Clinical Pharmacology in Drug Development of Small Molecules: Methods and Applications

Hong Lu, PhD
December 10, 2020
Nanjing International DMPK Symposium
Hong Lu, PhD

Hong Lu has over 15 years of experience as a clinical pharmacologist and pharmacometrician in the pharmaceutical industry. She is a scientific director in Quantitative Clinical Pharmacology at Takeda. Prior to Takeda, she had various positions of increasing scope and job responsibility at Vertex, Merck and Alkermes. Hong led clinpharm and biopharm filings for the NDA of ELUMIDOR (buprenorphine and samidorphan) and contributed to the development of ARISTADA (Aripiprazol Lauroxil); and was a pharmacometric lead of ORKAMBI (ivacaftor and lumacaftor) and contributed to the development of KALYDECO (Ivacaftor) and INCIVEK (Telaprevir).

Hong serves on International Society of Pharmacometrics New England (ISoP NE) Committee and on Membership Committee of American College of Clinical Pharmacology (ACCP). She has a special interest in developing clinical pharmacology tools for informed decision-making in drug development and in pharmacy practice.

Hong graduated from Peking Union Medical College in China and obtained a MS in Pharmacology from Boston University School of Medicine and a PhD in Pharmaceutical Science from University of Rhode Island.

Oral Presentations and Publications in 2020:

• Lu H (Symposium Chair), Fang LY (Symposium Co-Chair), Zhao L, Gomeni R, Wang YN, Graff A. Symposium 14: Applying Pharmacometrics to Precision Dosing in the Lifecycle of Long-acting Injectable Products: Drug Development, Regulatory Approval & Clinical Practice. The 2020 ACCP Annual Meeting, September 23, 2020
Disclaimer

- Examples presented in this talk are from publications and/or used for illustration purpose only.
- The views expressed in this talk represent my opinions and do not necessarily represent the views of Takeda.
Following completion of this activity, participants will be able to:

- Describe the strategic roadmap in clinical drug development of small molecules
- Describe the need and approaches for generating clinical pharmacology data in submitting a US Marketing Application
- Understand the general principles of timing and designing clinical pharmacology studies and population PK analysis.
Roadmap of Pharmaceutical Development

- Target Product Profile
- Clinical Development Plan
- Labeling
Critical Path in Clinical Development

IND: investigational new drug; SAD: single ascending dose; MAD: multiple ascending dose; OLES: open label extension study; NDA: new drug application; EOP2: end-of-Phase 2
Clinical Pharmacology and Modeling Studies: Logical Flow

SAD  MAD  Phase 2 Trial  Phase 3 Trials  OLES  NDA

Human PK and dose projection

TQT*: thorough QT; rBA: relative bioavailability; BE: bioequivalence; DDI: drug-drug interaction; popPK: population pharmacokinetics; MB: mass balance; RI: renal impairment; HI: hepatic impairment
Purposes of Clinical Pharmacology Work

- **Pharmacokinetics (PK) and Pharmacodynamics (PD) in humans**
  - Single- and multiple-doses PK characteristics
  - Dose proportionality
  - Absorption, Distribution, Metabolism and Excretion in human

- **Intrinsic and extrinsic factors** that influence the PK and PD profiles in humans
  - Physicochemical properties of the drug,
  - Product/formulation,
  - Administration route,
  - Patient’s intrinsic and extrinsic factors (e.g., organ dysfunction, diseases, concomitant medications, food)

- **Dose and dose regimen defense** in target indication and target population
  - **Clinical exposure boundary** for safety and efficacy
The ultimate goal is

To determine the dose and dose regimen that achieve the target exposures in all the relevant target populations.
The ultimate goal is to provide clinical pharmacology information (up to 50%) in a drug label.
How to Achieve the Goal

The Clinical Pharmacology and Biopharmaceutics (CPB) Review Template: The Question-Based Review (QBR)

Clinical Pharmacology Studies
- Single and multiple ascending dose PK
- Healthy vs. Patient PK
- Human ADME/Mass balance
- Drug interactions
- Pharmacogenomics
- Special population
  - Renal impairment
  - Hepatic impairment
  - Age, gender, ethnics
  - Pediatrics
- Special safety (e.g., QT prolongation; abuse liability)
- Population PK modeling
- PBPK modeling

Biopharmaceutical studies
- Bioavailability (BA) / Bioequivalence (BE)
- IVIVC
- Food effect

Exposure-Response (ER) analysis for efficacy and safety
- Dose selection and optimization
- Simulations for dosing regimen/dosing conditions

In vitro studies using human biomaterials
- In vitro pharmacology
- Protein binding; Blood-plasma partition;
- In vitro drug metabolism, transporter and drug interactions

Bioanalytical Assays
- Assay validation and performance reports
Single and Multiple Ascending Dose Study

- Typically First-in-human study
- Randomized, placebo controlled, healthy subjects
- Starting dose determined by pre-clinical toxicology data
- Maximal dose capped by the NOAEL exposure
- Information gained:
  - Safety/tolerability; maximum tolerated dose (MTD)
  - PK parameters (e.g., T_{max}, t_{1/2} and CL); PK variability, dose proportionality
  - Steady state PK parameters (accumulation ratio; time to steady state)
  - Preliminary exploration of elimination pathways; urine PK,
  - Exploratory metabolite profiling
  - Preliminary exploration of concentration-QT relationship
Typical SAD design

Alternating panel design, 4 periods, 8 dose levels, total N = 16

Example
• DOSE 1 = 25 mg; DOSE 2 = 50 mg; DOSE 3 = 100 mg; DOSE 4 = 200 mg; DOSE 5 = 400 mg; DOSE 6 = 800 mg; DOSE 7 = 1600 mg; DOSE 8 = 200 mg (fed).
• Each period, (PK, Holter ECG) data at fixed time points (e.g., predose, 0.5, 1, 2, 3, 4, 6, 12, 24 hrs)
• Urine PK at fixed time intervals up to 24 hrs postdose
Typical MAD design

Example
- DOSE 1 = 200 mg QD for 10 Days; DOSE 2 = 400 mg QD for 10 Days; DOSE 3 = 800 mg QD for 10 Days;
- Each period, PK data at fixed time points (intense PK on Day 1 and 10; pre-dose on Days 3 to 9);
- Urine PK at fixed time intervals up to 24 hrs postdose

<table>
<thead>
<tr>
<th>Panel</th>
<th>Number of Subjects</th>
<th>Treatment Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8</td>
<td>DOSE1/placebo</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>DOSE2/placebo</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>DOSE3/placebo</td>
</tr>
</tbody>
</table>
PK Parameters and Clinical Context (1)

**Parent drug and Active Metabolites**

- $T_{\text{max}}$
  - Represent the most appropriate time for safety assessment (e.g., ECG, PD)
- $T_{\text{1/2}}$
  - determining dosage interval
  - related to time to steady state after dose initiation or dose adjustment
  - influences the duration of monitoring after dosing and follow-up after withdrawal of therapy
  - determines adequate washout period between treatments (in crossover studies)
- $C_{\text{max}}$, $C_{\text{min}}$, AUC or MTD
  - Important for dose selection (viewed as relative to efficacy or safety via exposure-response analysis)
- Total Plasma CL and renal clearance ($CL_r$)
  - Inform the full or reduced design for renal/hepatic impairment study
PK Parameters and Clinical Context (2)

**Parent drug and Active Metabolites**

- PK variability
  - determines sample size for formal DDI, BA/BE, or food effect studies with pre-defined statistical criteria
- Dose proportionality
- Food effect results
  - Determines the dosing condition
  - enable definitive food effect study in late stage development
- Exploratory metabolite profiling
- PK-QTc analysis
  - enable a TQT waiver in late stage development
SAD/MAD PK readout and Interpretation
Example simulated and included for illustration purpose only

Single Dose PK (fasting)
- Rapid absorption ($t_{\text{max}}$ of 0.5 hr)
- Short terminal half-life ~7 hr
- High oral clearance (close to HBF)
- Dose proportional PK over 25-1600 mg
- Low PK variability in exposure (<35% for both AUC and $C_{\text{max}}$)

Multiple Daily Dose PK
- Steady-state reached after 3 to 4 days of treatment
- Little accumulation with once daily dosing
- Dose proportional PK over 200-800 mg

Metabolite Profiling
- No additional major metabolite identified in human

Urine PK
- Renal CL is 320 mL/min (greater than GFR);
- Urine excretion for parent drug is 21% of the dose; 39% for Metabolite

Food effect
- Minimal food effect

Clinical Conclusions
- Well tolerated up to 1600 mg single dose.
- Exposure at 800 mg once-daily in healthy volunteers are below the NOAEL exposure cap.
- Dosed with food in proof-of-concept study (PoC)
- Initiation of additional in vitro transporter studies with kidney transporters
PK/QTc Analysis from a SAD Trial

Example simulated and included for illustration purpose only

Holter-based ECG

Highest concentration ($C_{safe}$) at which 90% CI for true mean $\Delta\Delta QTc < 10$ msec

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>G. Mean</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>7.0</td>
<td>659</td>
</tr>
<tr>
<td>5</td>
<td>15.0</td>
<td>1151</td>
</tr>
<tr>
<td>10</td>
<td>33.0</td>
<td>1511</td>
</tr>
<tr>
<td>20</td>
<td>75.0</td>
<td>1511</td>
</tr>
<tr>
<td>40</td>
<td>166.0</td>
<td>1511</td>
</tr>
<tr>
<td>80</td>
<td>390.0</td>
<td>1511</td>
</tr>
</tbody>
</table>

Slope Estimate (Std. Error) $C_{safe}$

<table>
<thead>
<tr>
<th>Base Model</th>
<th>Slope Estimate</th>
<th>(Std. Error)</th>
<th>$C_{safe}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.005</td>
<td>0.002</td>
<td>1279</td>
</tr>
</tbody>
</table>
Assessment of the need for Clinical DDI Study

Decision Tree for Metabolism-Based Drug Interactions

- **In vitro metabolism information**
  - CYP 1A2, 2C8, 2C9, 2C19, 2D6, 3A
  - *Studies in human tissues*

- **NME not a substrate or NME a substrate but contribution of pathway not major**
  - Label as such based on *in vitro and in vivo disposition data* *\(^\text{1}\)*

- **NME is a substrate and contribution of pathway to elimination major or unclear**
  - Conduct *in vivo studies with most potent inhibitor(s)/inducer(s)*

- **NME is an inducer or inhibitor or no in vitro data**
  - Conduct *in vivo studies with most sensitive/specific substrate(s)*

- **NME not an inducer or inhibitor**
  - Label as such based on *in vitro data* *\(^\text{1}\)*

**Presence of significant interaction?**

- **Yes**
  - Study other inhibitors/inducers selected based on likely co-administration *\(^\text{1}\)*
    - Dosage adjustment needed?
      - Yes
      - No

- **No**
  - No further studies needed → general label based on *in vitro and in vivo data* *\(^\text{1}\)*

- **Study other substrates selected based on likely co-administration narrow therapeutic range**

- **Dosage adjustment needed?**
  - Yes
  - No

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*NME: New molecular entity

*Additional population pharmacokinetic analysis may assist the overall evaluation*
In Vitro Assessment of Drug Interaction Potential

- Metabolism is the major clearance mechanism for A and B in humans.
- Both A and B are primarily metabolized via CYP3A4.
- No PK interaction between A and B.
- A is a weak inhibitor of CYP2D6 and 3A4; B is a weak inhibitor of CYP2C19.
- Major metabolites showed no inhibitory or induction on any of CYP enzymes.
- A and B are not P-gp substrates.
- A, B and metabolites showed no inhibition on any of major transporters.

Investigational drug is a fixed dose combination of A and B

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 substrate</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>CYP3A4 inducer</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>CYP3A4 inhibitor</td>
<td>Weak</td>
<td>NO</td>
</tr>
<tr>
<td>CYP3A4 TDI</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>CYP2B6, 1A2 inducer</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>CYP1A2 inhibitor</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>CYP2B6 inhibitor</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>CYP2D6 inhibitor</td>
<td>Weak</td>
<td>NO</td>
</tr>
<tr>
<td>CYP2C8 inhibitor</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>CYP2C9 inhibitor</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>CYP2C19 inhibitor</td>
<td>NO</td>
<td>Weak</td>
</tr>
</tbody>
</table>

Example included for illustration purpose only
Clinical Drug Interaction Assessment Strategy

**Metabolism-based drug interactions**
- PBPK to assess Victim potential of
  - Itraconazole (strong CYP3A4 inhibitor)
  - Fluconazole (moderate CYP3A4 inhibitor)
  - Rifampin (strong CYP3A4 inducer)
  - Efavirenz (moderate CYP3A4 inducer)

- Clinical DDI studies with Rifampin or Itraconazole

- PBPK to assess perpetrator potential of
  - Midazolam (a model CYP3A4 substrate)
  - Dextromethorphan (a model CYP2D6 substrate)
  - Omeprazole (a model CYP2C19 substrate)

**Interactions with concurrent medications in target population**
- Identify most commonly used concomitant medications in target population
- Are they CYP3A4 inducers or inhibitors?
  - Assessment via population PK modeling
- Are they substrates of CYP3A4, 2D6 and 2C19?
  - Extrapolated from PBPK modeling
- Assess the need of additional clinical DDI study with co-meds
General Design Principles for Clinical DDI Study

- **Objective:** To evaluate potential of investigational drug as “Perpetrator” (an inhibitor/inducer \([I]\)) and “Victim” (substrate \([S]\)) of certain metabolizing enzymes/transporters

- **Preferably** **crossover design** (parallel - if long t½ drug); healthy subjects (or patients for safety considerations or if desirable to evaluate PD endpoints)

- **The choice of doses/dosing intervals/dosage forms of substrate and inhibitor/inducer, routes & timing of co-administration, number of doses should maximize possibility of detecting an interaction.**
  - Evaluating an investigational drug as a potential substrate (Victim)
    - Need a dosage within the linear PK range (highest dosage in this range not required)
    - Potentially can utilize a single dose
    - Study a strong probe inhibitor/inducer first
  - Evaluating an investigational drug as a precipitant (Perpetrator)
    - Highest clinical dosage level
    - Dose to steady-state of parent
    - More extended dosing when:
      - Metabolites contribute to DDI
      - Precipitant demonstrates time-dependent
      - Investigating the potential for induction
  - **Time co-administration to maximize the possibility of interaction**
DDI Results Reporting and Interpretation

- Exposure-response information on the drug is important in assessing the clinical significance of the change in AUC of substrate by inhibitor/inducer.

- Itraconazole did not meaningfully altered exposure, indicating no dose adjustment with 3A4 inhibitors.

- Rifampin reduced exposure by >50%, indicating no strong 3A4 inducers allowed with co-administration.

- Clinically DDI study results agreed well with PBPK modeling.

- Efavirenz was predicted to decrease exposure <50%, indicating no dose adjustment with mild to moderate 3A4 inducers.

Lu H, Hard ML, von Moltke L. Effects of Itraconazole or Rifampin on the Pharmacokinetics of Buprenorphine and Samidorphan when Sublingually Administered in Combination as ALKS 5461 in Healthy Subjects. ACCP 2018.
Human ADME study in parallel with Proof-of-concept study is an efficient and resource-conscious approach

**Drug development objectives answered by human ADME**

- Confirm (similarity of) metabolite profiles in humans vs. toxicology species
- Support choice of animal species for chronic toxicity studies
- Prediction of possible drug interactions; consequences of liver and renal failure; possibilities for improved formulations
- To assess potential retention of the investigational drug in the body

**Study objectives of human ADME**

- To assess the mass-balance: % recovery of 14C-labeled drug material from urine and feces
- To elucidate rates and routes of excretion
- To assess the absorption, bioavailability, and blood/plasma ratio
- To assess the metabolite profile and metabolite structures

**Human ADME study: when, why and how**

**Human ADME study in parallel with Proof-of-concept study is an efficient and resource-conscious approach**

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General Considerations for Human ADME Study

- Nonclinical dosimetry study
  - Rat Quantitative Whole-Body Autoradiography (QWBA) to determine radioactive dose in human
- Radiosynthesis
  - Choice of radioisotopes position in the drug molecule and type
  - Non-GMP batches and GMP batches preparation
- Availability of formulation and route of administration
- Study dose selection
  - Pharmacological active dose or a dosage within the linear PK range
- Tissue sampling
  - Plasma, whole blood, urine, feces
- Bioanalysis
  - AMS, LC-MS/MS, Liquid scintillation counting (LSC)
- Study conduct
  - Subject retention and discharge procedures
- Study results reporting and interpretation
  - Metabolite ID report and clinical study report
Population PK Modeling

- Functions describe typical time concentration time course
- Often represented as differential functions
  - Absorption model (e.g., first order, transit-compartment)
  - Elimination model (e.g. one- or two-compartment)

- Explains variability by subject characteristics (covariates)
- E.g., weight, age, genotype, special population

- Variability around structural model
- E.g., Between-subject, between-occasion, residual

Structural model
Covariate model
Statistical model
Balance Individual and Population Information

- Studies provide rich and sparse PK sampling schedules
- Studies include both healthy volunteers and patient population
- Studies provide PK data over a wide range of dose levels
- Studies provide large population information with subject characteristics
  - Special populations if possible (e.g., creatinine clearance)
  - Concurrent medications
  - Demographic data (e.g., age, gender, ethnics)
  - Formulations

<table>
<thead>
<tr>
<th>#data per subject available</th>
<th>#subjects available</th>
<th>Many</th>
<th>Few</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many</td>
<td>Both individual and population model are robust</td>
<td>Individual information is most robust</td>
<td></td>
</tr>
<tr>
<td>Few</td>
<td>Population information is most robust</td>
<td>Neither individual nor population information is robust</td>
<td></td>
</tr>
</tbody>
</table>
Age, gender, body weight, race, patient disease had no effect on the PK of the fixed dose combination.

Formulation resulted in no clinically significant impact on exposure.

Increased exposures in subjects with severe renal impairment and hepatic impairment were accounted by the covariate model.

- Increase predicted in subjects with mild and moderate renal impairment.


References


- Lu H, Hard ML, von Moltke L. Effects of Itraconazole or Rifampin on the Pharmacokinetics of Buprenorphine and Samidorphan when Sublingually Administered in Combination as ALKS 5461 in Healthy Subjects. ACCP 2018.
Backups
Clinical Pharmacology Applications by Drug Development Stage: Not a Cookbook

Inform Internal Decision Making

Preclinical to IND
- Biomarker/PD
- Toxicology/TK
- Nonclinical PK/PD
- Nonclinical ADME
- In vitro metabolism, CYP/Transporter assay
- Physicochemical Property/BCS

Early Phase (Phase 1 to PoC)
- SAD/MAD
  - Metabolite profiling
  - Preliminary food effect
- PK in Healthy vs. Patients
- Evaluate needs for DDI
- BA/BE studies (formulation switch)
- Enable Proof of Concept (PoC)
- Mass balance

Late Phase (Phase 2/3)
- Definitive DDI
- Renal/Hepatic
- Definitive food effect
- BE for to-be-marketed formulation
- Thorough QT study/ECG evaluation
- PK and PD sampling scheme
- Pediatric plan

Support Regulatory Submission

Key (Clinical) Studies
- Dose range selection for Phase 2
- SAD/MAD for popPK base model
- IVIVC consideration
- Concentration-QT consideration

Key Modeling Activities
- Dose optimization for Phase 3
- Exposure-response analysis to build clinical boundary
- PopPK Model refinement (covariates)
Clinical Pharmacology Studies: Designing, Conducting and Reporting

Clinical Pharmacology Plan (Early/Late)

Study Design and Core Elements:
Objective/endpoints/study & dose rationale/IE Criteria/sample size/SOA/bioanalysis

Drug Supply CRU Study team

Protocol Concept & Approval

Execution:
SET meeting/project timeline/site query/LSO/PK sample shipment & analysis/PK memo

Site initiation and FSI readiness:
ICF/CRF/SMP/SAP/TFL shells Protocol Deviation plan/protocol registration

Protocol Development & FDA/IRB submission

Clinical Database pre-lock:
protocol deviation summary/prelock listing review

Clinical Database post-lock:
SDTM/ADaM/Safety & PK TFLs/CSR template

Final Database lock and CSR:
Final SDTM/ADaM/TFLs; CSR draft & final CSR
Application of PKPD modeling in Drug Development of Large Molecules

Rong Deng, PhD
December 10, 2020
Nanjing International DMPK Symposium
Biosketches

Rong Deng, PhD

- Dr. Rong Deng is currently an independent consultant on preclinical Pharmacokinetics/Pharmacodynamics (PK/PD), translational PK/PD, clinical pharmacology and pharmacoanalytics. Before she worked as an independent consultant, she was a Principal Scientist in the Department of Clinical Pharmacology at Genentech. Dr. Deng is a subject matter expert on biologics PK and M&S. She has presented at multiple international and regulatory meetings (AAPS, AAPSNBC, PAGE, ASCPT, cFDA, FDA, EMA and etc), organized workshops and symposium on biologics PK and PK/PD modeling topics. Dr. Deng is the co-author of over 50 peer-reviewed publications/book chapters with a Ph.D. in Pharmaceutical Sciences from the University of Buffalo in 2005.

- Recent Oral Presentations and Publications (partial list)
Disclaimer

- All examples presented in this talk are from publications and used for illustration purpose only.
- The views expressed in this talk represent my opinions.
Objectives

Following completion of this activity, participants will be able to:

- Understand the PK difference between small molecules and large molecules
- Describe the strategic roadmap in clinical drug development of large molecules
- Understand the role of clinical pharmacology in clinical drug development of large molecules
Antibodies Are the Largest and Most Rapidly Expanding Class of Biopharmaceutical

As of October 14, 9 antibody therapeutics had been granted first approvals in the US in 2020, and an additional 17 are in regulatory review. *

*https://www.antibodysociety.org/resources/approved-antibodies/
## How Does PK Differ?

<table>
<thead>
<tr>
<th>Small Molecule Drugs</th>
<th>Monoclonal Antibodies</th>
<th>Antibody Drug Conjugates</th>
</tr>
</thead>
<tbody>
<tr>
<td>High potency and low specificity</td>
<td>Low potency and high specificity</td>
<td>High potency and high specificity</td>
</tr>
<tr>
<td>PK usually independent of PD</td>
<td>PK usually independent of PD</td>
<td>Same as MAB</td>
</tr>
<tr>
<td>Binding generally nonspecific (can affect multiple enzymes)</td>
<td>Binding very specific for target protein or antigen</td>
<td>Same as MAB</td>
</tr>
<tr>
<td>Linear PK at low doses (usually therapeutic doses); nonlinear PK at high doses (after saturation of metabolic enzymes)</td>
<td>Nonlinear PK at low doses; linear PK at high doses after saturation of target</td>
<td>Same as MAB</td>
</tr>
<tr>
<td>Relatively short $t_{1/2}$ (hours)</td>
<td>Long $t_{1/2}$ (days or weeks)</td>
<td>Long $t_{1/2}$ of antibody; sustained delivery of small molecule (formation rate limited)</td>
</tr>
<tr>
<td>Oral delivery often possible</td>
<td>Need parenteral dosing. Subcutaneous (SC) or intramuscular (IM) is possible</td>
<td>Need parenteral dosing. SC or IM has not been tested</td>
</tr>
<tr>
<td>Metabolism by cytochrome P450 or other phase I/phase II enzymes</td>
<td>Catabolism by proteolytic degradation</td>
<td>Catabolism by proteolytic degradation; small molecule component can undergo excretion unchanged or metabolism by cytochrome P450 enzymes or other phase I/phase II enzymes</td>
</tr>
<tr>
<td>Renal clearance often important</td>
<td>No renal clearance of intact antibody. May be eliminated by damaged kidneys. Antibody fragment might be eliminated by renal clearance.</td>
<td>Combination of mAb and small molecule; Released small molecule can be cleared renally and/or hepatically</td>
</tr>
<tr>
<td>High volume of distribution due to binding to tissues</td>
<td>Distribution usually limited to blood and extra-cellular space</td>
<td>Same as MAB</td>
</tr>
<tr>
<td>No immunogenicity</td>
<td>Immunogenicity may be seen</td>
<td>Same as MAB</td>
</tr>
<tr>
<td>Narrow therapeutic window</td>
<td>Large therapeutic window</td>
<td>Depends on potency of payload</td>
</tr>
</tbody>
</table>

PK Example: mAb vs SMD

- mAbs show slow clearance (mAb time units in days, SMD time units in hours)
- mAbs show often nonlinear PK in binding species
- Both mAb and SMD can exhibit species differences
  - (SMD: e.g. CYP450 metabolism, mAbs: e.g., target expression, affinity)
PK examples: ADC

<table>
<thead>
<tr>
<th>Antibody Related PK Assays</th>
<th>Small Molecule Related PK Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Antibody (Tab)</strong></td>
<td>Antibody Conjugated Drug</td>
</tr>
<tr>
<td>- Measures both conjugated &amp; unconjugated antibody</td>
<td>- Measures drug associated with antibody</td>
</tr>
<tr>
<td><strong>Conjugate Antibody</strong></td>
<td>Unconjugated Drug</td>
</tr>
<tr>
<td>- Measures only conjugated antibody</td>
<td>- Measures unconjugated drug</td>
</tr>
</tbody>
</table>


Applications of PK/PD Concepts during Preclinical and Clinical Drug Product Development

Cetuximab Preclinical PK/PD Study to Help Defining the Optimal Clinical Exposure

- The estimated $C_{ss, \text{avg}}$ is 73.1 µg/mL for Cetuximab in GEO human colon carcinoma xenograft model at the optimal dose of 0.25 mg/inj q3dx5
  - Reach 100% EGFR occupancy in tumor
- The estimated $C_{ss, \text{avg}}$ of Cetuximab in cancer patients is within the range of 50-100 µg/mL at current clinical dose

PK/PD studies in the preclinical stages including the receptor occupancy in the tumors lay a solid foundation for defining the optimal clinical drug exposure

Luo FR et al., Cancer Chemother Pharmacol. 2005 Nov;56(5):455-64.
Secukinumab PK/PD in Skin Provides Importantly Supportive Evidence of MOA

- High baseline free IL-17A levels in diluted dermal ISF from lesional psoriasis patients
- Significant secukinumab exposure in the target tissue skin (dermal interstitial fluid, blister fluid and skin biopsy samples)
  - Skin to serum ratio: 23% in healthy volunteers versus 28-39% in psoriasis patients
    - Different from reported skin partition coefficient value (~15%)*
- Significant decrease of β-defensin-2, a relevant IL-17A pathway marker after secukinumab treatment
  - Confirm the role of IL-17A homo- and heterodimers in psoriasis

*Shah D et al. MAbS. 2013 Mar-Apr;5(2):297-305

- First time to use open flow microperfusion (OFM) for PK/PD assessment of a therapeutic antibody and relevant biomarkers
- Disease status has impact on target expression level and mAb skin penetration
Integrated Platform Analysis for ADC

Strong correlation between total Ab and acMME

Key efficacy and safety endpoints tested correlate well with acMMAE exposure not with unconjugated MMAE

Platform analysis (PK and exposure-response analysis) suggested that acMMAE analyte alone might be adequate for vc-MMAE ADCs to support the clinical pharmacology strategy used during late-stage clinical development.
A previously established population PK (popPK) model as well as exposure-response results from patients with advanced melanoma or non–small cell lung cancer (NSCLC) were used to evaluate the potential application of a fixed dosing regimen with the aim of maintaining pembrolizumab exposures within the range demonstrated to provide near maximal efficacy and acceptable safety.

Doses of 200 mg and 2 mg/kg provide similar exposure distributions with no advantage to either dosing approach with respect to controlling PK variability. These findings suggest that weight-based and fixed-dose regimens are appropriate for pembrolizumab.

Simulations based on population PK to support the flat dosing
The pharmacokinetics of ustekinumab were comparable between Chinese and non-Chinese healthy male subjects when exposure parameters were adjusted by subject body weight. No need to have dose adjustment.

Population PK analysis: most mAbs have BW or BSA as the covariate on CL (17 out of 18 mAbs).

Given the many practical advantages and potentially larger therapeutic window of most mAb, fixed dosing is recommended with mAbs, due to their smaller PK variability relative to PD, safety and efficacy.

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Lack of Ethnic Effect on mAb PK

Japanese v. Non-Japanese subjects

PK differences were observed for some mAbs
1. Body weight and target expression level
2. No need for dose adjustment
High Level PKPD/Toxicity Study for Large Molecules in Drug Development

The Roles of Clinical Pharmacology in Drug Development

Understanding the relation between exposure to a drug and its clinical effects to enable right dose to right patient

Conclusions

- Clinical pharmacology play a crucial role in drug development for both small molecules and large molecules with some differences.
- Clinical pharmacology studies including modeling and simulation can contribute to:
  - Translation from preclinical to clinical
    - Candidate comparison, selection, human PK and dose prediction
  - Better understanding of MOA
  - Dose and schedule selection and adjustment for label recommendations
    - DDI
    - Special population
    - Ethnicity
  - Study design optimization
  - Predicting and characterizing ADME
  - And more .................
    - Risk/benefit characterization, outcome predictions from early clinical response
    - Comparator/standard-of-care differentiation and commercialization strategy
    - Precision dosing in clinical care
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Backups
PD measures can be direct or indirect depending on MOA of drug, target biology and location of targets

Deng R et al., Exp Opin Drug Metab Tox, 2012