Current Guidelines for Drug-drug Interaction Evaluation

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June 2018

21ST International Conference on Drug-Drug Interactions
OUTLINE

- Recommended DDI approaches from the recent FDA DDI Guidance
- Study design, data analysis, and clinical implications
- Challenges and Scientific Gaps
Regulatory’s Guidance

- FDA Draft Guidance's for Industry:
  - “In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies” issued Oct 2017
  - “Clinical Drug Interaction Studies - Study Design, Data Analysis & Clinical Implications” 2017
  - “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers”
  - “Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry” issued Dec 2016

- EMA Guideline: issued 2012
  - “Guideline on the investigation of drug interactions”
Is Investigational Drug A Substrate Of Metabolizing Enzymes?
DRUG-DRUG INTERACTIONS

• **Drug as a victim** (other drug alter its PK)
  
  • what are the metabolic pathways & enzymes involved in it’s metabolism?
  • what fraction of the drug is eliminated through this pathway?

• **Drug as a perpetrator** (alters PK of other drugs)
  
  • Does my drug affect enzyme activity (CYP inhibition; CYP induction)?
  • At what concentration is it an inhibitor/inducer
Is Investigational Drug A **Substrate** Of Metabolizing Enzymes?

• *In-vitro* phenotyping for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 & CYP3A4/5 enzymes. If not, check:
  • CYP enzymes including CYP2A6, CYP2J2, CYP4F2, and CYP2E1
  • Other Phase I enzymes including monoamine oxidase (MAO), flavin monooxygenase (FMO), xanthine oxidase (XO), and alcohol/aldehyde dehydrogenase
  • Phase II enzymes including UDP glucuronosyl transferases (UGTs)

• **Data Analysis and Interpretation:**
  • Significant if the enzyme is responsible for > **25%** of the drug’s elimination based on the *in-vitro* phenotyping studies & human PK data
  • Sponsor should conduct clinical DDI studies using strong index inhibitors and/or inducers
Determining if Drug is an Enzyme Substrate?

- System: S9, cytosol, rCYP, pooled HLM, Human Hepatocytes
- Use both chemical/antibodies inhibitors with HLM & rCYPs
- Metabolic pathway ID before FIH
- Identify number and structures of metabolites produced
- Robust and reproducible methods with appropriate positive controls
Considerations for CYP-Mediated Interactions

If No Clinical DDI with strong Index Inhibitors/inducers

No need for additional DDI studies of same enzyme

If Positive Clinical DDI with strong Index Inhibitors/inducers

Evaluate additional Clinical DDI studies or by Modeling
Determining If Investigational Drug Is Inhibitor Of Metabolizing Enzymes
DRUG-DRUG INTERACTIONS

• **Drug as a victim** (other drug alter its PK)
  • what are the metabolic pathways & enzymes involved in it’s metabolism?
  • what fraction of the drug is eliminated through this pathway?

• **Drug as a perpetrator** (alters PK of other drugs)
  • Does my drug affect enzyme activity (CYP inhibition; CYP induction)?
  • At what concentration is it an inhibitor/inducer
### In-vitro CYP Inhibition Study

- **System:** Pooled HLM (>10), recombinant CYP enzymes, or pooled hepatocytes (>10)
- **HLM protein concentration should be < 1 mg/mL.** Correct for binding when necessary
- **Solvents should be <1%, 0.5% is preferred**
- **Include vehicle control & no-solvent control**
- **Validated & reproducible analytical assays and Positive controls kinetic constants (\(k_i\), \(K_i\) and \(k_{inact}\)) should be comparable to literature**

### Reversible inhibition

- Initially, test drug at high concentration as much as possible
  - e.g., \(50 \times I_{max,u}\) or \(0.1 \times \text{dose/250 mL}\)
- If positive, then retest to calculate IC\(_{50}\) or \(k_i\)

### TDI:

- Initially, preincubate drug for at least 30 min before adding the substrate
- If significant time- and NADPH-dependent, then retest in a definitive study for estimation of \(K_i\) & \(k_{inact}\)
Mechanistic Static Model: Net Effect Model

\[
\frac{\text{AUC}'_{po}}{\text{AUC}_{po}} = \left( \frac{1}{[A_H \times B_H \times C_H] \times f_m + (1 - f_m)} \right) \times \left( \frac{1}{[A_G \times B_G \times C_G] \times (1 - F_G) + F_G} \right)
\]

**Inactivation (TDI)**

\[
A = \frac{k_{\text{deg}}}{k_{\text{deg}} + \left( \frac{[I] \times k_{\text{inact}}}{[I] + K_i} \right)}
\]

**Induction**

\[
B = 1 + \frac{d \times E_{\text{max}} \times [I]}{[I] + EC_{50}}
\]

**Reversible Inhibition**

\[
C = \frac{1}{1 + \left( \frac{[I]}{K_i} \right)}
\]

Incorporates:
- Inactivation, induction, and reversible inhibition equations
- Hepatic (H) and gut (G) component
- \( f_m \) (fraction of victim drug metabolized by the affected enzyme)
- \( F_G \) for CYP3A (fraction of the victim drug escaping first pass metabolism in the gut)
- The scaling parameter for induction (i.e., \( d \)) is estimated through linear regression to a value that minimized the GMFE of the prediction via linear weighted least-squares regression

**What value to use for \([I]\)?**

\[
[I] = \frac{D \cdot k_a \cdot F_a}{Q_g}
\]

**Inhibitor Concentration**

\[
\text{Systemic Conc at liver Inlet} = \text{f}_{u,p} \times \left[ C_{\text{max}} + k_a \cdot D \cdot F_a / Q_h / R_B \right]
\]
Determining If Investigational Drug Is Reversible Inhibitor Of Metabolizing Enzymes

In-vitro investigation for the major CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 & CYP3A4/5

Data Analysis:

1. Basic Model
   - \( R_1 = 1 + (I_{\text{max,u}} / K_i) \)
   - \( R_{1, \text{gut}} = 1 + (I_{\text{gut}} / K_i) \) where \( I_{\text{gut}} = \text{dose}/250 \text{ mL} \)

2. AUCR prediction [using inhibition data only] by:
   - Mechanistic Static Model
     \[
     \text{AUCR} = \left[ \frac{1}{\text{C}_H \times \text{f}_m + (1-\text{f}_m) \times \text{C}_G \times (1-\text{f}_G) + \text{f}_G} \right] \times \frac{1}{1 + \frac{I}{K_i}}
     \]
   - Dynamic Mechanistic Model such as PBPK Model

3. In-Vivo Studies using a sensitive index substrate

Data Interpretation

- If \( R_1 \geq 1.02 \)
- Or \( R_{1, \text{gut}} \geq 11 \)
- If AUCR \( \geq 1.25 \)

Conduct a clinical DDI
Determining If Investigational Drug is Time-dependent Inhibitor Of Metabolizing Enzymes
Determining If Investigational Drug Is Time-dependent Inhibitor Of Metabolizing Enzymes

**In-vitro** investigation for the major CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 & CYP3A4/5

**Data Analysis:**

1. **Basic Model**
   \[
   R_2 = \frac{(K_{obs} + K_{deg})}{K_{deg}}
   \]
   where
   \[
   K_{obs} = \frac{(K_{inact} \times 50 \times I_{max,u})}{(K_I + 50 \times I_{max,u})}
   \]

2. **AUCR prediction [using TDI data only] by:**
   - **Mechanistic Static Model**
     \[
     AUCR = \left[ \frac{1}{A_h \times f_m + (1-f_m)} \times \frac{1}{A_G \times (1-f_G) + f_G} \right]
     \]
   - **Dynamic Mechanistic Model such as PBPK Model**

3. **In-Vivo Studies** using a sensitive index substrate

**Data Interpretation**

- If \( R_2 \geq 1.25 \)
- If \( AUCR \geq 1.25 \)
  - Conduct a clinical DDI
Determining If Investigational Drug is an Inducer Of Metabolizing Enzymes
**In-vitro CYP Induction Study**

- **System:** Plateable, cryopreserved or freshly isolated, human hepatocytes from at least 3 donors
  - Immortalized hepatic cell lines could be used also
  - Cell reporter assay results are considered supportive and not definitive
- mRNA and/or enzyme activity levels are acceptable. If TDI, then mRNA approach is recommended
- In-vitro test system should be validated to show that all major 6 CYPs are functional and inducible with positive controls. System should be robust and reproducible
- Investigational drug concentration range should include drug concentration that is $10 \times I_{\text{max},u}$ solubility/cytotoxicity permits
- Measure concentrations of the actual unbound parent drug in the medium at several time points during the last day of incubation (same as EMA),
  - unless loss of the parent drug due to in vitro drug metabolism, degradation, or lysosomal trapping is negligible
  - Or if loss of the parent drug was quantified in the system before the induction assay and compensated for through the amount of drug added or the intervals between medium changes (Guidance is lacking??)
Determining If Investigational Drug Is An Inducer Of Metabolizing Enzymes

In-vitro investigation for the major CYP enzymes CYP1A2, CYP2B6 & CYP3A4/5

- Basic Model
  - Fold Change Method (pre-established cutoff, of fold induction, % relative to PC)
  - Correlation methods (RIS OR ** $I_{\text{max,u}} / EC_{50}$)

- Basic Kinetic Model
  
  \[
  R3 = \frac{1}{1 + (d \times E_{\text{max}} \times (10 \times I_{\text{max,u}}) / (EC_{50} + (10 \times I_{\text{max,u}})))}
  \]

- AUCR prediction [analyze induction data only] by:
  - Mechanistic Static Model
    
    \[
    \text{AUCR} = \frac{1}{B_h \times f_m + (1-f_m)} \times \frac{1}{B_G \times (1-f_G) + f_G}
    \]
  - Dynamic Mechanistic Model such as PBPK Model

- If no CYP3A4/5 induction, then evaluation of CYP2C8/2C9/2C19 is not necessary

Preset Cutoff

- $R3 \leq 0.8$
- $\text{AUCR} \leq 0.8$

Conduct a clinical DDI using a sensitive index substrate

**Expert Opin Drug Metab Toxicol. 6(11):1399-1416**
Clinical Investigation

Drug is an Inducer/Inhibitor Of Metabolizing Enzymes
Considerations for CYP-Mediated Interactions

Prioritize in-vivo DDI evaluations for various CYPs with sensitive index substrate of specific pathways based on rank ordered of predicted AUCR values (use largest R or AUCR value)

- If no clinical DDI
  - No need for additional in vivo evaluation of other CYPs with lower potencies (smaller AUCR)

- If Positive Clinical DDI
  - Evaluate other CYPs starting with the next largest AUCR clinically or PBPK modeling

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Metabolites: DDI Potential

- Use synthesized or purified metabolite standard or radiolabeled drug

- Study metabolism in vitro studies if Metabolite:
  
  - Is active based on in vitro pharmacology & tox assessment
  
  - Contributes to ≥50% of the overall activity, considering both in vitro receptor occupancy & in vivo exposure

- Study Inhibition in vitro studies if Metabolite:

  ✓ Less polar than parent drug
  ✓ Structural alert for TDI
  ✓ $\text{AUC}_{\text{metabolite}} \geq 0.25 \text{AUC}_{\text{parent}}$

  More polar than parent drug
  &
  $\text{AUC}_{\text{metabolite}} \geq \text{AUC}_{\text{parent}}$
Determining If Investigational Drug is Substrate/Inhibitor Of Transporters
Determining If Investigational Drug Is a Substrate/Inhibitor Of Transporters P-gp & BCRP

Drug is identified as a substrate in-vitro for P-gp or BCRP if:
- Efflux Ratio ER ≥ 2
- If ER is inhibited by 50% by a known inhibitor at a concentration at least 10X IC\textsubscript{50}

Drug is identified as an inhibitor in-vitro for P-gp or BCRP if:
- Orally administered drugs
- $I_{\text{gut}}/IC_{50} \geq 10$
  Where $I_{\text{gut}} = \text{dose of inhibitor}/250 \text{ mL}$

Sponsor may consider in-Vivo study based on drug’s safety margin, therapeutic index and likely co-medication that are known P-gp or BCRP substrates/inhibitors in the indicated patient population
Determining If Investigational Drug Is a Substrate/Inhibitor Of Hepatic Uptake Transporters OATP1B1 & OATP1B3

- Determine if:
  - drug’s clearance through hepatic metabolism or biliary secretion is ≥ 25% of the total drug’s clearance
  - drug’s uptake into the liver is clinically important (e.g., for biotransformation or to exert a pharmacological effect)

- Drug is identified as a substrate in-vitro, if:
  - uptake of the drug in OATP1B1/OATP1B3-transfected cells is ≥ 2-fold of the drug’s uptake in empty vector-transfected cells
  - If uptake is inhibited by ≤50% by a known inhibitor at a concentration at least 10X IC50

Determine IC50 values following pre-incubation with the investigational drug for ≥ 30 min (TDI)

Drug is identified as an inhibitor in-vitro if:

\[ R = 1 + \left( \frac{f_{u,p} \times l_{\text{in,max}}}{IC_{50}} \right) \geq 1.1 \]

\[ l_{\text{in,max}} = \left( \frac{l_{\text{max}} + (F_a F_g \times k_a \times \text{Dose})}{Q_h / R_B} \right) \]

Sponsor may consider in-Vivo study based on drug’s safety margin, therapeutic index and likely concomitant medication that are known OATP1B1/1B3 substrates/inhibitors
Determining If Investigational Drug Is a Substrate/Inhibitor Of Renal Transporters OAT, OCT & MATE

- Determine if active renal active secretion of the parent drug by the kidney is ≥ 25% of the total clearance
  
  Active secretion = CLr – (fu,p × GFR)

- Drug is identified as a substrate in-vitro for OAT1, OAT3, OCT2, MATE1 & MATE2-K if:
  
  ✓ Ratio of drug’s uptake in the cells expressing the transporter versus control cells is ≥ 2
  ✓ If uptake is inhibited by ≤50% by a known inhibitor at a concentration at least 10X IC\textsubscript{50}

Drug is identified as an inhibitor in-vitro if:

✓ \( \frac{I_{\text{max,u}}}{IC_{50}} \) value is ≥ 0.1 for OAT/OCT2

✓ \( \frac{I_{\text{max,u}}}{IC_{50}} \) value is ≥ 0.02 for MATEs

**Elevated serum Creatinine levels could be due to inhibition of these transporters.**

**Sponsor may consider in-Vivo study based on drug’s safety margin, therapeutic index and likely co-medication that are known substrates/inhibitors**
FDA Perspectives: Clinical DDI Studies

• Sponsor determines the need for and timing of clinical DDI studies.

• Evaluate DDIs before the product is administered to patients who are likely to take co-medications that could interact with the investigational drug.

• Collect enough DDI information to prevent patients from being unnecessarily excluded from any clinical study because of their concomitant medication use.

• Endogenous Induction biomarker substrate such as 4B-hydroxycholesterol.
Major Changes in 2017 FDA Guidance Compared to the 2012 one

• FDA guidance is more in-line with the 2012 EMA guidance

• The need for validated and reproducible analytical in vitro assays. Positive controls kinetic constants should be comparable to literature values, in a robust/reproducible manner. Include no-solvent & VC

• Account for $F_u$ in in-vitro ($k_i, K_i$). If <1%, use $F_u$ as 0.01

• Safety factors were implemented (e.g., $50 \times I_{max,u}$ for TDI & $10 \times I_{max,u}$ for induction), limited by solubility/cytotoxicity

• Tier approach in predicting DDI. Predict DDI using the different mechanistic models (Static or Dynamic) by one mechanism separately (i.e., inhibition or induction)

• Use the Sensitive Index Substrate approach with DDI studies

• Nominal vs measured concentration in in-vitro induction experiment
Service Provided @ DDI-Edge Consulting, LLC

- Help set up a new DDI, ADME lab and capabilities
- Design/critique/evaluate appropriate in vitro DDI studies following FDA and EMA guidelines
- Interpret in vitro ADME data (e.g., CYP Inhibition/TDI/Induction/clearance), in vivo DDI, & Biomarkers studies
- Provide DDI risk assessment and modeling to predict potential magnitude of DDI
- Write DDI section for INDs and Investigator's Brochures
- Provide suggestions/recommendations on regulatory documents (e.g., FDA/ EMA queries), as needed from an ADME or clinical pharmacology perspective

To request consulting service:
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