
Kellie S. Reynolds, Pharm.D.
Deputy Director, Division of Clinical Pharmacology IV
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER, FDA

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Today’s theme....

• The next chapter in the story
Previous chapters...

• Previous guidances (including draft guidances)
  – Over time
    • increased knowledge regarding potential drug-drug interaction (DDI) mechanisms
    • increased complexity of DDI evaluation in drug development
    • increased VOLUME of DDI guidances (number of pages)

Where is the information that you need?
2017 Draft Drug Interaction Guidances

Two separate guidances- in vitro and clinical

What happens when the in vitro chapter ends with a cliffhanger?

The drug might interact with other drugs…
I need to know!!
The investigation...
Stay focused on the issues

The goals are to determine:

• 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
The plot lines

• Timing of DDI evaluation
• Types of studies
• Study planning and conduct
• Interpretation of results
• DDI management strategies
Timing of clinical DDI studies

- In vitro studies indicate potential for DDIs
- When are clinical DDI results needed?

Before the product is administered to patients who are likely to take concomitant medications that could interact.
Types of DDI Studies

• Prospective and Retrospective
• Index studies (studies with index perpetrators and index substrates)
• Concomitant use studies
• In silico studies
Prospective and Retrospective Studies

• Prospective (stand-alone or nested)
  – specifically designed to detect DDI
  – DDI objective
  – often stand alone

• Retrospective
  – no DDI objective in protocol
  – results may be difficult to interpret
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)
• Extrapolate to other substrates and perpetrators
• May not be clinically relevant for intended patient population
Index inhibitors and inducers

• Based on OCP 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

• 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)
## Index Inhibitors

### CYP3A strong inhibitors

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Subjects</th>
<th>Strong inhibitor Dose</th>
<th>AUC cutoff for strong inhibitors</th>
<th>AUC ratio [90% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>triazolam and itraconazole (400 mg q.d.) Varhe et al. (1994)</td>
<td>9</td>
<td>200 mg q.d. (4 days)</td>
<td></td>
<td>8.73 [4.85, 12.61]</td>
</tr>
<tr>
<td>triazolam and clarithromycin (500mg b.i.d.) Greenblatt et al. (1998)</td>
<td>12</td>
<td>500 mg b.i.d. (2 days)</td>
<td></td>
<td>5.25 [3.82, 6.68]</td>
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<tr>
<td>midazolam and itraconazole (400 mg q.d.) Olkkola et al. (1994)</td>
<td>9</td>
<td>200 mg q.d. (4 days)</td>
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<td>6.64 [5.03, 8.25]</td>
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<td>Backman et al. (1996)</td>
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<tr>
<td></td>
<td>Olkkola et al. (1996)</td>
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<td>200 mg q.d. (6 days)</td>
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<tr>
<td></td>
<td>Ahonen et al. (1995)</td>
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<td>100 mg q.d. (4 days)</td>
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<tr>
<td></td>
<td>RE Model for midazolam and itraconazole</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>midazolam and clarithromycin (500mg b.i.d.) Gurley et al. (2006)</td>
<td>19</td>
<td>500 mg b.i.d (7 days)</td>
<td></td>
<td>8.39 [6.40, 10.38]</td>
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<tr>
<td></td>
<td>Quinney et al. (2008)</td>
<td>16</td>
<td>500 mg b.i.d. (7 days)</td>
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<td></td>
<td>Gorski et al. (1998)</td>
<td>16</td>
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<td>RE Model for midazolam and clarithromycin</td>
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</tr>
</tbody>
</table>

**Figure 1.** Forest plot illustrating the effect-size of strong CYP3A index inhibitors on sensitive CYP3A index substrates. Studies are ordered by substrate and inhibitor combination and by precision of the point estimate. Each study result is represented by a box and error bars showing fold increase in area under the concentration–time curve (AUC) and 90% confidence interval (CI). The pooled results are illustrated by the black diamonds showing pooled fold increase in AUC and 90% CI estimated with the random-effects (RE) model (modified from Sachar et al.5).

Sensitive index substrates

• Based on OCP systematic review of clinical DDI studies between FDA recommended index perpetrators and sensitive substrates.

• Sensitive index substrates:
  – CYP1A2: caffeine, tizanidine
  – CYP2C8: repaglinide
  – CYP2C9: warfarin, tolbutamide (both are moderately sensitive substrates)
  – CYP2C19: omeprazole
  – CYP2D6: desipramine, dextromethorphan, nebivolol
  – CYP3A: midazolam, triazolam

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
In silico DDI studies

- PBPK models can replace some in vivo 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
  - contact Office of Clinical Pharmacology to discuss additional uses of these models (email: ocp@fda.hhs.gov)
In silico DDI studies- example

• Sonidegib capsules (Odomzo)- trt of locally advanced basal cell carcinoma

• CYP3A substrate

• In vivo 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

• In vivo 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?
• 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
    • evaluate moderate inhibitor or inducer
    • consider relevant concomitant med studies

• Evaluation of polymorphic enzyme- PM vs EM evaluation may be appropriate
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 substrate of transporters

- In vivo transporter DDI evaluation may be relevant
  - Pgp and BCRP
    - knowledge about tissue penetration is critical (safety or efficacy reasons)
    - intestinal absorption may lead to variability in drug response
  - OATP1B1 and OATP1B3
    - hepatic uptake is needed for effect
    - hepatic elimination is significant
  - OAT1, OAT3, OCT2, MATE
    - active renal secretion or concerns about renal toxicity
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
- Another approach- begin with more selective inhibitors
- 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- OCP and sponsor discuss need for study
Study design factors

- Dose (perpetrator and substrate)
- Single or multiple dose
- Parallel or crossover design
- Co-medications and food
- Sample collection
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.

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Changes in grazoprevir AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>2.0-fold</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>3.0-fold</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>7.5-fold</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>12.9-fold</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>15.2-fold</td>
</tr>
</tbody>
</table>

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 (PK or PD)
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 adjust dose)
Leave the readers wanting more

• Topics not in the 2017 draft guidances
  – therapeutic proteins
  – pH dependent drug interactions
  – Section 7 of labeling (Drug Interactions)
You can influence the next chapter


FDA established this public docket to collect public comments. You may submit your comments to this public docket by July 9, 2018 to the Docket No. FDA-2018-N-1415 available at https://www.regulations.gov

Your comments do make a difference and can impact the outcomes of FDA regulatory policy. Share your knowledge and experience, and make your voice count.
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