{max,u}$	(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 CYPs&	[I] = 15×$C_{max,u}$	< 2-fold Induction at 15×$C_{max,u}$ or higher concentrations
	[I] = 10×$C_{max,u}$	R> 0.8 $R = \frac{1}{1 + d \times \frac{(E_{max} \times 10 \times C_{max,u})}{(EC_{50} + 10 \times C_{max,u})}}$

$C_{max,u}$ – 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: $AUC_{metabolite}$ ≥ 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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