The Role of Clinical Pharmacology in Biological Drug Development
(With A Focus on Protein Therapeutic Agents)

ASQ509-Special Interest Group
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Yow-Ming C. Wang, Ph.D.
Biologics Team Leader, Division of Clinical Pharmacology III,
Office of Clinical Pharmacology, Office of Translational Sciences
Center for Drug Evaluation and Research, Food and Drug Administration
Disclaimer

- The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the United States Food and Drug Administration.

- Throughout the talk, representative examples of commercial products may be given to illustrate a methodology or approach to problem solving. No commercial endorsement is implied or intended.
Overview

• Introduction - What are biological products?

• Clinical Pharmacology in a nutshell
• Role of clinical pharmacology in drug development
• A case example for PK-PD characterizations

• Highlights of other clinical pharmacology considerations

• Summary
INTRODUCTION
Biologics are Important Medicines
What’s fueling the biotech engine—2012 to 2013

US Sales $ billions

- Humira $4.6 billions
- Remicade $3.6 billions
- Lantus $4.5 billions
- NovoLog $3.0 billions
- Neulasta $3.5 billions
- Epogen $1.9 billions
- Enbrel $3.9 billions
- Orencia $0.8 billions

Aggarwal, 2014 Nature biotechnology
Regulatory Approval Required Before Commercialization

Approval letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA XXXXX

BLA APPROVAL

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosage
Biological Products

Center for Drug Evaluation and Research (CDER) -- examples

• **monoclonal antibodies** (mAb)
  – targeted therapies in cancer and other diseases
• **cytokines**
  – proteins involved in immune response
• **growth factors**
  – proteins that affect the growth of a cell
• **enzymes**
  – proteins that speed up biochemical reactions
• **immunomodulators**
  – proteins that affect immune response

(mostly produced by biotechnology methods)

Center for Biologics Evaluation and Research (CBER) -- examples

• allergenic extracts
  (e.g. for allergy shots and tests)
• blood and blood components
• gene therapy products
• devices and test kits
• human tissue and cellular products used in transplantation
• vaccines

Protein Therapeutic Agents
(or Biologics)
NDA vs. BLA Submissions to FDA

- **New Drug Application (NDA)**
  - Small molecule drugs
  - \(\alpha\)-amino acid polymers, recombinant, \(\leq 40\) amino acids (aa)
  - \(\alpha\)-amino acid polymers, chemically synthesized < 100 aa
  - **FD&C Act** under section 505: 505(b)(1), 505(b)(2), 505(J)

- **Biological License Application (BLA)**
  - \(\alpha\)-amino acid polymers, recombinant, > 40 aa
  - \(\alpha\)-amino acid polymers, chemically synthesized \(\geq 100\) aa
  - **PHS Act** under section 351: 351(a), 351(k)
    - By March 23, 2020, a biological product must be submitted under section 351 of the PHS Act (Affordable Care Act provision)

Source: FDA’s Biosimilars Question & Answer guidance
FD&C Act = Food Drug & Cosmetic Act
PHS Act = Public Health Service Act
Small Molecule Drugs vs. Protein Therapeutics

Example: Targeted therapies inhibiting HER-2 signaling

Normal HER-2 Signaling

Dimerization/activation

Phosphorylation

PI3K

Akt

BAD

mTOR

Survival

Cell cycle progression

Raf-1

MEK 1/2

MAPK

Res

MEKK

SEK

JNK

RAC

RHO

Nucleus

Trastuzumab (MW = 150 kD)

Lapatinib (MW = 581)

Trastuzumab (1/300x)
## Small Molecules vs. Protein Therapeutics (In the World of Relativity)

<table>
<thead>
<tr>
<th>Features</th>
<th>Small Molecules</th>
<th>Large Molecule (Biologics)</th>
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</thead>
<tbody>
<tr>
<td>Size</td>
<td>Small</td>
<td>Large</td>
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<tr>
<td>Method of manufacturing</td>
<td>Chemical Synthesis</td>
<td>Cell culture</td>
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<tr>
<td>Structural complexity</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>Biological Functionality</td>
<td>Simple (often singular)</td>
<td>Complex (often multiple)</td>
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<td>Structural elucidation of target binding</td>
<td>Easy</td>
<td>Difficult</td>
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<td>Molecular interaction with targets <em>MOA</em></td>
<td>Simple</td>
<td>Complex</td>
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<td>Bioanalytical assays for PK assessment</td>
<td>Simple &amp; Specific (e.g., LC-MS/MS)</td>
<td>Complex; require biologic agents (e.g., ELISA)</td>
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<td>Other molecular interactions relevant to PK and PD</td>
<td>Metabolic enzymes, Transporters, … etc.</td>
<td>FcγR, C1q, (ADCC, CDC), Fc-Rn, Immunogenicity, … etc.</td>
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<td>Assessments of PD effect</td>
<td>Simple</td>
<td>Complex, functionality-dependent</td>
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<td>Biochemical Outcome</td>
<td>Inhibition (or stimulation) of signal transduction</td>
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Approval Timeline for Biological Products in CDER

Mylotarg approved in 2000 and withdrawn in 2010.

- Mab-conjugate (n=4)
- Mab (n=45)
- Bispecific (n=7)
- Fc-fusion (n=7)
- Enzyme (n=22)
- Growth factor (n=10)
- Immunomodulator (IM) (n=15)
- Non-IM (n=9)

N=64 bind to receptors; N=23 bind to soluble ligands


Mylotarg approved in 2000 and withdrawn in 2010; blue arrows – immunotherapy: ipilimumab, pembrolizumab, nivolumab
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Mylotarg approved in 2000 and withdrawn in 2010; blue arrows – immunotherapy: ipilimumab, pembrolizumab, nivolumab

N=64 bind to receptors; N=23 bind to soluble ligands
CLINICAL PHARMACOLOGY IN A NUTSHELL
Pharmacokinetics & Pharmacodynamics

- **PK**: what the **body** does to the **drug** (drug concentration)
- **PD**: what the **drug** does to the **body** (drug effect)
- Putting it together: drug action over time

Source: [http://www.nature.com/ijir/journal/v19/n3/fig_tab/3901522f2.html](http://www.nature.com/ijir/journal/v19/n3/fig_tab/3901522f2.html)
Pharmacokinetics Can Vary Due to...
- PK refers to drug concentration in circulation (plasma, serum)
  • Body size, age, sex (M/F), kidney function, ... → intrinsic factors
  • Target level, immunogenicity → biologics specific intrinsic factors
  • Co-medication, ... → extrinsic factor
  ❖ Biologics are often given via intravenous, subcutaneous route.

Source: http://www.nature.com/ijir/journal/v19/n3/fig_tab/3901522f2.html
http://www.med.tmd.ac.jp/medicine/hospital/pharmacokinetics.html
Pharmacodynamics (Drug Effects)

- Depend on concentrations in circulation for most drugs
- Can vary among patients when achieved same concentrations
- Include ...
  - Undesirable effect – side effects
  - Desirable effect

Source: [www.studyblue.com](http://www.studyblue.com)

Source: [http://www.nature.com/ijir/journal/v19/n3/fig_tab/3901522f2.html](http://www.nature.com/ijir/journal/v19/n3/fig_tab/3901522f2.html)

Drug Action (Effect Over Time)


Source: http://www.nature.com/ijir/journal/v19/n3/fig_tab/3901522f2.html

https://www.studyblue.com/notes/note/n/10-1-pharm-pharmacokinetics/deck/3949024
Defining The Therapeutic Window

• The process involves
  – Collecting experimental data from animal studies and clinical trials (i.e., drug development)

• Requires the knowledge of
  – What are the desired effects & how to measure?
  – What are the undesired effects & how to measure?

• The mechanism of action (MOA) serves as foundation.

• Has practical impacts
  – How much of drug to administer?
  – How often to administer the drug?
Mechanism of Action

- In pharmacology, the term *mechanism of actions* (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect.
- A *mechanism of action* usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor.
- Shown in Section 12.1 of the US Prescribing Information (USPI, or package insert)
Mechanism of Action
Example: Targeted therapies inhibiting HER-2 signaling

Normal HER-2 Signaling

Dimerization/activation

HER2

Phosphorylation

PI3K

Akt

BAD

mTOR

Survival

Cell cycle progression

Proliferation, cell cycle progression, gene transcription

Cytoskeletal organization

Nucleus

Trastuzumab (MW = 150 kD)

Lapatinib (MW = 581)

(1/300x)
Mechanism of Action Example

1. **T-cell Activation**
   - T cell
   - CTLA-4
   - CD28
   - CD80/CD86
   - TCR
   - APC

2. **T-cell Inhibition**
   - T cell
   - CD28
   - CTLA-4
   - CD80/CD86
   - TCR
   - MHC

3. **T cell Remains Active**
   - T cell
   - CD28
   - CTLA-4
   - CD80/CD86
   - TCR
   - MHC
   - APC

---

Yervoy blocks CTLA-4
Mechanism of Action - Example

MAC: Macrophage; sTNF: Soluble TNF-\(\alpha\); T: T cell; TCD: CD4\(^+\) T cell; tmTNF: Transmembrane TNF-\(\alpha\); Treg: T regulatory cell.

Anti-TNF-\(\alpha\) agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls

*Immunotherapy* (2010) 2(6), 817–833

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ROLE OF CLINICAL PHARMACOLOGY IN DRUG DEVELOPMENT
Clinical Pharmacology Contribution to NDA/BLA

- **The right drug**
  - With appropriate MOA for the targeted disease condition

- **The right patient**
  - e.g., with specific genotype: (1) HER-2-positive for anti-HER2 mAb, (2) k-ras wild-type for anti-EGFR mAbs, ...

- **The right dose**
  - Achieving systemic exposure that is therapeutic effective
  - Intrinsic factors, e.g., body weight, ethnicity, age (pediatric, elderly), organ dysfunction (kidney, liver), ...
  - Extrinsic factors, e.g., drug-drug interactions, ...

- **The right time**
  - Dosing schedule, appropriate for maintaining therapeutic effects
Getting it Right

Preclinical | Phase 1 | Phase 2 | Phase 3 | Post-Marketing
---|---|---|---|---

Target validation | Proof of concept | Efficacy

Dose selection for FIH study

Dose-ranging

Tolerability

PD / clinical effect

PK, exposure

Efficacy

PK/PD, clinical effects dose-response exposure-response

The Right Drug

The Right Dose

The Right Time
Stakeholders In Drug Development

• Drug companies
• Regulatory agencies
• Physicians investigators
• Clinical research institutions & hospitals
• Participants in clinical studies
  – healthy subjects & patients
• Contract research organizations
  – trial logistics, study sample analysis, data analysis, report writing, ...
• ...

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Clinical Pharmacology in Drug Development

Discovered Research & Preclinical Development

- Pre-IND
- Preclinical Development – safety studies

Drug Dev Phases

- IND
- PK & PD + Clinical Response

Studies

- Pharmacology (PD)
  - In vitro
  - In vivo
- Tox & TK
- PK

INFO

- Exposure (animal)
- Safety
- Response
- PK-PD Modeling
- Human exposure projection

Impact

F1H dose selection

Learn and confirm

Dose selections

Dosing recommendation for labeling

- Clinical response
- Exposure (longer term)

BLA/NDA

- BLA/NDA Supplements

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CTD (Common Technical Document)

- 2.7.1 Biopharmaceutic Studies & Analytical Methods
- 2.7.2 Clin Pharm Studies

Module 1: Regional Administrative Information
1.1 Submission T of C
CTD Table of Contents 2.1
CTD Introduction 2.2

Module 2: Nonclinical Overview 2.4
Nonclinical Written and Tabulated Summaries 2.6
Clinical Overview 2.5
Clinical Summary 2.7

Module 3: Quality 3
3.1 T of C

Module 4: Nonclinical Study Reports 4
4.1 T of C

Module 5: Clinical Study Reports 5
5.1 T of C

Not Part of the CTD
Regulatory Review by A Multi-Disciplinary Team

Sponsors project manager

FDA Project manager

CMC (Chemistry, Manufacturing & Control)  Preclinical Pharm/Tox  Medical  Clinical Pharmacology  Statistics

Decision: Safe & Efficacious?

Some products may require additional disciplines such as microbiology and virology, and immunogenicity for biologics.
Final Results Shown in Prescribing Information

FULL PRESCRIBING INFORMATION: CONTENTS*

| 1 | INDICATIONS AND USAGE |
| 2 | DOSAGE AND ADMINISTRATION |
|   | 2.1 Recommended Dosage Regimen |
|   | 2.2 Preparation and Administration |
|   | 2.3 Use of Nplate With Concomitant Medical ITP Therapies |
| 3 | DOSAGE FORMS AND STRENGTHS |
| 4 | CONTRAINDICATIONS |
| 5 | WARNINGS AND PRECAUTIONS |
|   | 5.1 Risk of Progression of Myelodysplastic Syndrome/Myelogenous Leukemia |
|   | 5.2 Thrombotic/Thromboembolic Complications |
|   | 5.3 Loss of Response to Nplate |
|   | 5.4 Laboratory Monitoring |
| 6 | ADVERSE REACTIONS |
|   | 6.1 Clinical Trials Experience |
|   | 6.2 Postmarketing Experience |
|   | 6.3 Immunogenicity |
| 7 | DRUG INTERACTIONS |
| 8 | USE IN SPECIFIC Populations |
|   | 8.1 Pregnancy |
|   | 8.3 Nursing Mothers |
|   | 8.4 Pediatric Use |
|   | 8.5 Geriatric Use |
|   | 8.6 Renal Impairment |
|   | 8.7 Hepatic Impairment |
| 10 | OVERDOSE |
| 11 | DESCRIPTION |
| 12 | CLINICAL PHARMACOLOGY |
|   | 12.1 Mechanism of Action |
|   | 12.2 Pharmacodynamics |
|   | 12.3 Pharmacokinetics |
| 13 | NONCLINICAL TOXICOLOGY |
|   | 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
|   | 13.2 Animal Toxicology and/or Pharmacology |
| 14 | CLINICAL STUDIES |
|   | 14.1 Chronic ITP |
| 16 | HOW SUPPLIED/STORAGE AND HANDLING |
| 17 | PATIENT COUNSELING INFORMATION |
|   | 17.1 Information for Patients |

*Sections or subsections omitted from the full prescribing information are not listed.
PK-PD CHARACTERIZATIONS

Case example –

Romiplostim (Nplate™) Indicated for ITP in Adults

(a thrombopoietin-mimetic growth factor)

~ ITP = Immune Thrombocytopenia ~

http://www.nplate.com/
Understanding Clearance Mechanisms – Rodents

- FcRn receptors prolong the systemic residence time.

- Platelets play a role in systemic clearance at low dose, and this CL is saturable at high dose.
Understanding Clearance Mechanisms
– Rodents

- Kidney plays some role in systemic clearance.
- Catabolism is a major clearance pathway.
- Overall CL = linear + nonlinear (target mediated drug disposition, TMDD)
**First-In-Human Study PK/PD Data**

- Peptibody (Fc-fusion protein)
- Nonlinear PK
- Target-mediated elimination
- Robust PD – ↑ Platelet (PLT) counts
- PD effect peaks at 2 weeks (biological)
- Complex interplay: ↑ PLT → ↑ CL → ↓ [conc]

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Wang et al., CPT 2004

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PK/PD Data Support Dose Titration
– Baseline Platelet Counts Affects PK and PD

- Patients with **low** platelet count
  → **low** CL & **high** drug concentration

- Patients with **high** platelet count
  → **high** CL & **low** drug concentration

- Supports **Clinical Dose Regimen**
  – individual titration to target platelet count, a clinical endpoint

Wang et al., AAPSJ 2010

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PK/PD of Romiplostim – Putting it together, FIH data

The model

PK

PD

Dose-Response

Exposure-Response

Wang et al., AAPSJ 2010

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Nonlinear Elimination Pathway Depends on Dose & Platelet Count

- High platelet counts $\rightarrow$ high target load
  $\rightarrow$ Nearly all eliminated via nonlinear pathway (target-mediated CL)
- Platelet counts fluctuate over time in each patient while on treatment
- Supports clinical dose regimen – individual titration to target platelet count, a clinical endpoint

![Graph](image)

**Fig. 5.** Effect of dose and platelet counts at baseline on the fraction of dose eliminated via target-mediated clearance pathways vs. time following IV and SC dosing of romiplostim. Baseline platelet counts are $10 \times 10^9$ cells/L (red line), $50 \times 10^9$ cells/L (blue line), and $250 \times 10^9$ cells/L (green line). Wang et al., AAPSJ 2010
Final Product – Prescribing information
(Example of sections with clinical pharmacology data)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nplate increases platelet production through binding and activation of the TPO receptor, a mechanism analogous to endogenous TPO.

12.2 Pharmacodynamics

In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet counts. After a single subcutaneous dose of 1 to 10 mcg/kg Nplate in patients with chronic ITP, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2- to 3-week period. The platelet counts were above $50 \times 10^9/L$ for seven out of eight patients with chronic ITP who received six weekly doses of Nplate at 1 mcg/kg.

12.3 Pharmacokinetics

In the long-term extension study in patients with ITP receiving weekly treatment of Nplate subcutaneously, the pharmacokinetics of romiplostim over the dose range of 3 to 15 mcg/kg indicated that peak serum concentrations of romiplostim were observed about 7 to 50 hours post dose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum concentrations was observed ($n = 4$) after six weekly doses of Nplate (3 mcg/kg). The accumulation at higher doses of romiplostim is unknown.
HIGHLIGHTS OF OTHER CLINICAL PHARMACOLOGY CONSIDERATIONS

- Immunogenicity to biologics
- Intrinsic factor, e.g., body weight, kidney function
- Extrinsic factor, e.g., drug interaction
- Bioanalytical method for drug concentration
Immunogenicity to Biologics

Definitions

• **Immunogenicity**: defined as the propensity to generate immune responses to the biological product or to induce immunologically related adverse clinical events.

• **ADA**: antidrug antibody, binding antibody

• **NAb**: neutralizing antibody

Biologics ➔ Immune response ➔ ADA (IgM, IgG, IgE, ...) ➔ NAb

adverse effects? ➔ affect pharmacological functions, e.g., PD, efficacy
Immunogenicity of Biologics
(example of clinical impacts)

• Erythropoietin-mimetics – Pure Red Cell Aplasia (PRCA)
  – Neutralizing antibody cross-reacts with endogenous erythropoietin
  – Rare event*: 5 cases of confirmed PRCA among 15,333 patients enrolled in “The Prospective Immunogenicity Surveillance Registry (PRIMS)”

• Enzyme replacement therapy for infantile-onset Pompe disease
  – CRIM⁻ subjects, who do not expressing endogenous enzymes, rapidly develop anti-drug antibody with high titer ⊗
  – Management strategy evaluated: immune tolerance induction regimen ⊘, e.g., methotrexate, rituximab, bortezomib, ...

• Some biologics associated with secondary treatment failure when the antidrug antibody neutralizes the drug effects
  – Management strategy to address immunogenicity development generally not standardized

*Macdougall et al. 2015 Nephrol Dial Transplant; ⊗ Myozyme prescribing information; ⊘ FDA Public Workshop (June 2014)
Immunogenicity & Secondary Treatment Failure

- % of infliximab bound to anti-drug antibody (ADA) ↑ over time
- Infliximab (S-), active drug, concentration ↓ with ↑ of ADA

Bendtzen et al. 2006 Arthritis Rheumatism
PK Negatively Affected Before Efficacy

(PK is more sensitive than efficacy endpoints)

- Antibody+ patients - lower adalimumab concentration & higher dropout rate
- Therefore, clinical pharmacology plays a critical role in immunogenicity impact assessment in clinical development.

**Figure 4.** Overall Patient Dropout and Dropout Due to Treatment Failure
Evaluating and Reporting the Immunogenicity Impacts for Biological Products—a Clinical Pharmacology Perspective

Yow-Ming C. Wang,1,2 Jie Wang,1 Yuen Yi Hon,1 Lin Zhou,1 Lanyan Fang,1 and Hae Young Ahn1

Concordance definition:
• ADA+ → higher clearance (lower exposure) & reduced efficacy
• ADA+ → no effect on clearance & no effect on efficacy
A Survey of Applications of Biological Products for Drug Interference of Immunogenicity Assays

Yow-Ming C. Wang • Lanyan Fang • Lin Zhou • Jie Wang • Hae-Young Ahn

Fig. 1 A schematic example of immunogenicity assay. (ADA: anti-drug antibody).
Intrinsic Factors

Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials
(Journal of Clinical Pharmacology, 2009;49:1012-1024)

Diane D. Wang, PhD, Shuzhong Zhang, PhD, Hong Zhao, PhD, Angela Y. Men, PhD, and Kourosh Parivar, MS

Impact of renal impairment on PK
(Yang et al 2003, Clinical Pharmacology Therapeutics)

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
Guidance for Industry
(December 2014)

Guidance for Industry
Collection of Race and Ethnicity Data in Clinical Trials
(September 2005)
Extrinsic Factors – Drug-Drug Interaction

CYP-Mediated Therapeutic Protein-Drug Interactions
Clinical Findings, Proposed Mechanisms and Regulatory Implications

Jang-Ik Lee, Lei Zhang, Angela Y. Men, Leslie A. Kenna and Shiew-Mei Huang

Biological Products for the Treatment of Psoriasis: Therapeutic Targets, Pharmacodynamics and Disease-Drug-Drug Interaction Implications

Jie Wang, Yow-Ming C. Wang, and Hae-Young Ahn

Therapeutic Protein–Drug Interactions and Implications for Drug Development

S-M Huang, H Zhao, J-I Lee, K Reynolds, L Zhang, R Temple and LJ Lesko

- Interaction related to proinflammatory cytokines
- Interactions related to mechanism-of-action
Cytokine Modulators May Affect CYP Enzymes & Substrates

When the treatment improves the disease condition...

- Decreased exposure of CYP Substrates
- Potential loss of efficacy for small molecule drugs
Example: Tocilizumab Disease-DDI Study
- First clinical DDDI study of a cytokine modulator

Tocilizumab:
• Target: IL-6 receptor
• Indications: RA, sJIA
• Dose regimens:
  4-8 mg/kg Q4W (adults)
  8 or 12 mg/kg Q2W (pediatrics)

Source: Schmitt et al 2011

Confirms IL-6 inhibition affects CYP3A4
KEPIVANCE (palifermin, KGF)

... Heparin co-administration resulted in a 5-fold increase in palifermin systemic exposure. Avoid co-administration of palifermin with heparin. If heparin is used to maintain an intravenous line, rinse the line with saline prior to and after Kepivance administration.

Do not administer Kepivance within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. In a clinical trial, administration of Kepivance within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.

Human growth hormone (Genotropin)
Common PK Assays for Protein Biotherapeutics

- Immunoassays, primarily ligand binding assays (LBA)
  - Majority of protein products, ligands, biomarkers
- Enzyme activity assay
  - Examples: enzyme products
- Multiple assays for various analyses
  - Example: antibody drug conjugate
- Other methods in development
  - Example: mass spectrometry assay
Bioanalytical Validation for Biologics

- Fundamental Validation Parameters
  - Accuracy, Precision, Selectivity & Specificity, Sensitivity, Reproducibility, Stability, ...
- Procedures that demonstrate a method is reliable and reproducible for the intended use

Resources -
- Guidelines from global regulatory authorities
- 2001 FDA guidance - Bioanalytical Method Validation (undergoing revision)
Presentation Summary

• Introduction - What are biological products?
  – FDA regulated biological products
  – Summary of FDA approved biological products
• Clinical Pharmacology in a nutshell
• Role of clinical pharmacology in drug development
• A case example of PK-PD characterizations
  – Romiplostim (Nplate™)
• Highlights of other clinical pharmacology considerations
  – Intrinsic factors, extrinsic factors
  – Immunogenicity
  – Bioanalytical methods for exposure characterization
Thank You.

Questions?