Pharmacokinetics in Clinical Trials

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Center for Drug Evaluation and Research
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CDER Small Business Assistance Training
Outline

- Define pharmacokinetics
- Discuss types of pharmacokinetic studies performed in drug development
- Provide examples of different types of pharmacokinetic studies
- Illustrate the importance of bioequivalence studies
- Define the role of DSI to ensure data integrity
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Pharmacokinetics (PK)

- Defined as the quantitative analysis of the time course of a drug
- Pharmacokinetics describes what the body does to a drug
- Commonly referred to as “ADME”
  - absorption
  - distribution
  - metabolism
  - excretion
Pharmacokinetics (cont.)

• Provides a basis for dose selection in early clinical trials
• Identifies the linearity and dose-proportionality across a range of doses
• Supports dose adjustments for specific populations
• Supports dose adjustments with drug interactions (either perpetrator or victim drug)
Relationship Between Pharmacokinetics (PK) and Pharmacodynamics (PD)

- Absorption
- Distribution
- Metabolism
- Excretion
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Goals of Initial Pharmacokinetic Studies

- Provide an assessment of the safety and tolerability in healthy subjects (may be a first in human study)
- Provide an understanding of the pharmacokinetics of the drug
- Identify possible sources/determinants of between-subject variability
Types of Phase 1 Pharmacokinetic Studies

- Mass balance (ADME)
- Single dose/multiple ascending dose
- Bioavailability/bioequivalence
- Food effect (oral formulations)
- Specific populations
  - age/gender
  - renal impairment
  - hepatic impairment
  - pediatrics
  - obesity
- Drug interactions
- Thorough QTc (cardiac repolarization)
- Drug penetration
Mass Balance (ADME)

- Commonly $^{14}$C-radiolabeled drug
- Usually single dose
- Usually healthy male subjects
- Provides valuable information regarding metabolism and excretion, especially for drugs that are metabolized and excreted via renal & hepatic mechanisms
- Can be performed early in development, but may be performed at any stage
Mass Balance (ADME)

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200327Orig1s000ClinPharmR.pdf
Mass Balance (ADME)

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/200327Orig1s000ClinPharmR.pdf
Mass Balance (ADME)
Single Dose/Multiple Dose Pharmacokinetics

- Assesses the pharmacokinetics of the compound across a range of doses (including clinically relevant doses)
- Assesses linearity and dose proportionality
- Multiple dosing can assess time-dependent effects
- Usually performed in healthy male and female subjects
Single-Dose Concentration-Time Profiles

![Graph showing concentration-time profiles for different dose levels (50 mg, 100 mg, 250 mg, 500 mg, 750 mg, 1000 mg). The y-axis represents Mean(SE) Concentration in ng/mL, ranging from 10 to 100,000. The x-axis represents time in hours, ranging from 0 to 24. Each dose level has a distinct line and symbol.](image-url)
## Single-Dose PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>50 mg (N=6)</th>
<th>100 mg (N=6)</th>
<th>250 mg (N=6)</th>
<th>500 mg (N=6)</th>
<th>750 mg (N=6)</th>
<th>1000 mg (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>1.51 ± 0.25</td>
<td>3.08 ± 0.96</td>
<td>10.1 ± 1.68</td>
<td>16.6 ± 2.11</td>
<td>23.4 ± 4.92</td>
<td>30.5 ± 4.32</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.92 (0.90-1.08)</td>
<td>0.92 (0.92-1.10)</td>
<td>0.92 (0.92-1.25)</td>
<td>1.08 (0.92-1.08)</td>
<td>1.00 (0.92-1.08)</td>
<td>0.92 (0.92-1.02)</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{inf}}$ (ug*h/mL)</td>
<td>3.95 ± 0.73</td>
<td>6.72 ± 1.67</td>
<td>23.4 ± 5.38</td>
<td>44.8 ± 2.86</td>
<td>57.6 ± 9.75</td>
<td>80.9 ± 8.63</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>2.03 ± 0.15</td>
<td>2.23 ± 0.42</td>
<td>2.33 ± 0.26</td>
<td>2.53 ± 0.28</td>
<td>2.62 ± 0.29</td>
<td>2.90 ± 0.14</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>11.5 ± 2.33</td>
<td>13.7 ± 2.94</td>
<td>9.87 ± 2.35</td>
<td>9.89 ± 0.63</td>
<td>11.8 ± 2.07</td>
<td>11.0 ± 1.17</td>
</tr>
<tr>
<td>$V_z$ (L)</td>
<td>33.4 ± 4.46</td>
<td>42.9 ± 4.19</td>
<td>32.8 ± 7.17</td>
<td>35.9 ± 3.45</td>
<td>44.4 ± 8.08</td>
<td>46.0 ± 5.23</td>
</tr>
</tbody>
</table>

$AUC_{\text{inf}}$, area under concentration-time curve from time 0 to infinity; $C_{\text{max}}$, maximum observed concentration; CL, plasma clearance; $t_{1/2}$, elimination half-life; $T_{\text{max}}$, time of $C_{\text{max}}$; $V_z$, volume of distribution of terminal phase.
Multiple-Dose Concentration-Time Profiles (Day 1)

Multiple-Dose Concentration-Time Profiles (Day 7)

Bioavailability (BA)

• The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action

• Can provide an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation compared to a reference material (i.e., solution, suspension, or intravenous dosage form)
Absolute Bioavailability

F = 16.1%
Bioequivalence (BE)

• The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of active when administered at the same molar dose under similar conditions

• The approaches for demonstrating bioequivalence generally follows similar approaches for measuring bioavailability
Bioequivalence

![Graph showing concentration over time for Formulation A and Formulation B.]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Estimate</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>0.974</td>
<td>0.895 to 1.060</td>
</tr>
<tr>
<td>$\text{AUC}_{0-1}$</td>
<td>1.003</td>
<td>0.930 to 1.082</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>1.004</td>
<td>0.932 to 1.083</td>
</tr>
</tbody>
</table>
Food Effect

• Administration of food with oral drug products may influence the BA and/or BE

• Focus on the effects of food on the release of the drug substance from the drug product as well as the absorption of the drug substance

• Usually a single-dose, two-period, two-treatment, two-sequence crossover study comparing a high-fat meal and the fasted state

• High-fat meal = 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively
Food Effect - High Fat Meal

Plasma concentration (ng/mL)

Time post-dose (h)

○ = after a high fat breakfast
● = after an overnight fast
Specific Populations

- Evaluates the impact of an intrinsic factor on the PK of the drug
  - Age (elderly and pediatrics)
  - Gender (male and female subjects)
  - Renal or hepatic impairment
  - Obesity
  - Pregnancy
- Usually a single-dose study
- Recommended to perform study prior to Phase 3
- Supports dose adjustments of the drug in the specific population
Specific Populations - Elderly

![Graph showing plasma concentration over time for healthy elderly and healthy young individuals.](image-url)
Specific Populations - Gender

![Graph showing concentration over time for male and female populations.](image-url)
Specific Populations - Renal Impairment

- >80 mL/min
- 50-80 mL/min
- 30-50 mL/min
- <30 mL/min
- HD (Off dialysis)
- CAPD
Specific Populations - Hepatic Impairment

The graph illustrates the concentration of a substance over time for different hepatic function statuses:

- **Normal Hepatic Function**
- **Mild Hepatic Impairment**
- **Moderate Hepatic Impairment**

The concentration is measured in ng/mL, and the time is measured in hours (h).
Impact of Renal and Hepatic Impairment

![Graph showing the impact of renal and hepatic impairment on intrinsic factor. The graph displays the percentage change in exposure (percentage) for both Cmax and AUC across mild, moderate, and severe levels of renal and hepatic impairment. The x-axis represents the intrinsic factor (renal and hepatic impairment levels), and the y-axis shows the percentage change in exposure. The graph indicates that renal impairment affects Cmax and AUC more significantly than hepatic impairment.]
Drug-Drug Interaction Studies

• Evaluate the pharmacokinetics of both or either drug when two drugs are co-administered
• Supports dose adjustments when a drug interaction occurs (either perpetrator or victim drug)
• Can be single or multiple dose
• Usually performed in healthy male and female subjects
Impact of Ketoconazole
Impact of Rifampin

- Drug X alone
- Drug X + rifampin
Tissue Penetration Studies

• Provide an assessment of drug concentrations at the site of action
• Type of study depends upon drug class/site of action (e.g., penetration into skin blisters, microdialysis, or bronchoalveolar lavage for anti-infectives)
• Can be single-dose or multiple-dose
• May be performed in healthy subjects or patients with the disease of interest
Tissue Penetration

![Graph showing tissue penetration over time with concentrations in mcg/mL and time in hours. The graph compares concentrations in Plasma and Skin blister samples.](image-url)
Thorough QTc Studies

- Determines whether a drug has a threshold pharmacologic effect on cardiac repolarization
- The threshold for regulatory concern is an upper bound of the 95% CI around the mean effect on QTc of 10 ms
- Performed in healthy male and female subjects
- Usually single-dose (for drugs with short half lives and no metabolites)
- Usually a crossover study design (but can be parallel study)
- Should evaluate concentrations higher than those achieved following the anticipated clinical dose
Thorough QTc Study (4-Way Crossover)

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Bioequivalence

- The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of action when administered at the same molar dose under similar conditions
- Links the clinical trial formulation with the to-be-marketed formulation (NDAs)
- Links the innovator formulation with the generic formulation (ANDAs)
How is BE Determined?

• Usually based on pharmacokinetic measures of Cmax and AUC for systemically available drugs

• Test and Reference products are considered bioequivalent when the 90% CI of the geometric mean ratios (T/R) of Cmax and AUC are within 80% to 125%
Bioequivalence Endpoints*

- In vivo test in humans in which the concentration of the active moiety in whole blood, plasma, serum or other appropriate biological fluid is measured as a function of time

*In decreasing order of accuracy, sensitivity, and reproducibility
Bioequivalence Endpoints (cont.)

• In vivo test in humans in which the urinary excretion of the active moiety is measured as a function of time
  – This is not appropriate if urinary excretion is not a significant mechanism of elimination
Bioequivalence Endpoints (cont.)

• In vivo test in humans in which an appropriate acute pharmacological effect of the active moiety is measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility
  – This approach may be applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution
Bioequivalence Endpoints (cont.)

- Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence
When is a Bioequivalence Study Necessary?

• For NDAs:
  – When the to-be-marketed formulation is different than the clinical trial formulation
  – When changes are made to the marketed formulation

• For ANDAs comparing the generic versus the innovator formulation
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• Define the role of DSI to ensure data integrity of BE studies
Role of the Division of Scientific Investigations (DSI)

- Upon request, DSI performs inspections with the Office of Regulatory Affairs (ORA) of the bioanalytical and/or clinical sites to verify the accuracy, quality, and integrity of the data.
- Critical points of inspection of bioanalytical sites:
  - Analytical method validation
  - Acceptance criteria during in-study validation
  - Handling of samples
  - Repeat analysis of samples
  - Equipment logs, SOPs
  - Correspondence logs
  - Confirmation of data included in final study report
Inspections of Bioanalytical Sites

• Confirms that the data supporting a regulatory decision are valid and accurate
Role of the Division of Scientific Investigations (DSI)

• Critical points of inspection of clinical sites:
  – Subject safety
  – Dosing
  – Drug products
  – Blood draw times
  – Sample processing
  – Adverse events
  – Protocol adherence
  – Reserve samples
Subject Safety

- Were the rights, health, and welfare of the subjects protected
  - Was informed consent obtained?
  - Was adequate medical supervision provided?
Dosing

- Who received what?
  - Actual treatment administered
  - Test versus reference
  - Was the randomization scheme adhered to?
- When did they receive it?
  - Actual dosing time
Drug Products

• Accountability
  – Number of tablets administered, returned, remaining

• Lot numbers
  – Verify information provided to FDA

• Control of drug storage area
  – Security, temperature, humidity
Blood Draw Time

- Were samples processed according to the protocol?
  - Temperature, centrifugation, within specified time frame
- Were processed samples (e.g., plasma, serum) stored appropriately?
Adverse Events

• Were all adverse events reported?
Protocol Adherence

• Including/exclusion criteria
  – Were inclusion/exclusion criteria met?

• Were protocol required screening activities conducted?
  – e.g., clinical chemistry, hematology, pregnancy tests, vital signs, ECGs, physical exams, etc.

• Was adherence to protocol restrictions documented at each dosing period?
  – Rx and OTC drugs prior to dosing and throughout study
  – Caffeine/alcohol prior to dosing
Reserve Samples

• Retained samples that are representative of the actual drug products used in the study
  – Reserve samples help the FDA to investigate instances of possible fraud in BE testing

• Reserve samples must be:
  – Randomly selected at the study site
  – Positively identified as having come from the same sample used in the specific BE study
  – Maintained in sufficient quantity to permit FDA to perform 5x all of the release tests required in the application

21 CFR 320.28 “Retention of bioavailability samples” and 21 CFR 320.63 “Retention of bioequivalence samples”
Reserve Samples (cont.)

• Reserve samples must be:
  - Retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or if the application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used.
  - Stored under conditions consistent with product labeling
  - Reserve samples are sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis

21 CFR 320.28 “Retention of bioavailability samples” and 21 CFR 320.63 “Retention of bioequivalence samples”
Questions???
Specific Populations - Renal Impairment
<table>
<thead>
<tr>
<th>Renal impairment [Group]</th>
<th>( \text{AUC}_{0-\infty} )</th>
<th>( \text{Estimate} )</th>
<th>90 % CI</th>
<th>( \text{p-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal [A-D]</td>
<td>36929</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Mild [A]</td>
<td>59455</td>
<td>1.61</td>
<td>(1.33, 1.95)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Moderate [B]</td>
<td>104505</td>
<td>2.83</td>
<td>(2.33, 3.43)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Severe [D]</td>
<td>188409</td>
<td>5.10</td>
<td>(4.20, 6.19)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>End Stage (Pre) [C]</td>
<td>99659</td>
<td>2.70</td>
<td>(2.12, 3.44)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>End Stage (Post) [C]</td>
<td>269541</td>
<td>7.30</td>
<td>(5.73, 9.30)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Tissue Penetration Studies

- Plasma
- Alveolar cells
- Epithelial lining fluid
- Plasma

Graph showing concentrations over time (hours) for plasma and epithelial lining fluid.