Clinical Pharmacology 1: Phase 1 Studies and Early Drug Development

Shirley K. Seo, Ph.D.
FDA/OMTP/CDER
Office of Translational Sciences
Office of Clinical Pharmacology, Division 4
Objectives

- Describe Phase 1 clinical pharmacology studies:
  - Goals
  - Key design elements
  - Information gained from these studies
- List clinical pharmacology characteristics of an ideal drug
- Describe how clinical pharmacology information from Phase 1 can help design Phase 2/3 trials
- Discuss the timing of clinical pharmacology studies during drug development
Phase 1 of Drug Development

Phase 1
- studies designed mainly to investigate the safety/tolerability (if possible, identify MTD), pharmacokinetics and pharmacodynamics of an investigational drug in humans
Clinical Pharmacology

- Study of the **Pharmacokinetics (PK)** and **Pharmacodynamics (PD)** of a drug in humans

**PK**: what the body does to the drug (Absorption, Distribution, Metabolism, Excretion)

**PD**: what the drug does to the body

<table>
<thead>
<tr>
<th>Concentration (log)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (log)</td>
</tr>
</tbody>
</table>

Commonly referred to as an exposure-response (ER) profile
The Ultimate Goal:

RIGHT DRUG

RIGHT PATIENT

GOAL

RIGHT DOSE

RIGHT TIME
How do we achieve the goal?

Drug Product Labeling

Bioequivalence
Drug-Drug Interactions

Hepatic Impairment?
Renal Impairment?

Phase 3 Safety & Efficacy
Phase 3 PK Study
• population PK
• exposure/response

Phase 2/3

Pediatric patients?

Gender?
Race?
Elderly?

Enzymes and transporters
Human Mass Balance
Food Effects?

Phase 2

Protein Binding
In Vitro Metabolism

BA Studies
Phase 1 PK
• dose-proportionality
• dose accumulation

Phase 1 (First-in-Human studies)

Validated Analytical Methods

Phase 1 PK
• dose-proportionality
• dose accumulation
Types of Clinical Pharmacology Studies
Single Dose/Multiple Dose Escalation Studies

Starting dose determined by preclinical tox studies

Typically the first-in-human study (or studies)

Randomized, placebo-controlled, healthy volunteers (or patients, in certain cases)

Information gained:
- Safety/tolerability, identify maximum tolerated dose
- General PK characteristics, variability, linearity, dose proportionality
- Steady-state parameters
- Preliminary exploration of drug elimination
ADME Study

Objective: To understand the full clearance mechanisms of the drug and its metabolites in humans

(aka Mass Balance Study)

Information gained:
- Primary mechanism(s) of elimination and excretion from the body
- Proportion of parent drug converted to metabolite(s)

Radio-labeled (C\textsuperscript{14}) drug molecule

Measure concentrations of parent and metabolite(s) and determine amount of radioactivity in plasma, urine, feces

Single dose, healthy males (n=4 to 6) with intended route of administration
Bioavailability (BA) Studies

- Objective: To evaluate the rate ($C_{\text{max}}$, $T_{\text{max}}$) and extent (AUC) of absorption of drug from a test formulation (vs. reference formulation)

- Typically crossover, single dose study in healthy subjects; measure extent and rate of absorption of parent drug and major active metabolites (if any)
  - Can assess relative (one formulation vs. another) or absolute (vs. IV formulation) bioavailability

Information gained:
- Comparison of amount of drug that reaches systemic circulation from each tested formulation
Food Effect Study

Objective: To evaluate the effect of food on rate and extent of drug absorption from a given formulation

- Single dose study in healthy subjects using highest strength of drug product.
- Fed state should be FDA high-fat high-calorie meal
- PK assessments similar to BA study
- No food effect if 90% CI of fed/fasted Cmax and AUC ratios within 80-125%.
- The clinical significance of any observed food effect would be determined based on drug’s exposure-response profile.

Information gained:
- How to administer drug in clinical trials
- Labeling instructions on how to administer drug with respect to food
Hepatic Impairment Study Decision Tree

Investigational Agent

Chronic, Systemic Drug, Use Likely in Hepatically impaired

>20% of absorbed drug eliminated by liver (wide TI); <20% if Narrow TI drug; % eliminated by liver unknown

Study Recommended

Full Study (Normal vs. Child-Pugh A, B, C)

Population PK (if patients included in Ph 2/3 trials)

Single-Use, Inhalational <20% absorbed drug eliminated by liver (wide TI drug); eliminated entirely by kidneys

No Study Recommended

Label Accordingly

Reduced Study (Normal vs. Child Pugh B)

Positive Results for Child-Pugh B: Dose Reduction; Use with caution in Child-Pugh-C

Negative Results for Child-Pugh B: No dosage Adjustment for Child-Pugh A & B
Hepatic Impairment Study

• Study Designs:
  Full study design: Single dose, parallel groups, males & females with varying degrees of hepatic impairment (≥6 per group)
  – Normal Hepatic Function (matched for age, gender & BW to subjects with hepatic impairment)
  – Child-Pugh Class A (Mild)
  – Child-Pugh Class B (Moderate)
  – Child-Pugh Class C (Severe)

Reduced study design: Normal vs. Child-Pugh B (Moderate) (≥8 per group)

Pop-PK approach (pre-planned analysis):
  – Should include patients w/ varying degrees of hepatic impairment in phase 2 and 3 trials
  – Should include appropriate evaluation of severity of liver disease

Information gained:
  - Effect of hepatic impairment on PK of parent drug and metabolites
  - Dosage recommendations for various stages of hepatic impairment
Renal Impairment Study
Decision Tree (source: 2010 RI guidance)

1. Metabolites (active/toxic) follow the same decision tree.
2. The sponsor has the option of conducting a reduced study in ESRD patients or a full study.
3. To be conducted in ESRD patients not yet on dialysis.
4. The results are "positive" when the PK changes are clinically significant based on exposure-response of the drug.
5. See section IV.B for the full PK study design, or additional studies can be conducted including a population PK evaluation.
Renal Impairment Study

Study designs:

Full study design:
- Generally single dose, parallel groups, “healthy” males and females with varying degrees of renal function (≥6 per group, based on CrCl):
  - Normal (≥90 mL/min)
  - Mild (60-89 mL/min)
  - Moderate (30-59 mL/min)
  - Severe (15-29 mL/min)
  - ESRD (<15 mL/min) dialysis and non-dialysis

Reduced study design:
- Same general design as full, except only study severes and normals

Pop-PK approach
- Include appropriate number of subjects in each impairment group

Information gained:
- Effect of renal impairment on drug clearance; dosage recommendations for various stages of renal impairment
- Effect of hemodialysis (HD) on drug exposure; info on whether dialysis could be used as treatment for drug overdosage
Drug Interaction Studies

Use in vitro tests to determine if drug is a substrate for or an inhibitor/inducer of common drug metabolizing enzymes (i.e., CYP3A, CYP2C9, CYP2C19, etc)

Conduct drug interaction studies to confirm involvement of drug

Implications for labeling range from informative wording (i.e., drug X is not a substrate for CYP3A-mediated metabolism) all the way to a contraindication

Additional detailed information can be found in the Drug Interaction Guidance (draft 2012)
Drug Interaction Studies

Some key points to consider:

- Several factors should be taken into account to maximize the possibility of detecting an interaction (and also be clinically relevant):
  - Dose of inhibitor/inducer
  - Route(s) of administration
  - Timing of co-administration
  - Number of doses

- Degree of effect (inhibition/induction) is typically classified by change in the substrate AUC:
  - e.g., Drug causes \( \geq 5 \)-fold increase in midazolam AUC \( \rightarrow \) “potent” inhibitor of CYP3A4

- Exposure-response information on the drug is important in assessing the clinical significance of the change in AUC of substrate by inhibitor/inducer.
Thorough QT Study (TQT)

- In vivo safety study required for all systemically available NMEs (regardless of in vitro or non-clinical findings)

- Objective: To identify drugs that prolong QT interval (95% CI upper bound ≥ 10 ms), which may need more thorough ECG monitoring in pivotal trials

- Typically, single dose study in healthy subjects; evaluate therapeutic and “supratherapeutic” doses of drug versus positive control (e.g., moxifloxacin)

Additional detailed information can be found in:
ICH Guidelines, E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Recommendations for design, conduct, analysis, and interpretation of clinical studies
Desirable Clinical Pharmacology Properties of a Drug

• **ABSORPTION:**
  – High absolute bioavailability with low variability
  – Exhibits linear PK (e.g. dose-proportional increases in Cmax & AUC) over therapeutic dose range
    • Single-dose study design sufficient: BA, PK in renal impairment, hepatic impairment & DDI
  – AUC, Cmax not significantly affected by concomitant food, pH-altering medications, grapefruit, alcohol, etc.
  – BCS Class I (high solubility + high permeability)
    • can qualify for biowaiver of future additional BA/BE studies
Desirable Clinical Pharmacology Properties of a Drug

- DISTRIBUTION:
  - Reaches the target site(s) of action immediately and at effective/nontoxic concentrations; doesn’t accumulate in non-target organs
  - Not significantly (>80 to >95%) bound to plasma proteins; extent of protein binding not concentration- and time-dependent
    - only free or unbound drug is active
    - less prone to DDI with highly protein bound drugs (e.g., warfarin)
    - PK in terms of total drug concentrations often sufficient (e.g., in PK studies in renal and hepatic impairment)
Desirable Clinical Pharmacology Properties of a Drug

- **METABOLISM/EXCRETION:**
  - Not extensively metabolized or exclusively metabolized by a CYP enzyme
    - CL less likely to be affected by hepatic impairment and/or concomitant administration of other drugs that affect one or more metabolizing enzymes
  - Not metabolized by polymorphic enzymes (e.g., CYPs 2D6, 2C19, 2C9, NAT2)
    - does not require genotyping in PK and other clinical studies
  - CL not highly variable and not dependent on ‘covariates’ such as age, race, gender, disease/comorbidities
  - CL not time-dependent (e.g., metabolic auto-induction, diurnal variation)
    - does not require longer duration of studies for PK profiling
Desirable Clinical Pharmacology Properties of a Drug

- **OTHERS:**
  - Not a Narrow Therapeutic Index Drug
    - slight changes in drug exposure less likely to impact efficacy/safety
    - less likely to require therapeutic drug monitoring in clinical trials and clinical practice to minimize toxicities and lack of efficacy
  - Does not prolong the QT interval
    - less likely to have Torsades de Pointe risk
  - Not a significant inhibitor or inducer of CYP3A, P-gp, etc.
    - less likely to have DDI with concomitantly administered drugs
PK Parameters and Design of Phase 2/3 Trials

Parent Drug and Active Metabolites:

- **$T_{\text{max}}$**
  - represents the most appropriate time(s) to perform safety assessments (e.g., vital signs, ECG, other immediate PD effects)

- **$t_{\frac{1}{2}}$**
  - considered when determining dosage interval
  - related to time to steady state ($t_{ss}$) after dose initiation or dose adjustment; considered in evaluating need for a loading dose
  - influences the duration of monitoring after dosing and follow-up after withdrawal of therapy
  - determines adequate washout period between treatments (in crossover studies)

- **Cmax, Cmin, AUC**
  - important for dose selection (viewed relative to MEC and MTC)
  - eg. PK/PD parameters predicting efficacy of anti-infectives
PK and Drug Effect

- Cmax
- AUC
- Tmax
- Cmin
- Duration of action

Therapeutic Window:
- MTC
- MEC

(time of effect)

(Peak effect)
Timing of Early and Clinical Pharmacology Studies

Pre-Clinical
- Assay Dev’t & Validation including stability
- Blood/Plasma ratio; Protein Binding

Clinical

Phase 1
- SAD/MAD PK*
- Food-effect

Phase 2
- PK & PD in patients
- Exposure-Response Analyses

Phase 3
- “Pivotal” Bioequivalence
- PK & PD in patients
- PK in Renal Impairment
- PK in Hepatic Impairment
- TQT

Phase 4
- PK in Peds, Geriatrics, Pregnancy/Lactating
- In vitro metabolism/transport: substrate/inhibition/induction
- PGx: CYP genotyping
- PGx: Biomarkers of Response
- Mass Balance
- In vivo DDI studies
Phase 1 Studies: Impact on Labeling

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Labor and Delivery
   8.3 Nursing Mothers
   8.4 Pediatric Use
   8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
   9.1 Controlled Substance
   9.2 Abuse
   9.3 Dependence
10 OVERDOSAGE
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
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
Clinical Pharmacology Guidance Documents

- Clinical Lactation Studies (2005*)
- Clinical Pharmacogenomics (2011)
- General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (1998*)
- In Vivo Drug Metabolism/Drug Interaction Studies (1999)
- Pharmacokinetics in Patients with Impaired Hepatic Function (2003)
- Pharmacokinetics in Patients with Impaired Renal Function (2010*, 1998)
- Pharmacokinetics in Pregnancy (2004*)
- Population Pharmacokinetics (1999)

* Draft
Biopharmaceutics Guidance Documents

- Bioanalytical Method Validation (2013 - NEW!)
- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (2003*)
- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (2003)
- Statistical Approaches to Establishing Bioequivalence (2001)
- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000)

* Draft
Labeling Examples
Food Effect Example:
REYATAZ® (atazanavir) oral capsules

- Administration of a single dose of atazanavir (800 mg) with a light meal increased Cmax by 57% and AUC by 70%; a high-fat meal increased AUC by 35% with no change in Cmax. The %CVs of AUC and Cmax decreased by approximately one-half compared to the fasting state.

- Clinical trials were conducted under fed conditions.

Label directs administration with food.
• In an ADME study, ~93% of the dose was excreted in urine by 12 hours.
• Because doripenem is primarily eliminated by the kidneys, a full PK study in patients with renal impairment was conducted. The study demonstrated a significant difference in PK between patients with moderate and severe renal impairment compared to those with normal renal function. Also, 52% of the dose was recovered in the dialysate following dialysis.
• In Phase 2/3 trials, dosage was adjusted based on CrCL.

The label recommends dosage reduction for patients with moderate or severe renal impairment… and hemodialysis as a treatment for overdosage.
Hepatic Impairment Example: ISENTRESS® (raltegravir) oral tablets

- A mass balance study showed that raltegravir is eliminated primarily by glucuronidation in the liver. Renal clearance is a minor pathway of elimination.
- In the hepatic impairment study (reduced study design), there were no clinically significant pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects.
- PopPK analysis of Phase 2/3 trial data further indicates that the PK of raltegravir in Child Pugh B patients were not different from patients with normal hepatic function.

Labeling states: No dosage reduction for patients with moderate or mild hepatic impairment is recommended. The effect of severe hepatic impairment on the PK of the drug was not studied.
To summarize, Clinical Pharmacology studies...

- are conducted to gain a fundamental understanding of the pharmacokinetics (PK; exposure) and the pharmacodynamics (PD; biologic effect) of the drug.

- provide useful information for the design of Phase 3 clinical trials (e.g., using dose-response and exposure-response analyses).

- inform patient care
  - identification of correct dosing regimen(s) in all relevant subpopulations of patients