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OFFICE OF CLINICAL PHARMACOLOGY

Updates on FDA's Drug-Drug Interaction (DDI) Final Guidances

Kellie S. Reynolds, Pharm.D.
Director, Division of Infectious Disease Pharmacology

Xinning Yang, Ph.D.
Policy Lead, Guidance & Policy Team

Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
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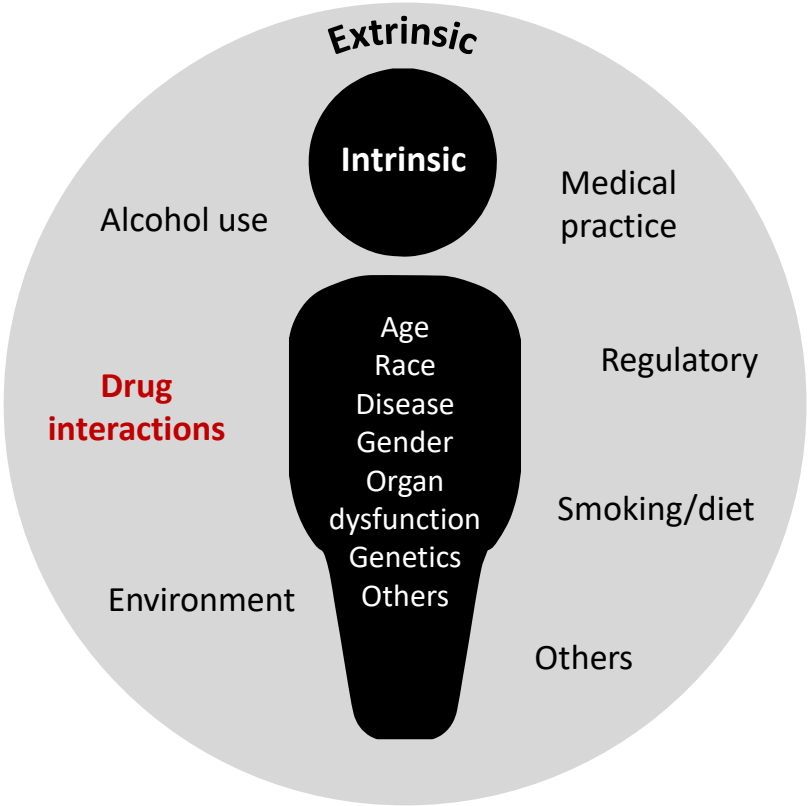
Factors Affecting Drug Exposure and Response

Critical Step:
Evaluate how these factors affect drug exposure and response



Ultimate goal:
Optimal dosing for patients with these individual factors

Adapted from: Huang S-M, Temple R, Clin Pharmacol Ther 84: 287-294, 2008
FDA Clinical Pharmacology guidance documents:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

Evolution of FDA DDI Guidances

- 1997 (In vitro)
- 1999 (In vivo)
- 2006 (Draft; In vitro and In vivo)
  - P-gp
  - Detailed appendices- methodology
- 2012 (Draft; In vitro and In vivo)
  - More transporters
  - Model-based DDI evaluations
  - Labeling recommendations
  - Removed the appendices
- 2017 (Draft)
  - Two separate guidances: in vitro and in vivo (clinical)
  - In vitro guidance includes appendices
- 2020 FINAL!! Two guidances

2020 DDI Guidances: Scope

- Scope: Evaluation of cytochrome P450 (CYP) or transporter mediated DDIs

- Topics not addressed in the 2020 guidances
  - Therapeutic protein DDIs
  - Gastric pH change-dependent DDIs
  - DDIs involving oral contraceptives
  - Protein displacement-mediated DDIs
  - Phase 2 enzyme-mediated DDIs
  - Pharmacodynamic DDIs
  - Detailed guidance on product labeling language

Goals of a DDI program during drug development

Determine the following:

- Whether the investigational drug alters the pharmacokinetics of other drugs
- Whether other drugs alter the pharmacokinetics of the investigational drug
- The magnitude of changes in pharmacokinetic parameters
- The clinical significance of the observed or expected DDIs
- The appropriate management strategies for clinically **significant** DDIs

Timing of DDI evaluations

- Early- in vitro evaluations
  - Screen for DDI potential
- Determine timing of clinical DDI studies relative to other studies in development program
- Assess clinical DDIs before the product is administered to patients likely to take medications that could interact
  - Reduce exclusion criteria in clinical trials

FDA's In Vitro Drug Interaction Studies Guidance

Xinning Yang, Ph.D.
Policy Lead, Guidance & Policy Team
Office of Clinical Pharmacology (OCP)
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In Vitro → In Vivo

- In vitro Guidance
  - Define the potential for DDI of an investigational drug as substrate or perpetrator
  - Help determine when and which clinical DDI assessments are needed

In Vitro DDI Evaluation

- CYP enzymes
  - -- NME as substrate
  - -- NME as inhibitor
  - -- **NME as inducer**
- Transporters
  - -- NME as substrate
  - -- **NME as inhibitor**
- **DDI potential of Metabolites**
- Case example

In Vitro Evaluation – As Substrate

- Metabolic phenotyping: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A
- If the above CYP enzymes do not play a major role, consider other enzymes

  CYP2A6, CYP2J2, CYP4F2, and CYP2E1

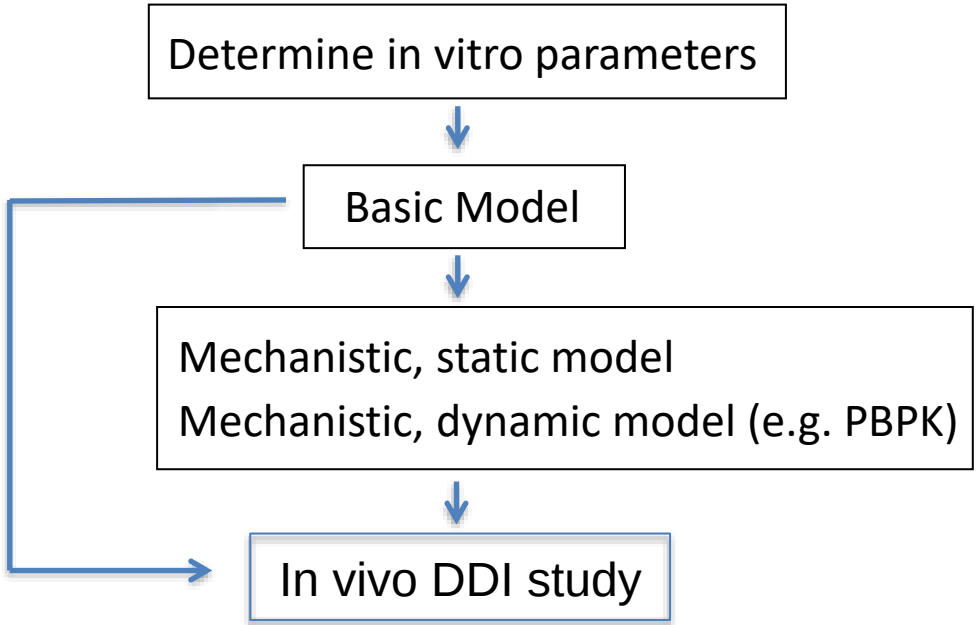
  Other Phase I enzymes including aldehyde oxidase (AO), carboxylesterase (CES), monoamine oxidase (MAO), flavin monooxygenase (FMO), xanthine oxidase (XO), and alcohol/aldehyde dehydrogenase (ADH/ALDH)

  Phase II enzymes, e.g., UDP glucuronosyl transferases (UGTs) and sulfotransferases (SULTs)
- If $\geq$ 25% clearance by an enzyme (in vitro phenotyping; human PK), need to consider further clinical evaluation, i.e., evaluate effect of inhibitor and inducer of the enzyme on the PK of the NME

Determine if NME is an Inhibitor or Inducer of Metabolic Enzymes

CYP inhibitor
(CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A)

CYP inducer
(CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A4)



Determine whether drug is an inhibitor of CYP enzymes - Basic model

If the R value is above the cut-off, further evaluation of the DDI potential is needed.

- **Reversible inhibition**

$\mathbf{R_1} = 1 + (I_{max,u} / K_i) \geq \mathbf{1.02}$

I_{max}: steady-state C_{max} of the inhibitor in plasma;
'u' means unbound (free) drug (Imax,u = Imax x fu,p);
Ki is unbound inhibition constant determined in vitro

$\mathbf{R_{1,gut}} = 1 + (I_{gut} / K_i) \geq \mathbf{11}$

Only For CYP3A, $R_{1,gut}$ should also be calculated;
I_{gut}: Dose/250mL (a rough estimate of intestinal luminal concentration of inhibitor.

- **Time-dependent inhibition (TDI)**

$\mathbf{R_2} = (k_{obs} + k_{deg}) / k_{deg} \geq \mathbf{1.25}$ Where $k_{obs} = (k_{inact} \times 50 \times I_{max,u}) / (K_I + 50 \times I_{max,u})$

Rationale for the Cut-offs

- Conducted analysis based on 119 clinical studies with midazolam as the substrate
- Compared different inhibitor concentrations, i.e., total Cmax or unbound Cmax as the inhibitor concentration and corresponding cut-off values

Model	Model description	Algorithm (R or AUCR) and [I] definition	N^a	Cutoff criteria	FN (n^b)	FP (n^b)	TN (n^b)	TP (n^b)	FNR (%)	FPR (%)	NPE (%)	PPE (%)	RMSE	GMFE
1[c]	Reversible basic (FDA[d])	$R = 1 + [I]/K_i$ and [I]: $[I]_{max}$	117	$R > 1.1$	18	10	21	68	21	32	46.2	12.8	417	3.84
2[c]	Reversible basic (EMA[e])	$R = 1 + 50.[I]/K_i$ and [I]: $[I]_{max,u}$	117	$R \geq 2.0$	20	8	23	66	23	26	46.5	10.8	214	4.15
3	Reversible $[I]_{gut}$ (FDA[d] and EMA[e])	$R = 1 + [I]/K_i$ and [I]: $[I]_{gut}$ (Eq. 1)	116	$R > 11$	0	23	8	85	0	74	0	21.3	$>10^5$	324

- Thus, changed from $C_{max}/Ki \geq 0.1 \rightarrow C_{max,\ unbound}/Ki \geq 0.02$ for reversible inhibitors for harmonization among regulators since prediction performance is similar.
- Also modified the criteria for TDIs from total C_{max} to $C_{max,\ unbound}$ to align with EMA (except that [I]gut is not required).

Viera ML, et al. Clin Pharmacol Ther 95(2):189-198 (2014).

Determine if NME is an Inducer of CYP enzymes

- Evaluate **CYP1A2, CYP2B6, and CYP3A4** initially.
- If no induction of CYP3A4 is observed, evaluating the induction potential of **CYP2C enzymes** not needed because CYP3A and CYP2C enzymes are induced via activation of the pregnane X receptor (PXR) and CYP3A is more sensitive to inducer effect
- If the drug induces CYP3A4, evaluate the drug's potential to induce **CYP2C enzymes.**
- Phase II enzymes (e.g., **UGT**) may be co-induced with CYP3A.
- **Down-regulation.** Newly added to acknowledge the phenomenon. Clear recommendation not provided due to limited knowledge. (Hariparsad, Ramsden, et al. Drug Metab Dispos, 2017, Oct;45(10):1049-1059)

Evaluate Induction Potential of CYPs

mRNA Fold-change method

- Examine the fold-changes in CYP enzyme mRNA levels when incubated with the investigational drug at a series of concentrations

- Induction potential needs to be further evaluated if meet *both* of the following
  (1) concentration-dependent ↑ in mRNA expression of a CYP enzyme
  (2) the fold-change of CYP mRNA expression relative to the vehicle control is **≥ 2-fold** at the expected hepatic concentrations of the drug.

- *Expected* concentrations in liver assumed to be a certain fold of Imax,u (e.g., 30-fold of mean unbound maximal steady-state plasma concentration of the drug at therapeutic dose).

IVIVE for CYP Induction Less Mature than Inhibition

- An analysis based on clinical studies with 51 drugs focusing on CYP3A induction

Regulator and Equation	Input (Inducer)	False Negative		False Positive		Within 2-fold	
		Median	Worst case	Median	Worst case	Median	Worst case
		%	%	%	%	%	%
F2 (50-fold $C_{max,ss,u}$)	$C_{max,ss,u}$	14.8[a]	11.1[b]	82.6	87.0	NC	NC
F2 (30-fold $C_{max,ss,u}$)	$C_{max,ss,u}$	14.8[a]	14.8[a]	69.6	78.3	NC	NC
F2 (0.25 gut)	0.1 × Dose/250 ml	5.3[c]	5.3[c]	80.0	93.3	NC	NC
RIS	$C_{max,ss,u}$	7.4[d]	0	82.6	87.0	38	36
RIS	$Portal_{,ss,u}$	0	0	93.3	100	42	39
$R_3 = 0.8$, $d = 1$, SF = 10X	$C_{max,ss,u}$	11.1[b]	7.4[d]	78.3	87.0	36	30
$R_3 = 0.8$, $d = 1$, SF = 50X	$C_{max,ss,u}$	0	0	91.3	95.7	24	20

- For mRNA fold-change method, 30x Cmax,u had less false positive than 50x Cmax,u and same false negative when plasma protein binding was capped at 99%.

Kenny JR, et al. Drug Metab Dispos. 2018 Sep;46(9):1285-1303.

Evaluate Induction Potential of CYPs

- **Correlation method (mRNA)**
  - Predicted positive criteria is defined by known positive and negative controls (e.g., relative induction score (RIS))

- **Basic kinetic model (mRNA)**

  $\mathbf{R_3} = 1 / [1 + (d \times Emax \times 10 \times Imax,u) / (EC_{50} + 10 \times Imax,u)] \leq 0.8$

- **Enzyme Activity** was added besides mRNA.

  However, no clear recommendation on how to evaluate activity data provided. Need further evaluation.

Yoshida K, et al. J Pharm Sci. 2017 Sep;106(9):2209-2213

Transporter-Mediated Drug Interactions

- Determine if NME is a substrate of transporters
- Determine if NME is an inhibitor of transporters

Investigational Drug as a Substrate of Transporters

If a drug is a transporter substrate, the need for clinical DDI studies is determined by drug's putative site of action, route of elimination, likely concomitant drugs, and safety considerations.

- **P-gp and BCRP** (**Efflux Transporters**, in intestine, liver, kidney, blood-brain barrier, etc.)
  When intestinal absorption, biliary excretion, or renal active secretion is likely to be a major cause of the variability in a drug pharmacokinetics and response

- **OATP1B1 and OATP1B3** (**Hepatic uptake transporters**)
  Hepatic/biliary elimination is significant pathway of clearance and
  Physiochemical properties and preclinical findings (e.g., anion at physiological pH, low passive permeability, high hepatic concentrations relative to other tissues)

- **OAT1, OAT3, OCT2, MATE1, MATE2/K** (**Renal uptake or efflux transporters)**
  Significant active renal secretion (≥ 25% of systemic clearance of the drug) or concerns about renal toxicity

Investigational Drug as an Inhibitor of Transporters

- Evaluate an NME as an inhibitor for
  - P-gp, BCRP;
    OATP1B1, OATP1B3;
    OAT1, OAT3, OCT2, MATE1, MATE-2K
  - Applicable for most drugs (a drug not being a substrate of a transporter does not necessarily mean it cannot be an inhibitor)

- Basic Models for predicting in vivo inhibition potential of transporters by the NME is relevant inhibitor concentration compared to inhibitory potency
  $[I]/IC_{50} \geq$ cutoff value? If yes, inhibition is possible.

- Induction - in vitro methods are not well established
  P-gp is also regulated by PXR but less sensitive than CYP3A.

Decision for In Vivo Potential of DDI mediated by Transporter Inhibition

Transporters	2012 Draft guidance	2017 Draft Guidance	Final Guidance
P-gp/BCRP	$I_1/IC_{50} \geq 0.1$ or $I_2/IC_{50} \geq 10$	$I_2/IC_{50} \geq 10$ (for oral drugs)	Same as 2017
OATP1B1/ OATP1B3	Step 1: $I_{total,\ max}/IC_{50} \geq 0.1$ Step 2: $I_{unbound,\ inlet,\ max}/IC_{50} \geq 0.25$	$I_{unbound,\ inlet,\ max}/IC_{50} \geq 0.1$	Same as 2017
OAT1/OAT3	$I_{unbound,\ max}/IC_{50} \geq 0.1$	Remained the same	Same as 2017
OCT2/MATE1/ MATE2-K	$I_{unbound,\ max}/IC_{50} \geq 0.1$ (only for OCT2)	$I_{unbound,\ max}/IC_{50} \geq$ 0.1 (for OCT2) or 0.02 for (MATEs newly added)	$I_{unbound,\ max}/IC_{50} \geq$ **0.1**

The sponsor should consider whether to conduct an in vivo study based on whether the likely concomitant medications used in the indicated patient populations are known substrates of these transporters affected.

DDI Potential of Metabolites

For CYPs

- **As a substrate:** for metabolites with safety concern or significantly contributing to overall efficacy (estimated based on potency, protein binding, tissue distribution of metabolites relative to parent)

- **As an inhibitor:**
  for metabolites more polar than parent: $AUC_{metabolite} \geq AUC_{parent}$
  for metabolites less polar than parent: $AUC_{metabolite} \geq 25\% \times AUC_{parent}$
  for metabolite that acts as time-dependent inhibitor (TDI), consider a lower exposure than parent
  Exposure comparison based on **Molar units**!

For Transporters

May also be considered.

Yu H & Tweedie DDrug Metab Dispos. 2013 Mar;41(3):536-40.

In Vitro Experiments and Bioanalytical Assays

- In vitro experiments and bioanalytical methods are not necessarily GLP-standard.
- Bioanalytical assays should meet general requirements to ensure reliable measurements.
- Standardize and validate in vitro experiment conditions to ensure data with good quality (e.g., including proper controls, check recovery/mass balance, pay attention to potential non-specific binding).

Case Example

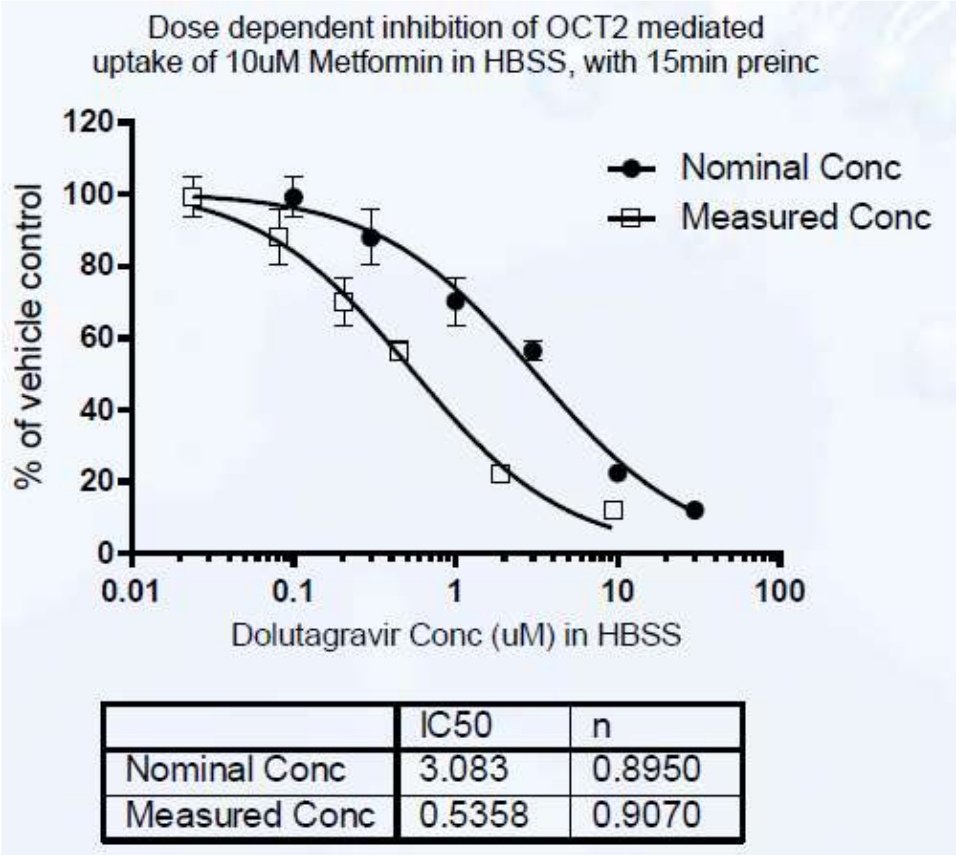
- Is there a potential for dolutegravir to inhibit OCT2 in vivo and cause clinically significant drug interactions? Is there a need to further conduct an in vivo DDI study with OCT2 substrate(s)?
  Cmax ~4 µg/mL at 50 mg b.i.d. Plasma protein bound ≥ 98.9%. IC_{50} value for OCT2 was 1.93 µM (or 0.8 µg/mL).
- $C_{max,u}/IC_{50}$ = 0.05 < 0.1 → No further DDI assessment is needed.

- Later literature reported a lower IC_{50} 0.11 µM.
- Confirmed by another source (0.21 µM).
- Using the new data, $C_{max,u}/IC_{50}$ = 0.89 > 0.1, it would be concluded that dolutegravir may cause clinically relevant DDI.
- Dolutegravir ↑metformin AUC up to 2.45-fold (may be due to inhibition of renal clearance and also change in oral absorption)

NDA 204790 Clinical Pharmacology review at Drugs@FDA;
Lepist EI, Kidney Int. Kidney Int. 2014 Aug; 86(2):350-7.
Song IH, et. al. J Acquir Immune Defic Syndr. 2016 Aug 1;72(4):400-7

TIVICAY USPI (labeling)
Chu X, et al. Drug Metab Dispos. 2016 Sep;44(9):1498-509

Possible Reason of Discrepancy



	IC50	n
Nominal Conc	3.083	0.8950
Measured Conc	0.5358	0.9070

Assay model	Polarized MDCK-OCT2
Substrate	Metformin, 10uM

Non-specific binding may be a reason.

From Dr. Yong Huang, Optivia Biotechnology Inc. April 2015

FDA's Clinical Drug Interaction Studies Guidance

Kellie S. Reynolds, Pharm.D.
Director, Division of Infectious Disease Pharmacology
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
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Key topics

- Types of studies
- Study planning and conduct
- Evaluation and interpretation of results
- DDI management strategies

Types of DDI Studies Terminology

- Prospective and Retrospective
- Standalone and Nested
- Index
- Concomitant use
- In silico

Prospective and Retrospective Studies

- Prospective
  - Protocol includes DDI objective
  - Specifically designed to detect or quantify DDI
  - Stand-alone or nested
- Retrospective
  - No DDI objective in protocol
  - Results may be difficult to interpret

Standalone and Nested Studies

- Standalone study - main objective is DDI evaluation

- Nested - Prespecified analysis within a larger study (ex: phase 3 study)

Index Studies

- Use perpetrators or substrates with well defined properties (level of inhibition, induction, and metabolic pathway)
  - Investigate drug as substrate: Use index inhibitors and inducers (strong = worst case)
  - Investigate drug as inhibitor or inducer: Use index substrate (sensitive = worst case)
- May not be clinically relevant for intended patient population
- Extrapolate to other substrates and perpetrators
- Inform need for additional DDI studies

More terminology

(before discussing the lists of index drugs)

- Based on the effect on a sensitive index CYP substrate
  - strong inhibitor: increases the AUC ≥ 5-fold
  - moderate inhibitor: increases the AUC ≥ 2- to < 5-fold
  - weak inhibitor: increases the AUC ≥ 1.25- to < 2-fold

  - strong inducer: decreases the AUC ≥ 80 percent
  - moderate inducer: decreases the AUC ≥ 50 to < 80 percent
  - weak inducer: decreases the AUC ≥ 20 to < 50 percent

- Based on the effect of a strong index inhibitor
  - sensitive substrate: AUC is increased ≥ 5-fold
  - moderate sensitive substrate: AUC is increased ≥ 2- to < 5-fold

Index inhibitors

- Selected based on systematic review of clinical DDI studies between FDA recommended index perpetrators and sensitive substrates
- Strong index inhibitors:
  - CYP1A2: fluvoxamine
  - CYP2C8: gemfibrozil, clopidogrel
  - CYP2C9: fluconazole (moderate inhibitor)
  - CYP2C19: fluvoxamine
  - CYP2D6: fluoxetine, paroxetine
  - CYP3A: clarithromycin, itraconazole

– Note- there are caveats for some of the inhibitors (explained on the website)

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm
(FDA Drug Development and Drug Interaction page)

Index inducers

- Selected based on systematic review of clinical DDI studies between FDA recommended index perpetrators and sensitive substrates
- (Strong) index inducers:
  - CYP2B6: rifampin (moderate inducer)
  - CYP2C8: rifampin (moderate inducer)
  - CYP2C9: rifampin (moderate inducer)
  - CYP2C19: rifampin
  - CYP3A: rifampin, phenytoin

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm
(FDA Drug Development and Drug Interaction page)

Sensitive index substrates

- Selected based on systematic review of clinical DDI studies between FDA recommended index perpetrators and sensitive substrates
- Sensitive index substrates:
  - CYP1A2: caffeine, tizanidine
  - CYP2C8: repaglinide
  - CYP2C9: S-warfarin, tolbutamide (both are moderately sensitive substrates)
  - CYP2C19: omeprazole, lansoprazole
  - CYP2D6: desipramine, dextromethorphan, nebivolol
  - CYP3A: midazolam, triazolam

- Note- there are caveats for some of the substrates (explained on the website)

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm
(FDA Drug Development and Drug Interaction page)

Concomitant use studies

- Drugs relevant to intended population
- Potential to interact (mechanism)
- May be difficult to extrapolate to other drug pairs (or groups)
- Transporter-based drug-drug interaction studies are often concomitant use studies
  - No transporter index drugs have been identified

In silico DDI studies

- Physiologically based pharmacokinetic (PBPK) models can replace some clinical studies
- Examples:
  - Impact of weak and moderate CYP2D6 and 3A4 inhibitors
  - Impact of weak and moderate CYP3A4 inducers
- Verify model by comparing clinical and PBPK evaluation: effect of strong perpetrator
- An evolving science
  - New uses are being considered

In silico DDI studies- example

- Sonidegib capsules (Odomzo)- treatment of locally advanced basal cell carcinoma
- CYP3A substrate
- Clinical DDI studies were conducted with strong CYP3A inhibitor (ketoconazole) and strong CYP3A inducer (rifampin)
  - with ketoconazole- AUC increased 2.2x; Cmax increased 1.5x
  - with rifampin- AUC decreased 72%; Cmax decreased 54%

In silico DDI studies- example

- Sonidegib, continued
- Clinical DDI studies were conducted with strong CYP3A inhibitor (ketoconazole) and strong CYP3A inducer (rifampin)
  - With keto- AUC increased 2.2x; Cmax increased 1.5x
  - With rif- AUC decreased 72%; Cmax decreased 54%

- PBPK
  - With moderate inhibitor (erythromycin)- AUC would increase 1.8x (14d) and 2.8x (4 months)
  - With moderate inducer (efavirenz)- AUC would decrease 56% (14d) and 69% (4 months)

Study Planning and Conduct

- What studies need to be conducted?
- What are important study design factors?

Investigational drug as a CYP-substrate

- Start with a strong index inhibitor and strong index inducer (worst case)
  - If no clinically significant interaction- STOP!!
  - If clinically significant interaction, consider need to:
    - evaluate moderate inhibitor or inducer
    - conduct relevant concomitant med studies
- Evaluation of polymorphic enzyme- PM vs EM evaluation may be appropriate
  - Effect of PM is expected to be similar to the effect of a strong inhibitor

Investigational drug as an inhibitor or inducer of CYP enzymes

Start with a sensitive index substrate (worst case)

- If no clinically significant interaction- STOP!!
- If clinically significant interaction
  - Consider relevant concomitant med studies
- Substrates may not be specific for one enzyme and may also be substrate for transporters.
  - Consider selectivity of investigational drug for the enzyme under study

Investigational drug as a substrate of transporters

- Conduct DDI study with a known inhibitor
- Select inhibitor based on the goal of the study
- Usually select inhibitor based on likelihood of co-administration (lack of index inhibitors)
- Possible worst case evaluation
  - Cyclosporine inhibits multiple transporters (Pgp, OATP, BCRP)
  - If positive, use inhibitor that is more selective
- Studies are not easily extrapolated to other drugs

Investigational drug as an inhibitor or inducer of transporters

Inhibition -

- Determine whether studies are relevant
  - likely concomitant medications and their safety profile
- Select substrate for DDI study
  - Most transporter substrates are not selective
  - Can select based on likely concomitant drugs

Induction- FDA and sponsor discuss need for study

Study Planning and Conduct

- What studies need to be conducted?
- What are important study design factors?

Study Planning
Initial considerations

- What is the study objective? Examples -
  - Maximize potential to identify an interaction
  - Understand how the study conditions relate to clinical scenario
- Will the substrate and perpetrator be used acutely or chronically?
- Are there any exposure-related safety concerns with the substrate?
- What are the PK and PD characteristics of the drugs?
- Is it important to assess both induction and inhibition?
- What is the potential mechanism of the DDI (e.g., time-dependent inhibition)?

Study Planning
Stand-alone DDI studies

- Study Population- usually healthy volunteers, unless there are safety concerns
- Number of subjects- sufficient to detect a clinically significant DDI
- Dose
  - Perpetrator- maximum dose
  - Substrate- linear PK (any dose); dose dependent PK (therapeutic dose most likely to interact)
- Single or multiple dose
  - single dose perpetrator OK if it is not a potential time dependent inhibitor or an inducer and relevant concentrations are reached
  - single dose substrate OK if it is possible to extrapolate to clinical use

Study Planning
Stand-alone DDI studies

- Parallel vs crossover- crossover preferred; parallel useful for long half-life drugs
- Timing of drug administration- typically administer at the same time
  - consider staggered administration if perpetrator is an inhibitor of one enz/transporter and inducer for another; different food conditions for drugs
- Sample collection
  - Adequate to characterize AUC, Cmax, (if relevant) Cmin

Study planning

Cocktail studies (a type of stand-alone study)

- Goal: simultaneously evaluate drug's inhibition and induction potential for multiple CYPs and transporters. (with or without prior in vitro studies)
- Cocktail criteria:
  - Substrates are specific for individual CYP enzyme or transporter
  - No interactions among the substrates
- Other study design criteria apply
- Results can be interpreted like other DDI studies, if design is appropriate

Study planning
Nested Studies

- For optimal information
  - Number of subjects (with and without other drug)
  - Sample collection
  - Data collection (timing, food intake, other meds)

Interpreting study results

The question- Is there a clinically significant increase or decrease in substrate exposure in the presence of the perpetrator?

- Determine no-effect boundaries
  - **Preferred approach- use knowledge of the concentration-response relationship.**
  - In the absence of concentration-response information, use 80-125 default 90% CI.
  - Interpretation of effect of drug as a perpetrator requires knowledge about other drugs

Interpreting Study Results

- Grazoprevir is approved for the treatment of chronic hepatitis C infection (one component of Zepatier™)
- The drug is associated with ALT elevation
- The concentrations of grazoprevir are increased when it is co-administered with various drugs as follows

Interacting drug	Changes in grazoprevir AUC
Ritonavir	2.0-fold
Ketoconazole	3.0-fold
Darunavir/ritonavir	7.5-fold
Lopinavir/ritonavir	12.9-fold
Cyclosporine	15.2-fold

The use of these drugs with grazoprevir is contraindicated **based on the exposure-response relationship for safety (ALT elevation) of grazoprevir**

ZEPATIER™ USPI
http://regist2.virology-education.com/2013/8hepcam/docs/12_Caro.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208261Orig1s000ClinPharmR.pdf
(Modified from slide created by Su-Young Choi)

DDI Management Strategies

- When: co-administration of drugs leads to concerns greater than those present when the drugs are administered alone
- Some considerations
  - Distribution of DDI data (proportion of patients expected to have too high or too low concentrations)
  - Anticipated duration of concomitant use
  - Medical need for the drugs, including alternatives
  - Availability of monitoring parameters (therapeutic drug monitoring, laboratory tests)

DDI Management Strategies

Possible instructions for management:

- Change dose level or frequency
- Stagger administration
- Prohibit concomitant use
- Monitor concentration, lab results, signs, or symptoms (and possibly adjust dose)

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*former FDA

Resources

- FDA guidance for industry: In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, www.fda.gov/media/134582/download
- FDA guidance for industry: Clinical Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, https://www.fda.gov/media/134581/download
- FDA DDI website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions
- In Vitro-In Vivo Extrapolation of Metabolism- and Transporter-Mediated Drug-Drug Interactions-Overview of Basic Prediction Methods. *J Pharm Sci*. 2017 Sep;106(9):2209-2213
- Clinical Drug–Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access, *J Pharm Sci*. 2017 Sep;106(9):2214-2218.
- FDA Public Workshop 'Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making'. https://www.fda.gov/drugs/news-events-human-drugs/development-best-practices-physiologically-based-pharmacokinetic-modeling-support-clinical

Summary

When evaluating the DDI potential of a drug…

- Keep the big picture in mind
  - Determine whether there are clinically significant DDIs
  - Determine how to manage clinically significant DDIs
- Address key issues
  - Begin with in vitro evaluation
  - Evaluate specific clinical interactions and their magnitude; interpret significance
- Details are important
  - The key to scientific and clinical relevance

We will take a *very* short break and come back to answer questions.


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