Pharmacokinetic/metabolism properties of a NDE/NME screened in all phases of the drug development continuum.

**Pharmacokinetic Analysis**

**Conventional vs. Population Approach**

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>Healthy volunteers or patients</td>
<td>Target patient population, Special population (pediatrics, elderly)</td>
</tr>
<tr>
<td>Size</td>
<td>Small (~12)</td>
<td>Large (30-1000's)</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>Well-controlled</td>
<td>~Clinical practice</td>
</tr>
<tr>
<td>PK Sampling</td>
<td>Dense</td>
<td>Sparse</td>
</tr>
<tr>
<td>Data Collection/Analysis</td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td>Inter-individual Variability</td>
<td>Minimal</td>
<td>Demographics, Disease states, etc.</td>
</tr>
<tr>
<td>PK/PD Relationships</td>
<td>Limited</td>
<td>Extensive</td>
</tr>
</tbody>
</table>

**Descriptive Studies - General PK**

- Small sample size (n = 4–12); generally not powered
- Characterize basic PK parameters (CL, V, F, t 1/2, fu) for parent drug
- Oral and IV (not always feasible) dose
- Single and multiple dose
- Identify major metabolites in blood, urine, feces
- If 14C-labeled drug, determine dose recovery and routes of excretion
- Dose escalation
  - dose proportionality of AUC
  - assess drug tolerability

**In Vivo Intestinal MDZ Metabolism**

- 1 mg IV or 2 mg PO during anhepatic phase of a liver transplant operation (Paine et al., CPT, 1996)

**Arterial MDZ, 1-OH-MDZ, 1-OH-MDZ-Glucuronide Conc-Time Profile**

- IV Dose
- Duodenal Dose
### Special Populations

**Examples:** liver and renal disease, elderly, pediatric, gender, genetic subgroups (e.g., poor metabolizers)

- Generally moderate sample size; powered to detect a minimum difference based on expected population variability
- Characterize basic PK parameters (CL, V, t\(_{1/2}\), F) for parent drug
- Oral dose, unless IV indicated
- Measure active metabolites only
- Urine recovery of parent and known metabolites
- Assess drug tolerability at indicated doses

---

### Population Pharmacokinetics (Pop-PK)

- Characterize PK and PD in target patient population using sparse sampling and pharmaco-statistical methodologies.
- Large number of subjects (> 100, up to thousands)
- Oral dose: define time of dose and blood collection during Phase III or IV trials
- **Fixed Effects:** basic PK parameters (CL, V, t\(_{1/2}\)) for parent drug; obtain true population means and variance
- **Random Effects:** sources of between and within-subject variability (e.g., age, smoking, concomitant drug therapy)
- Apply different statistical methods to analyze data, depending on objectives (Mixed effect ANOVA, NONMEM)

---

### Drug-Drug Interaction Studies

- **Proof of Equivalency:** Design study to prove there is no difference between test and control; i.e., drug X does not alter the PK of drug Y
  - Sample size based on within subject variability
  - Point estimate and confidence interval with specified range; e.g., AUC ratio (test/control) between 0.80 and 1.25
- **Hypothesis Testing:** Test for an expected difference between treatment and control
  - Sample size based on minimum expected difference and population variability, generally smaller than studies to prove no difference
  - T-test or ANOVA
- Oral dose: characterize basic PK (AUC) or PD parameters

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### Data Analysis: FDA Recommended

<table>
<thead>
<tr>
<th>Method of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK and/or PD as a Surrogate</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Acceptance Criteria</th>
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</thead>
<tbody>
<tr>
<td>90% Confidence Intervals</td>
</tr>
<tr>
<td>No Effect Boundaries</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Estimate</td>
</tr>
<tr>
<td>Null Hypothesis (P values)</td>
</tr>
<tr>
<td>Mean, SD</td>
</tr>
<tr>
<td>Clinical Relevance</td>
</tr>
</tbody>
</table>

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### General Considerations for Pharmacokinetic DDI Study

- Will NDE alter exposure to other drugs?
  - Inhibition of DME or transporter
  - Induction of DME or transporter
- Will other drugs alter exposure to NDE?
  - Enzymes responsible for NME metabolism
  - Contribution of metabolism to elimination

---

### Types of DDI Study Designs

**Clinical Pharmacology (Conventional):**
- Probes (e.g. midazolam, desipramine)
  - ± positive comparator
- Inhibitor/inducer (e.g., ketoconazole, quinidine)

**Phase 3 Trials (Population):**
- Confirming
- Screening

**Clinical Practice:**
- Combination therapy (e.g. oncology)
Conventional DDI Study Designs

Parallel design? Randomized crossover for positive comparator design:

Randomized crossover design (+ positive comparator):

Data Analysis:
Confidence Interval Approach

Example: 90% CI with clinical acceptance range b/w 0.5 to 2.0 or 0.8 to 1.25

AUC

CL/F

0.1 0.5 1.0 2.0 5.0

Yuan GJ et al., Clin Pharmacol Ther 61 (2): 147, 1997 (ASCPT 3/97, San Diego, CA)

Dose Adjustment Based on PK/PD

Labeled dose, AUC, or effective concentration (100%)

Safety (Adverse Effect) Curve

Efficacy Curve

Response (PD)

Dose, AUC, or Concentration (PK)

[Exposure]

Narrow Therapeutic Range

Response (PD)

Efficacy Curve

Safety (Adverse Effect) Curve

Dose, AUC, or Concentration (PK)

[Exposure]

Aprepitant - Midazolam (CYP3A)

Interaction Study

- Healthy young males
- Open-label, randomized, single-period design, parallel dose arms
- Two aprepitant doses: 125/80-mg and 40/25-mg regimen, qd x 5 days
- N = 8 subjects/dose group
- Single dose oral midazolam: pre-study, days 1 and 5
- Determine PK: AUC, C_{max} and 1_{1/2}

Sample Size Calculation for a 3A Study

- Given Mean CV C_{max} = 30%, AUC = 22% and a balanced two-period crossover design sample size may be calculated for the probability of correctly concluding no interaction
- Study size based on ratio of test and the requirement that a 90% confidence interval is contained within a range of 0.8 and 1.25

If β = 0.2, power = 0.8, α = 0.05

C_{max} μ_{T}/μ_{R}:

0.85 0.9 0.95 1.0 1.05 1.10 1.15

Sample Size:

292 80 40 32 38 68 156

AUC μ_{T}/μ_{R}:

0.85 0.9 0.95 1.0 1.05 1.10 1.15

Sample Size = 168 46 24 20 24 40 90
Aprepitant - Midazolam (CYP3A) Interaction Study: Conclusions

- Investigators chose a null hypothesis approach; was ratio different from 1.0?
- No evidence of a power calculation to determine sample size
- Concluded that the 125/80 dose schedule inhibited CYP3A activity; classed as a moderate inhibitor (2-5 fold effect)
- Claimed that 40/25-mg dose had no effect, but statistically a weak claim (did not adhere to 0.80-1.25 bioequivalency standard)
- Labeling reflects 125/80-mg results, since that is the recommended dose to prevent nausea during chemotherapy