Current Guidelines for Drug-drug Interaction Evaluation

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OUTLINE

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

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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- FDA Draft Guidance's for Industry: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

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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

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Determining If Investigational Drug Is **Inhibitor** Of Metabolizing Enzymes

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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 $0.1 \times$ 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

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

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

Inactivation (TDI)

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

Induction

$$C = \frac{1}{1 + \frac{[I]}{K_i}}$$

Reversible Inhibition

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} Inhibitor Concentration

Systemic Conc at liver Inlet

Inlet $C_{max,u,\,inlet}$ $[I]_h = f_{u,p} \times [C_{max} + k_a \cdot D \cdot F_a / Q_h / R_B]$

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

DMD 2008 36(8):1698-1708
DMD 2009 37(8):1658-1666

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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
   - $R_1 = 1 + (I_{max,u} / K_i)$
   - $R_{1,gut} = 1 + (I_{gut} / K_i)$ where I_{gut}=dose/250 mL
2. AUCR prediction [using inhibition data only] by:
   - Mechanistic Static Model

$$AUCR = \left[\frac{1}{C_H \times f_m + (1 - f_m)} \times \frac{1}{C_G \times (1 - f_G) + f_G} \right]$$

$$C = \frac{1}{1 + \frac{[I]}{K_i}}$$

   - 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 $R_{1,gut} \geq 11$

If AUCR ≥ 1.25

Conduct a clinical DDI

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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

   $R_2 = (K_{obs} + K_{deg}) / K_{deg}$

   where $K_{obs} = (K_{inact} \times 50 \times I_{max,u}) / (K_I + 50 \times I_{max,u})$

2. AUCR prediction [using TDI data only] by:
   - Mechanistic Static Model

     $$AUCR = \left[\frac{1}{A_h \times f_m + (1-f_m)} \times \frac{1}{A_G \times (1-f_G) + f_G} \right]$$

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

   - 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 ≥ 1.25

Conduct a clinical DDI

Determining If Investigational Drug is an Inducer Of Metabolizing Enzymes

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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 X $I_{max,u}$ 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??)

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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 ** $I_{max,u}$ / EC_{50})
- Basic Kinetic Model

$$R3 = 1/[1+(d \times E_{max} \times (10 \times I_{max,u}) / (EC_{50} + (10 \times I_{max,u}))]$$

- AUCR prediction [analyze induction data only] by:
  - Mechanistic Static Model]

$$AUCR = \left[\frac{1}{B_h \times f_m + (1-f_m)} \times \frac{1}{B_G \times (1-f_G) + f_G} \right]$$

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

  - Dynamic Mechanistic Model such as PBPK Model
- If no CYP3A4/5 induction, then evaluation of CYP2C8/2C9/2C19 is not necessary

Preset Cutoff

R3 ≤ 0.8

AUCR ≤ 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 & ✓ $AUC_{metabolite} \geq 0.25\ AUC_{parent}$	More polar than parent drug & $AUC_{metabolite} \geq AUC_{parent}$

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_{50}

Drug is identified as an inhibitor *in-vitro* for P-gp or BCRP if:

- ✓ Orally administered drugs
- ✓ $I_{gut}/IC_{50} \geq 10$

Where I_{gut} = dose of inhibitor/250 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 IC_{50}

Determine IC_{50} values following pre-incubation with the investigational drug for ≥ 30 min (TDI)

Drug is identified as an inhibitor *in-vitro* if:

✓ $R = 1 + ((f_{u,p} \times I_{in,max})/IC_{50}) \geq 1.1$

$I_{in,max} = (I_{max} + (F_a F_g \times k_a \times Dose))/Q_h/R_B$

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 = CL_r – (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_{50}

Drug is identified as an inhibitor *in-vitro* if:

- ✓ $I_{max,u}/IC_{50}$ value is ≥ 0.1 for OAT/OCT2
- ✓ $I_{max,u}/IC_{50}$ 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 4*B-hydroxycholestrol.*

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 X $I_{max,u}$ for TDI & 10 X $I_{max,u}$ 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:

- Fill up the form at https://ddi-edge.squarespace.com/
- Or call me at 860-287-0855
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