Considerations for a Scientifically Rational Approach to Biologics-Small Molecule DDI Studies

New England Drug Metabolism Discussion Group Summer Symposium

Lewis J. Klunk, Ph.D.
VP, DMPK Biogen Idec, Cambridge, MA
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Outline

- Small molecules (SM) vs biologics (TP)
- Methodological considerations and technical challenges for evaluating SM vs TP DDI
- Study design considerations
- Known TP DDI studies and possible mechanisms
- Biogen examples of TP DDI studies
- FDA perspective
- Bio/PhRMA perspective
- Biogen Idec perspective and approach
- Conclusions
TP-SM DDI Discussions must consider

- Type of TP molecule
  - Mab
  - Cytokine or cytokine modulator
  - Other
- Disposition of the therapeutic protein
- Disposition of the small molecule
- Targets of the molecules
- Indication—disease being treated
- Therapeutic index
- Medical need—weigh benefit/risk
What are we concerned about in potential DDIs?

- Whether coadministered drugs cause
  - Clinically significant change in safety
  - Clinically significant change in efficacy
- Whether it is “clinically significant”
  - Depends on therapeutic area
  - Depends on type of adverse effect/toxicity
  - Depends on therapeutic index/safety margin
- “Clinically significant” = Would result in a dose adjustment
Characteristics of Small Molecules vs Therapeutic Proteins: Relevant Considerations for DDI
Small molecules Vs Therapeutic Proteins

**Small Molecules**
- Low molecular weight (<1000 Da).
- Synthetic
- Mostly well defined physicochemical properties
- Oral administration usually possible
- Rapidly enter systemic circulation through blood capillaries
- Distribution to any combination of organs/tissues/cells
- Metabolized typically by liver and gut CYPs into non-active and active metabolites
- Short serum half-lives
- Suitable for QD or BID dosing

**Therapeutic Proteins**
- High molecular weight (>>1000 Da).
- Biologically produced-can be engineered
- Complex physiochemical properties (e.g. tertiary structure)
- Undergo post transcriptional modifications, e.g., glycosylation
- Usually administered parenterally
- Reach circulation primarily via parenteral route: iv, direct; or sc via lymphatic system
- Distribution usually limited to plasma and/or extracellular fluids
- Catabolism by proteolytic degradation to peptides and amino acids
- Relatively long serum half-lives
- Dosing usually far less frequent
Small molecules Vs Therapeutic Proteins

**Small Molecules**
- Can produce specific toxicity due to parent or metabolites (often “off target”)
- Generally active in multiple animal species
- Non-antigenic, but can show unpredictable antigenicity

**Therapeutic Proteins**
- Mostly receptor mediated toxicity, including both super pharmacodynamic responses and biological toxicity (often “exaggerated pharmacology”)
- Relevant and irrelevant animals-models
- Potential for antigenicity (with MW > 10 kDa)
Clearance Mechanisms

- Small molecules:
  - Renal excretion
  - Hepatic
    - Biliary excretion
    - Metabolism (P450, UGT, Sulfotransferases, etc)
  - Intestinal
    - CYP, UGT, etc.
    - Often involves transporters
- Therapeutic Proteins
  - Target mediated
  - Immune mediated (sometimes)
  - Cellular (liver and other) degradation (peptidases)
  - Renal excretion
- Small molecules and therapeutic proteins do not share clearance mechanisms.
  - Non-competing
  - Parallel
Small Molecule Drug-Drug Interactions

- Pharmacokinetic Interactions
  - Competing clearance pathways
  - Results in clearance decreases (e.g., via enzyme inhibition) or increases (e.g., via enzyme induction) leading to increases or decreases of the blood/tissue level of one drug by a co-administered drug
  - Account for the majority of clinically important interactions

- Pharmacodynamic Interactions
  - Altering receptor sensitivity/physiological function
  - Only a few cases reported
Therapeutic Protein Drug Interactions

- Less common
- Not as clearly defined as SM interactions
- Pharmacological interactions?
Methodological Considerations and Technical Challenges for Evaluating Small Molecules vs Therapeutic Proteins DDI
Regulatory Documents


Model Systems to Study Drug Interactions for Small Molecules

- **In Vitro Systems**
  - Can be used to predict clinical interactions
  - cDNA expressed enzymes (rCYP’s)
  - microsomes (subcellular fraction of ER)
  - hepatocytes (primary cultures)
- **In Vivo Systems**
  - animals (mouse, rat, dog, monkey, transgenics)
  - humans (healthy volunteers, patients)

Speed → Simplicity → Complexity → Confidence
In Vitro Assessments of DDI For Small Molecules

• Drug Metabolizing Enzyme Identification
  – Use specific chemical or antibodies as specific enzyme inhibitors
  – Use individual human recombinant CYP enzymes
  – Use correlation analysis

• CYP Inhibition
  – Determine whether an NME is a reversible inhibitor
    \[
    \frac{[I]}{Ki} > 1 \quad \text{Likely}
    \frac{[I]}{Ki} > 0.1 \quad \text{Possible}
    0.1 > \frac{[I]}{Ki} \quad \text{Remote}
    \]

  – Determine whether an NME is a mechanism-based inhibitor
    • A 30-minute pre-incubation is recommended
    • Detection of time-dependent inhibition kinetics indicates follow-up with human DDI studies

• CYP Induction
  – Use chemical inducers as a positive control
  – Considered an inducer if $\geq 40\%$ of the positive control
In Vitro Assessments of DDI For Therapeutic Proteins

- For protein-small molecule drug-drug interactions, there are currently no acceptable in vitro systems available
- Difficult to predict potential clinical interactions
In Vivo Assessments of Small Molecule DDI

• Probe studies
  – (e.g., Pittsburgh cocktail)
  – probe drugs for specific CYPs
  – Measure effect of drug on probe PK

• Discrete studies to assess in vivo DDI of specific co-meds with the target drug

• Usually similar to Phase 1 designs
  – Most often healthy volunteers
  – Prospective data analysis
  – Non compartmental analysis of data

• Quantify and confirm impact of DDI on PK parameters
  – Known and/or suspected DDI only

• Population PK approaches (Phase III)

• Highly formalized and regulatory agency recognized
  – FDA/EMA guidance documents
In Vivo Assessments of Therapeutic Protein DDI

- Stand alone study
- POP-PK approaches
Clinical DDI Study Design Considerations
To design an appropriate DDI study we must first define “A clinically meaningful change in systemic exposure”

Per FDA Guidance on Drug Interaction Studies:
“…..sponsor to recommend specific no effect boundaries, or clinical equivalence intervals, for a drug-drug interaction. No effect boundaries represent the interval within which a change in a systemic exposure measure is considered not clinically meaningful.”

Not clinically meaningful = no dose adjustment required

Two approaches to defining no effect boundaries (with 90% confidence):

1. No effect boundaries can be based on population average dose or concentration/response relationships, PK/PD models, and other available information for the substrate drug to define a degree of difference caused by the interaction that is of no clinical consequence.

2. In the absence of no effect boundaries, a sponsor can use a default no effect boundary of 80-125% for both the investigational drug and the approved drugs used in the study.
Standard DDI Study Designs for Biologics

- **Crossover:** D followed by D+ID vs D+ID followed by D
  - Not always feasible for biologics because of very long washout period

- **Parallel:** D vs D+ID
  - *e.g.*
    - Group 1  SM
    - Group 2  TP
    - Group 3  SM+TP

- **Sequential –one way XO (longitudinal):** Single arm D followed by D+ID
  - *e.g.*
    - SM followed by SM+TP

- **General characteristics:**
  - Studies carried out in healthy volunteers or patients
    - Ethical considerations may dictate patients only
  - Often single dose
  - Prospectively designed studies are best

Legend:
- D - Drug of interest
- ID – Interacting drug
Typical Sequential DDI Study Designs with Biologics

Single TP (A) dose sufficient to study impact on SM (B) PK

Multiple doses of SM (B) may be required to cover the full PK range of a TP (A)

Figure 1. Effect of concomitant A (therapeutic monoclonal antibody) on pharmacokinetics of B (small molecule).

Figure 2. Effect of concomitant A (small molecule) on pharmacokinetics of B (therapeutic monoclonal antibody).

Population Based DDI Study Designs for Biologics

- **Basic principle:** analyze concomitant medication(s) as covariates for PK parameters in NLME modeling context

- **Usually on Phase 2 or 3 datasets**
  - DDI POP-PK datasets

- **Retrospective analysis**
  - No specific design for concomitant medication analysis
  - Prone to inadequacies in data (sample size, sampling points, etc.)

- **Add-on design to existing studies**
  - Pre-specifies certain design characteristics
  - Best cost/benefit ratio

- **Prospective studies**
  - Elaborate design to meet DDI objectives
  - Rare, only for DDI of exceptional significance
Known Therapeutic Protein DDIs and Possible Mechanisms
# Effect on PK of TP with Small Molecules

<table>
<thead>
<tr>
<th>TP</th>
<th>SM</th>
<th>Effect on PK of TP</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Methotrexate</td>
<td>29 &amp; 44% decrease in clearance of TP after single and multiple dosing, respectively</td>
<td>FDA Website</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Paclitaxel</td>
<td>1.5-fold increase in serum level of TP</td>
<td>FDA website</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Paclitaxel</td>
<td>1.5-fold increase in serum level of TP</td>
<td>Kovarik et. al. (2006)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Digoxin</td>
<td>4.2 and 12.5% reduction in Cmax and AUC of TP</td>
<td>Zhou et. al. (2004)</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Azothiopurine</td>
<td>20% Reduction in clearance</td>
<td>Kovarik et al. (2001)</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>MMF</td>
<td>50% reduction in clearance</td>
<td>Kovarik et al. (2001)</td>
</tr>
</tbody>
</table>

References

Seitz and Zhou, J Clin Pharmacol. 2007

Kovarik et al. (2001)

Kovarik et al. (2006)

FDA Website

FDA website
Effect on PK of Small Molecules with TP

<table>
<thead>
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<th>TP</th>
<th>SM</th>
<th>Effect of TP on PK of SM</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-alpha A</td>
<td>Antipyrine</td>
<td>5 to 47% decrease in antipyrine clearance</td>
<td>Brockmeyer et al (1998)</td>
</tr>
<tr>
<td>Interferon-alpha A</td>
<td>Theophylline</td>
<td>31 to 81% decrease in theophylline clearance</td>
<td>Jonkman et al. (1989)</td>
</tr>
<tr>
<td>Peginterferon-alpha-2</td>
<td>Theophylline</td>
<td>25% increase in theophylline AUC</td>
<td>Williams et al. (1987)</td>
</tr>
<tr>
<td>Peginterferon-alpha-2</td>
<td>Methadone</td>
<td>24 and 17% increase in methadone Cmax and AUC</td>
<td>Berk et al. (2007)</td>
</tr>
<tr>
<td>Peginterferon-alpha-2</td>
<td>Fluorouracil</td>
<td>1.3 to 1.5 fold increase in the AUC of 5-FU</td>
<td>Grem et al. (1997)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Paclitaxel</td>
<td>25 and 9% reduction of Cmax and AUC of paclitaxel</td>
<td>Furtlehner et al. (2005)</td>
</tr>
<tr>
<td>Murine mAb OKT3</td>
<td>Cyclosporine</td>
<td>Significant increase in CSA trough levels</td>
<td>Vasquez &amp; Pollak (1997)</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Tacrolimus</td>
<td>Significant drug-drug interactions</td>
<td>Sifontisa et. al. (2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diligent TAC monitoring and dose titrations in the early</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>post transplantation period are warranted</td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Irinotecan</td>
<td>42% decrease in Cmax of lactone form</td>
<td>Ettinger et. al. (2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15% decrease in Cmax of Carboxylate</td>
<td>Ettinger et. al. (2006)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Doxorubicin</td>
<td>A 12% increase in Doxorubicine AUC</td>
<td>Bianchi et al. (2003)</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Cyclosporine</td>
<td>CsA blood conc. increased in the first 10 days</td>
<td>Strehlau et al. (2000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CsA conc. declined at days 28-50</td>
<td></td>
</tr>
</tbody>
</table>

References:
- L. Klunk 9 June 10
Possible Mechanisms for Drug-Drug Interactions between Therapeutic Proteins and Small Molecules
Possible Mechanisms for DDI between TP and Small Molecules

- Modulation of drug metabolizing enzymes by TP
  - Interferons
  - Cytokines (interleukins, TNF-α)
  - Decrease CYP mRNA and enzyme activity
- NF-κB mediated effects on CYP or drug transporters
- Effect P-gp (e.g., interferon and increased bioavailability of digoxin)
- Inhibition of renal excretion transporters
Effect of Interferon\(\alpha\)-2b on CYP1A2, 2C19 and 2D6 Activities

High dose IFN\(\alpha\)-2b decrease CYP1A2, 2C19 and 2D6 in melanoma patients. Dose dependent increase in AUC of 5-FU

Fig. 1. Correlation between dose of interferon-\(\alpha\) (IFN\(\alpha\)) and area under the concentration-time curve to the last analysed sampling time (AUC\(_{\text{last}}\)) of fluorouracil (5FU AUC).


L. Klunk 9 June 10
Effect of IFNb on CYP2C19 and 2D6 in MS Patient

- Interferon-β treatment in patients with multiple sclerosis does not alter CYP2C19 or CYP2D6 activity (IFNβ, Avonex, Rebif or Betaferon).

Figure 1 (S)/(R) mephenytoin ratio (upper panel) and debrisoquine metabolic ratio (MR) (lower panel) before and during administration of interferon (IFN)-β in patients with MS with two, one, or zero wild-type (wt) or mutated (mut) alleles, respectively. The different CYP2C19 and CYP2D6 genotypes are indicated as filled, semi or unfilled squares and refer to the CYP2C19*2 (upper panel) and the CYP2D6*3 or CYP2D6*4 (lower panel) mutations, respectively. The dotted lines indicate the antimodes of the two ratios. There was no significant difference in the (S)/(R) mephenytoin ratio (mean difference 0.04; 95% CI −0.03, 0.11) or the debrisoquine MR (0.29; 95% CI −0.44, 1.02) before and during regular IFN-β treatment in EM (P = 0.5 and P = 0.4 for the respective probe drugs; n = 9 subjects). There was a complete concordance between geno- and phenotype for both enzymes. Mut/mut (■); wt/mut (□); and wt/wt (□).


L. Klunk 9 June 10
Role of NF-κB in Modulation of CYP Expression and Activity in Disease States

- Direct regulation - binds to CYP promoters
- Indirect by suppression of CYP regulators (e.g., AHR, CAR, PXR)
- Post transcriptional induction of heme oxidase
- Effect CYP stability


*L. Klunk 9 June 10*
What we learned from literature DDI studies

- There are few clinically significant changes in the PK of TP with co-administration of small molecules
- Some changes in the PK of small molecules with co-administration of TPs observed
- A clinically significant drug interaction may occur between some of the TP and small molecules with narrow TI (tacrolimus, MMF, cyclosporine).
  - monitoring and dose titrations in the early post transplantation period are warranted in patients receiving TP to minimize the risk of drug toxicity.
FDA Survey

- Therapeutic proteins approved by FDA by end of 2008 (68 NME)
  - Drug labels for 56% included some information on drug interactions
    - Most of these were cytokines (81%)
    - Mabs which were cytokine modulators (65%)

Examples of Therapeutic Proteins That Effect CYP Enzymes

<table>
<thead>
<tr>
<th>CYP enzyme</th>
<th>Cytokines/cytokine modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>IFN-α, IFNα-2b, IFN-β, IL-2, IL-6, hGH&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>IL-1</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>IL-2, IL-10</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Tocilizumab&lt;sup&gt;b&lt;/sup&gt;, IFNα-2b, FN-β, IL-2, TNF-α, IL-6, hGH</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>IFNα-2b</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>IL-2, IFNα-2b</td>
</tr>
<tr>
<td>CYP3A</td>
<td>Basiliximab, muromonab-CD3, tocilizumab&lt;sup&gt;b&lt;/sup&gt;, IL-1, IL-2, IL-6, IL-10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Decreased activity unless noted
<sup>b</sup> = Increased activity

Table 1 List of CYP enzymes with altered activities (decreased, unless noted<sup>a,b</sup>) in the presence of specific cytokines, cytokine modulators, and human growth hormone, based on in vitro and/or in vivo studies in humans.
Biogen Examples of TP DDI studies
Therapeutic Protein + Small Molecule Combination Studies at Biogen Idec

Example 1: Therapeutic Protein +/- Standard of Care

[Standard of Care = Small Molecule 1 (SM1) + Small Molecule 2 (SM2)]

DDI component designed after Phase 3 was already in progress

As stated in the PK Analysis Plan:

The objectives of this pharmacokinetics analysis are:

- To characterize the pharmacokinetics of TP, SM1, and SM2 in patients.
- To determine the effect of treatment occasion (Cycle 1, 3, and 6) on the pharmacokinetics of TP in patients.
- To determine the effect of TP on the pharmacokinetics of SM1 and SM2 in patients.
- To determine the effect of SM1 and SM2 on the pharmacokinetics of TP
Protein-Small Molecule Combination Studies at Biogen Idec

Intent was to collect 9 plasma samples each from:
N = 20 TP + SM1+SM2
N = 20 SM1+SM2

Actually only collected 9 plasma samples each from:
N = 15 TP + SM1+SM2
N = 11 SM1+SM2

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>SM1 (Mean ± SD [CV%])</th>
<th>SM2 (Mean ± SD [CV%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$AUC_{0-12h}$ (ng·hr/mL)</td>
</tr>
<tr>
<td>SM1+SM2 (n = 11) without TP</td>
<td>9566 ± 4744 (50)</td>
<td>91943 ± 116252 (126)</td>
</tr>
<tr>
<td>TP+SM1+SM2 (n = 15*) with TP</td>
<td>13790 ± 7671 (56)</td>
<td>144310 ± 143201 (99)</td>
</tr>
</tbody>
</table>

* Only 15 of the 20 patients were evaluable
Protein-Small Molecule Combination Studies at Biogen Idec

Example 1: Therapeutic Protein (TP) +/- Standard of Care
[Standard of Care = Small Molecule 1 (SM1) + Small Molecule 2 (SM2)]

CONCLUSION: No clinically significant interaction

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Protein Therapeutic + Small Molecule Combination Studies at Biogen Idec

Example 1: Therapeutic Protein (TP)+/- Standard of Care
[Standard of Care = Small Molecule 1 (SM1) + Small Molecule 2 (SM2)]

**DDI component designed after Phase 3 was already in progress**

As stated in the PK Analysis Plan:

The objectives of this pharmacokinetics analysis are:

- To characterize the pharmacokinetics of TP, SM1, and SM2 in patients.
- To determine the effect of treatment occasion (Cycle 1, 3, and 6) on the pharmacokinetics of TP in patients.
- To determine the effect of TP on the pharmacokinetics of SM1 and SM2 in patients.
- To determine the effect of SM1 and SM2 on the pharmacokinetics of TP

However, there was no TP only arm in this or any previous study of TP in this patient population. Therefore, PK of TP in the TP+SM1+SM2 arm needed to be compared with TP PK from a previous study in a different patient population.

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Protein-Small Molecule Combination Studies at Biogen Idec

Example 1: Therapeutic Protein (TP) +/- Standard of Care
[Standard of Care = Small Molecule 1 (SM1) + Small Molecule 2 (SM2)]

Observed Plasma Concentration-Time Profiles of TP in Current Patients Versus Simulated TP Pharmacokinetic Profiles Based on Previous Population PK Parameters

After the first dose in current patients, TP clears faster than it did in previous patients, presumably due to higher initial target burden (substantiated by data not shown). However, at steady-state (after receptor saturation) TP PK appears similar in both populations.

CONCLUSION: SM1+SM2 seems to have no effect on TP PK.
Protein-Small Molecule Combination Studies at Biogen Idec

Example 2:
Small Molecule 3 (SM3) +/- Therapeutic Protein 2 (TP2)

Study Design: Collect blood samples for TP2 concentration analysis predose and 10 min after infusion (trough and peak) after weekly dose #1, #2, #3, and #7

Collect blood samples for SM3 concentration analysis predose, 10 min and 7 days after each Q4W infusion (peak, Day 7, and trough) for courses 1 through 6 and one sample at the end of treatment

Evaluate whether TP2 alters PK of SM3
Protein-Small Molecule Combination Studies at Biogen Idec

Example 2: Small Molecule 3 (SM3) +/- Therapeutic Protein 2 (TP2)

<table>
<thead>
<tr>
<th>PK Measurement</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM3 only</td>
<td>SM3 + TP2 (q2wk) (N=28)</td>
<td>SM3 only</td>
</tr>
<tr>
<td>SM3 only</td>
<td>SM3 + TP2 (qwk) (N=28)</td>
<td>SM3 only</td>
</tr>
<tr>
<td>SM3 only</td>
<td>SM3 + TP2 (q2wk) (N=28)</td>
<td>SM3 + TP2 (qwk) (N=8)</td>
</tr>
<tr>
<td>SM3 only</td>
<td>SM3 + TP2 (qwk) (N=28)</td>
<td>SM3 + TP2 (qwk) (N=8)</td>
</tr>
<tr>
<td>C&lt;sub&gt;10&lt;/sub&gt; (µg/mL)</td>
<td>15.20 (62)</td>
<td>20.41 (51)</td>
</tr>
<tr>
<td></td>
<td>12.73 (66)</td>
<td>16.21 (60)</td>
</tr>
<tr>
<td></td>
<td>14.19 (71)</td>
<td>16.69 (63)</td>
</tr>
</tbody>
</table>

Data are presented as mean (%CV); C<sub>10</sub>: Concentration 10 minutes post-SM3

Conclusion: No clinically significant interactions
Conclusion from Studies at Biogen Idec

- No clinically significant interactions observed
FDA Developing Perspective
In what cases are dedicated drug interaction studies recommended?

- **TP = a cytokine, cytokine antagonist or peptide hormone**
  - Effect of the TP on the exposure to CYP substrate drugs (e.g., CYP probe cocktail) in humans
  - *In vitro* screening may be helpful for *in vivo* design

- **TP in combination with a drug (esp, a narrow therapeutic range [NTR] or anti-cancer drug)**
  - Effect of TP on the PK and PD of the (SM) drug in humans
  - Effect of the (SM) drug on the PK and PD of the TP in humans

- **TP likely to be used concomitantly with an NTR drug**
  - Effect of TP on the PK and PD of the NTR drug in humans

Jang-Ik Lee, FDA-PhRMA Meeting, May 9, 2009
Bio/PhRMA Developing Perspective
Need for Therapeutic Protein DDI studies: An Industry Perspective

• TP = a cytokine, cytokine antagonist or peptide hormone
  – Known/presumed MOA should serve to indicate need & planning for clinical DDI study (i.e., case-by-case need)
  – Non-human primate PK DDI studies or in vitro drug metabolism DDI screens will generally be of little predictive value

• TP in combination with a drug (esp, a narrow therapeutic range [NTR] or anti-cancer drug)
  – Need for studies should be case-by-case (i.e., most TP should have no effect on PK/PD of NTR-small NCE drugs)

• TP likely to be used concomitantly with an NTR drug
  – Need for studies should be case-by-case (i.e., most TP should have no effect on PK/PD of NTR-small NCE drugs)

PhRMA DMTG
FDA-Pharma Industry Biologics DDI Steering Committee

- Big Pharma
- Biotech
- FDA
- Focus for Therapeutic Proteins:
  - Mab
  - Cytokines
  - Fusion proteins
  - PK and metabolism based DDI
  - As perpetrators and victims of P450 metabolized small molecules
Biogen Idec Developing Perspective
Considerations

1. Patient Safety
2. Efficacy
3. Speed of getting new drugs to patients
4. Cost of drug development
Decision Tree for TP-SM DDI Study

Type of TP

Cytokine
- Known inhibition/interaction of CYP450?
  - Yes
    - SM clearance by CYP significant? Or SM requires TDM?
      - Yes
        - Narrow TR?
          - Yes
            - Collect samples & store
          - No
      - No
    - No
  - No

Mab
- Is there an MOA rationale to suggest potential interaction
  - Yes
    - No dedicated DDI study
    - Reg. Agency Review
      - POC?
        - Yes
          - POP-PK/PD Design and/or Analysis:
            - Retrospective
            - Prospective
          - Analyze
        - No
          - Discard
  - No

Other
- Collect samples & store
  - POC?
    - Yes
      - Analyze
    - No
      - Discard

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Risk Based Decision Strategy

- Science driven: Allows a scientifically rational decision on whether DDI study is warranted
- If warranted, uses “collect and hold” strategy
- Requires that analyte have sufficient storage stability
- Eliminates unneeded or “low value” clinical studies
- Helps speed drug development and lower costs
- Should satisfy DDI requirements
Conclusions

- Few clinically significant changes in the PK of TP with small molecules have been seen.
- Some changes in the PK of small molecules with TP have been observed.
- Need for SM-TP DDI studies should be considered on a case-by-case basis and should be science driven.
- Clinical DDI studies of TP with small molecules may be needed when therapeutic drug monitoring (e.g., MMF, cyclosporine, etc) is needed.
- Consider a collect and hold strategy.
- POP-PK approaches should be considered.
- Regulatory input should be obtained on plans.
Acknowledgements

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• Qin Wang
• Liyu Yang