Society for Clinical Trials 34th Annual Meeting

Workshop P2
Clinical Pharmacology and Pharmacometrics for Statisticians and Clinical Trialists

Sunday, May 19, 2013
8:00 AM - Noon
Berkeley Room
Principles of Pharmacometrics

Kevin Sweeney
• George Box wrote that "essentially, all models are wrong, but some are useful" (in *Empirical Model-Building and Response Surfaces*, Wiley, 1987)

• Essentially, models account for fixed effects (structural components like drug clearance or ED$_{50}$) and random effects (between subject variability, residual variability), but biological systems are very complex
• Simply stated, MBDD is the development and application of models that help inform decision making (Lalonde et. al, CPT, 82, 21–32, 2007)
  – clinical and pre-clinical data
  – all phases of drug development

• Consistent with “learn and confirm” concepts, as originally stated by Sheiner (CPT, 61:275, 1997)
  – the “learn” phase occurs during early drug development (Phase 1 and 2), identifying appropriate therapeutic doses
  – the “confirm” phase occurs in later drug development (Phase 3), demonstrating acceptable safety and efficacy
  – MBDD applicable in this cycle, identifying dose-exposure relationship, effect size and uncertainty, shape of dose-response relationship, rational dose for intended use
MBDD – “Learn/Confirm” Progression

Drug development and model building
Learning and confirming

Continuum of learn/confirm/predict at each decision point

Preclinical  M&S  Phase I  M&S  Phase IIa  M&S  Phase IIb  M&S  Phase III  Registration labeling  M&S  Phase IV

Efficacy
Toxicology
PK-PD

Toleration
Human PK-PD

Efficacy and safety
Dose/exposure-response
Dose adjustments

Therapeutic index
Covariate effects

Results relative to competitors, regional differences, therapeutic index

Uncertainty
Confidence in drug and disease
Many applications of MBDD are focused on modeling efforts with population approaches, to include…

- pharmacokinetic (PK) analysis to identify relevant patient-specific information (covariates) that also describes between subject variability in parameters of interest
- pharmacodynamic (PD) analysis that describes relationship between safety/efficacy endpoints and dose or exposure (PKPD)
- model-based meta analysis (MBMA) of published literature data to help understand relevant effect size, useful for positioning a compound in development into the competitive landscape

Advantageous to perform longitudinal PD analysis over landmark analysis, as all data over study period contributes to better understanding of disease progression and treatment effects
MBDD Schematic

- Trial performance metrics
- Quantitative decision criteria
- Data analysis model
- PK-PD and disease models
- Competitor information and meta-analysis
- Design and trial execution models

Model-based drug development
MBDD – Core Elements

• PKPD and Disease Models
  – describe temporal relationships between dose (exposure) and response

• Meta Analysis of Competitor Data
  – estimation of effect size and uncertainty from published aggregate study level data

• Design and Trial Execution Models
  – implementation of adaptive design models for dosing and drop-out/compliance models

• Data Analysis Models
  – prospectively defined statistical analysis models

• Quantitative Decision Criteria
  – rules applied to distribution of expected treatment effect, i.e., 80% confidence that the true effect > lower confidence value

• Trial Performance Metrics
  – probability of making a “correct” decision, irrespective of decision with a “go” or “no go” result
Model Building

• Let data drive complexity of model
  – PK: one compartment disposition with linear elimination and input, progress to multi-compartment disposition and complex absorption processes as necessary
  – PD: step change, linear and nonlinear drug effect

• Fixed effects (CL, E\text{MAX}, ED_{50}) and random effects (between subject and residual variability)

• At each step, more complex model tested for significant benefit in predictive performance

• Test final model performance with visual predictive check (simulation), bootstrap confidence intervals
Pharmacometrics Applications

• Models used can be quite simplistic as in most population PK applications, trending towards quite complex for systems biology/pharmacology applications
  – Translational model to help understand potential dose limitations in first in human trials
  – Systems model to better understand beta amyloid (Abeta) trafficking between specific body spaces
  – Logistic regression to understand hypoglycemic adverse event dose response
  – Population pharmacokinetics
Translational Modeling of Cmax

Mean Cmax NOAEL = 133 ng/mL
Systems Biology Model of Abeta

CSF (C)

Plasma (P)

Abeta Abeta

k

B

C

kCP

Lymph (L)

APP

kSYN

Abeta

Abeta

Abeta

APP

Neuron

kSYN

kLP

KBP

kPB

BBB

kT

kTP

kBT

kCP

kBC

kCB

kBL

kBDG

Plaque

Brain (B, ISF)

Abeta

Tissue (T)
Logistic Regression Model of Hypoglycemia

Pr(Hypoglycemia) by Dose

- Observed HAE, Pooled Data

37% Exceeds 20% Reference

Glimepiride
Expected

Dose (mg)
• Identify best “base” model, which captures concentration time profile of subjects, and includes relevant between subject and residual variability

• Identify non-collinear patient-specific covariates based on physiology and/or pharmacology, e.g., creatinine clearance on drug clearance, body size on clearance and volume of distribution, dose on absorption rate constant, concomitant medication on clearance to assess DDIs

• Advocate full model approach, all covariates on base model, estimate and bootstrap, clinical significance of covariate from confidence interval assessment

• Diagnostic plots to evaluate each step

• Perform visual predictive check to assess overall model performance, ability to simulate data from which model was built
Population Pharmacokinetics Analysis (2)

0.3 mg/kg

1.0 mg/kg

12 mg/kg

18 mg/kg

3.0 mg/kg

6 mg/kg

Source: 452PredCheck_Conc_byDose_1001.png
Case Study #1:
Estimate Target Performance
Pioglitazone
Background

• Quantify magnitude (uncertainty) and time frame of HbA1c- and FPG-lowering effects of the TZD (thiazolidinediones) class of diabetic agents

• Effect thought to be mediated through activation of the peroxisome proliferator-activated receptor gamma (PPARγ), improving insulin sensitivity

• Aggregate data obtained from placebo-controlled trials, including pioglitazone and rosiglitazone
  – Pioglitazone (Actos): 8 literature sources, 28 active treatment arms with 147 total data points
  – Rosiglitazone (Avandia): 9 literature sources, 25 active treatment arms with 125 total data points
Methods (1)

- Longitudinal modeling of data was implemented to provide information on time-frame of response, $E_{\text{MAX}}$ model characterized magnitude of response
- Data observed to 26 weeks, predictions made to 52 weeks using final longitudinal model
- Model accounted for placebo response over time (disease progression) in addition to drug effect (dose) over time
- Results presented are placebo-adjusted change from baseline values
Methods (2)

• Intrinsic activity assumed to be similar in class, attempts made to tease out potency differences between pioglitazone and rosiglitazone

• Accomplished by estimating pioglitazone ED$_{50}$ with scale factor characterizing the relative potency of rosiglitazone

• Focus of analysis was pioglitazone (target performance), rosiglitazone data added to improve model stability

• Baseline effect estimated, normalized to a HbA1c value of 8% and FPG value of 120 mg/dL
Results (1): HbA1c Effect by Week

Dashed lines represent -0.5% and -1.0% as reference.
Results (2): Temporal Profile of HbA1c

Red line represents expected pioglitazone 30 mg mean (90% CI) HbA1c response

Regimen Max Response = -1%
## Results (3): HbA1c Lowering

<table>
<thead>
<tr>
<th>Weeks</th>
<th>LCB</th>
<th>Mean</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>-0.31</td>
<td>-0.23</td>
<td>-0.16</td>
</tr>
<tr>
<td>8</td>
<td>-0.55</td>
<td>-0.41</td>
<td>-0.30</td>
</tr>
<tr>
<td>12</td>
<td>-0.73</td>
<td>-0.55</td>
<td>-0.41</td>
</tr>
<tr>
<td>16</td>
<td>-0.87</td>
<td>-0.67</td>
<td>-0.50</td>
</tr>
<tr>
<td>26</td>
<td>-1.09</td>
<td>-0.85</td>
<td>-0.65</td>
</tr>
<tr>
<td>52</td>
<td>-1.32</td>
<td>-1.03</td>
<td>-0.79</td>
</tr>
</tbody>
</table>
Results (4): FPG Effect by Week

- Dashed line represents -50 mg/dL as a reference in all panels.
Results (5): Temporal Profile of FPG

Red line represents expected pioglitazone 30 mg mean (90% CI) FPG CFB response.
## Results (6): FPG Lowering

<table>
<thead>
<tr>
<th>Weeks</th>
<th>LCB</th>
<th>Mean</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>-27</td>
<td>-23</td>
<td>-19</td>
</tr>
<tr>
<td>8</td>
<td>-37</td>
<td>-32</td>
<td>-27</td>
</tr>
<tr>
<td>12</td>
<td>-41</td>
<td>-35</td>
<td>-30</td>
</tr>
<tr>
<td>16</td>
<td>-43</td>
<td>-37</td>
<td>-31</td>
</tr>
<tr>
<td>26</td>
<td>-44</td>
<td>-37</td>
<td>-32</td>
</tr>
<tr>
<td>52</td>
<td>-44</td>
<td>-37</td>
<td>-32</td>
</tr>
</tbody>
</table>
Conclusion

• Longitudinal $E_{\text{MAX}}$ model adequately described HbA1c and FPG CFB data
• Rosiglitazone estimated to be ~8-fold more potent than pioglitazone in HbA1c/FPG lowering
• All placebo-corrected, HbA1c and FPG CFB confidence intervals exclude zero, significant lowering effect
• Target profile for TZD-like drug, 1-year
  – HbA1c: -1.03% (-1.32, -0.79)
  – FPG: -37 mg/dL (-44, -32)
Case Study #2
HbA1c Lowering Performance
• Study conducted (12-week) testing mechanism of glucose lowering/HbA1c reduction

• Resultant study data modeled, providing estimates of maximal effect, potency, baseline effect on $E_{\text{MAX}}$ and temporal profile of efficacy endpoints

• Make a statement regarding expectation of mean response, and uncertainty of that response

• Generate probability of attaining marginal difference of endpoint
Methods (1)

\[ Y_{ij} = HbA1c_{Baseline,i} - \left( PBO_i + \frac{E_{MAX} \times Dose}{ED_{50} + Dose} \right) \times \left( \frac{Time}{T_{50} + Time} \right) \times \left( \frac{Time}{24} \right)^{GAM} + \varepsilon_{ij} \]

- Individual longitudinal data, \( E_{MAX} \) model was fitted to the data
- \( Y_{ij} \) = the observed HbA1c at the \( j^{th} \) time in the \( i^{th} \) individual
- \( E_{MAX} \) = the maximal response
- \( ED_{50} \) = the potency, dose required to elicit half of \( E_{MAX} \)
- \( T_{50} \) = time to 50% steady-state profile
- \( GAM \) = durability effect (negative = loss)
- \( \varepsilon_{ij} \) = the residual variability at the \( j^{th} \) time in the \( i^{th} \) individual
Methods (2): Model of HbA1c Time Course

\[ \frac{E_{MAX} \times \text{Dose}}{ED_{50} + \text{Dose}} \]

Magnitude of Effect

\[ \frac{\text{Time}}{\text{Time} + T_{50}} \]

Onset of Effect

\[ \left( \frac{\text{Time}}{24} \right)^{GAM} \]

Loss of Effect

Time (week)
Methods (3)

• Longitudinal $E_{\text{MAX}}$ dose-response model fitted to observed HbA1c data (observed cases, not LOCF)

• Final model point estimates of relevant model parameters and covariance matrix used to simulate 10,000 vectors of parameter space

• Response for relevant doses generated from simulated parameter vectors

• Confidence intervals generated to characterize uncertainty in response and probability of achieving a clinically relevant reduction in HbA1c also calculated
Methods (4)

• 1,000 clinical trials simulated, difference between test drug and lead competitor generated, varied by number of subjects per trial

• For each simulated trial, the 95% CI of the difference between the two treatments was calculated (drug – competitor, negative favors test drug)

• The outcome was classified as:
  – Superior if upper 95% CI < 0 as drug is significantly better than competitor (green)
  – Non-inferior if upper 95% CI < 0.3 (green + blue, anything superior is also non-inferior)
  – Inferior if lower 95% CI > 0 (if significantly worse than competitor but also non-inferior is not classified as inferior) (red)
  – Inconclusive is none of the above (orange)
## Results (1): 12-Week Performance

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Predicted Mean Response (%)</th>
<th>80% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.49</td>
<td>-0.65, -0.31</td>
</tr>
<tr>
<td>5</td>
<td>-0.64</td>
<td>-0.78, -0.50</td>
</tr>
<tr>
<td>10</td>
<td>-0.67</td>
<td>-0.81, -0.53</td>
</tr>
<tr>
<td>25</td>
<td>-0.70</td>
<td>-0.84, -0.55</td>
</tr>
</tbody>
</table>

- Longitudinal $E_{\text{MAX}}$ dose-response model results used to generate dose-specific mean HbA1c reduction with uncertainty expressed as an 80% CI
- Assumes baseline HbA1c of 8% (study entry inclusion criteria)
### Results (2): 12-Week Pr(Target)

<table>
<thead>
<tr>
<th>Baseline HbA1c</th>
<th>Dose</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5mg</td>
<td>10mg</td>
<td>25mg</td>
</tr>
<tr>
<td>7.75%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr (≤ -0.6%)</td>
<td>0.433</td>
<td>0.557</td>
<td>0.630</td>
</tr>
<tr>
<td>Pr (≤ -0.7%)</td>
<td>0.133</td>
<td>0.203</td>
<td>0.271</td>
</tr>
<tr>
<td>8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr (≤ -0.6%)</td>
<td>0.648</td>
<td>0.753</td>
<td>0.807</td>
</tr>
<tr>
<td>Pr (≤ -0.7%)</td>
<td>0.291</td>
<td>0.406</td>
<td>0.489</td>
</tr>
</tbody>
</table>

- Probability of achieving a clinically relevant HbA1c reduction of 0.6% or 0.7%, conditional on baseline HbA1c level.
### Results (3): 24-Week Performance

A longitudinal \( E_{\text{MAX}} \) dose-response model was used to predict dose-specific mean HbA1c reduction with uncertainty expressed as an 80% CI. Assumptions include a baseline HbA1c level of 8% (study entry inclusion criteria).

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Predicted Mean Response (%)</th>
<th>80% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.60</td>
<td>-0.80, -0.38</td>
</tr>
<tr>
<td>5</td>
<td>-0.78</td>
<td>-0.96, -0.61</td>
</tr>
<tr>
<td>10</td>
<td>-0.82</td>
<td>-1.00, -0.65</td>
</tr>
<tr>
<td>25</td>
<td>-0.85</td>
<td>-1.03, -0.67</td>
</tr>
</tbody>
</table>
### Results (4): 24-Week Pr(Target)

<table>
<thead>
<tr>
<th>Baseline HbA1c</th>
<th>Dose</th>
<th>5mg</th>
<th>10mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr (≤ -0.6%)</td>
<td></td>
<td>0.815</td>
<td>0.879</td>
<td>0.6906</td>
</tr>
<tr>
<td>Pr (≤ -0.7%)</td>
<td></td>
<td>0.540</td>
<td>0.649</td>
<td>0.713</td>
</tr>
<tr>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr (≤ -0.6%)</td>
<td></td>
<td>0.907</td>
<td>0.948</td>
<td>0.961</td>
</tr>
<tr>
<td>Pr (≤ -0.7%)</td>
<td></td>
<td>0.727</td>
<td>0.813</td>
<td>0.853</td>
</tr>
</tbody>
</table>

- Probability of achieving a clinically relevant HbA1c reduction of 0.6% or 0.7%, conditional on baseline HbA1c level.
Results (5): Trial Decision Criteria

- Superior
- Non-Inferior
- Inconclusive
- Inferior

-0.3% 0.3%
Results (6): Comparison, Sample Size

10 mg vs. Lead Competitor

5 mg vs. Lead Competitor

Outcome
superior
non inferior
inconclusive
inferior

Sample size/arm

Probability of outcome
Conclusions

- Longitudinal $E_{\text{MAX}}$ model adequately described individual %CFB HbA1c
- The 5, 10 and 25 mg doses appear to be similar with respect to HbA1c lowering effect at 12 weeks
- Probability of achieving at least a 0.6% placebo-adjusted CFB reduction in HbA1c at 24 weeks (registration trial length) appears to be $>90\%$ for the 5, 10 and 25 mg doses, with a baseline HbA1c of 8%
- If a head-to-head trial were run, with at least 80% probability of showing non-inferiority, need $\sim 200$ subjects (100/arm) at 5 or 10 mg
PHARMACOKINETICS

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Tufts University School of Medicine
and
Tufts Medical Center
Boston MA

dj.greenblatt@tufts.edu
<table>
<thead>
<tr>
<th>Subject</th>
<th>Independent variable</th>
<th>Dependent variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Time</td>
<td>Concentration</td>
</tr>
<tr>
<td>Pharmadynamics</td>
<td>Time</td>
<td>Effect</td>
</tr>
<tr>
<td>Kinetic-dynamic modeling</td>
<td>Concentration</td>
<td>Effect</td>
</tr>
<tr>
<td>Concentration</td>
<td>Result</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>Too low</td>
<td>Lack of efficacy</td>
<td></td>
</tr>
<tr>
<td>Correct</td>
<td>Desired therapeutic effect</td>
<td></td>
</tr>
<tr>
<td>Too high</td>
<td>Toxicity</td>
<td></td>
</tr>
</tbody>
</table>
CORE CONCEPTS

• Volume of distribution
• Elimination half-life
• Clearance
CONCENTRATION = \frac{AMOUNT}{VOLUME}
\[ V_d = \frac{X}{C} \]
VOLUME OF DISTRIBUTION

- Is imaginary
- Does not tell you where the drug is
- Is not the sum of anatomic volumes of sites of uptake
- Quantitatively reflects peripheral tissue uptake
- Is related to lipid solubility
I.V. dose = 2 mg

Concentration = 14.3 ng/ml

\( V_d = 140 \text{ Liters} \)

\[
= 2.0 \text{ Liters/kg (in a 70-kg person)}
\]
# LINEAR vs. LOGARITHMIC CONCENTRATION SCALE

<table>
<thead>
<tr>
<th></th>
<th>Linear</th>
<th>Logarithmic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual image</td>
<td>Correct</td>
<td>Distorted</td>
</tr>
<tr>
<td>Graphically-based</td>
<td>Dangerous</td>
<td>Possible</td>
</tr>
<tr>
<td>calculations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
YOU CAN’T DRAW PICTURES
OF CLEARANCE
CLEARANCE

- Independent variable best describing the capacity for drug removal

- Most have units of volume/time

- Usually accomplished by a clearing organ

- Upper limit: blood flow to clearing organ
Physician

Compliance

Dosing rate \( = C_{ss} \) response

Clearance

Physiology
COMPLIANCE

- Acting in accordance with another’s command, demand, request, rule, or wish
- Acquiescence
- Disposition or tendency to yield to others

ADHERENCE

- Faithful attachment, devotion
- Close following
- Carrying out without deviation
LOW AUC, LOW SYSTEMIC EXPOSURE, HIGH CLEARANCE

HIGH AUC, HIGH SYSTEMIC EXPOSURE, LOW CLEARANCE

LOW AUC, LOW SYSTEMIC EXPOSURE, HIGH CLEARANCE
Excretion of unchanged drug

Renal clearance

Hepatic clearance

Metabolites
21

HOURS AFTER DOSE

PLASMA CONCENTRATION

Cmax

ORAL DOSE

LAG TIME

Tmax

HOURS AFTER DOSE
QUANTITATIVE MEASURES

$C_{\text{max}}$ : Peak plasma concentration

$T_{\text{max}}$ : Time of peak concentration

$\text{AUC}$ : Area under the plasma concentration curve (systemic exposure)
<table>
<thead>
<tr>
<th>Rate of absorption</th>
<th>$C_{\text{max}}$</th>
<th>$T_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid</td>
<td>High</td>
<td>Short</td>
</tr>
<tr>
<td>Slow</td>
<td>Low</td>
<td>Long</td>
</tr>
</tbody>
</table>
SYSTEMIC AVAILABILITY (ABSOLUTE BIOAVAILABILITY)

\[ F = \frac{AUC_{PO}}{AUC_{IV}} \]

(AUC values must be total, not truncated)
<table>
<thead>
<tr>
<th>Drug</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.80</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>0.70</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>0.50</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.45</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.30</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>0.02</td>
</tr>
</tbody>
</table>
RELATIVE ORAL BIOAVAILABILITY

Relative $F = \frac{AUC_{\text{test product}}}{AUC_{\text{reference product}}}$
BIOEQUIVALENCE OF GENERIC DRUGS

Fundamental premise:

Bioequivalence

Implies

Therapeutic equivalence
GENERIC SUBSTITUTION

• Is part of the landscape

• Cannot be blamed for clinical changes without plasma level documentation
DOSE = D, INTERVAL = T_{1/2}

PLASMA CONCENTRATION

MULTIPLES OF HALF-LIFE
INTERDOSE FLUCTUATION

“Up and down” variation in plasma level, determined by how the total daily dose is divided into discrete doses.
Physician

Compliance

Dosing rate \over \text{Clearance} = C_{ss} \rightarrow \text{response}

Physiology
<table>
<thead>
<tr>
<th>Doses Per day</th>
<th>% compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>77%</td>
</tr>
<tr>
<td>4</td>
<td>39%</td>
</tr>
</tbody>
</table>

JAMA 1989; 261: 3273
“Slow-release” preparations blunt the peaks, allowing less frequent dosage.
IR oxycodone, 5 mg q 6 hr

OxyContin, 10 mg q 12 hr
Physician

Compliance

\[ \frac{\text{Dosing rate}}{\text{Clearance}} = C_{ss} \rightarrow \text{response} \]

Physiology
AGE
GENDER
DIET
SMOKING
ALCOHOL
ENVIRONMENT
OTHER DRUGS
ILLNESS
HEREDITY
UNKNOWN

CLEARANCE
\[ C_{\text{max}} \text{ (ng/mL)} \]

**PERCENT**

30 60 90 120 150 180 210 240 270 300 330

\[ \text{Log Normal} \]

\[ \text{Normal} \]

\[ * = \text{geometric mean} \]

\[-SD \quad \bar{x} \quad +SD\]
DRUG ACCUMULATION

• Not the same as $C_{ss}$ or $\overline{C}_{ss}$

• A *relative* term: exposure at steady-state compared to first dose

• Depends on the relation between dose interval ($T$) and $t_{1/2}$
If $T >> t_{1/2}$, not much accumulation.

If $T << t_{1/2}$, a lot of accumulation.
GIVEN THE PREVALENCE OF POLYPHARMACY, CLINICALLY IMPORTANT DRUG INTERACTIONS ARE UNUSUAL
• Require increased vigilance or monitoring
• Require dose adjustment
• Require avoidance of a drug
• Are hazardous or life-threatening
Drug-Drug Interactions and Pharmacogenomic Variation as Sources of Clinical Pharmacologic Variability: Principles and Evaluation in Drug Development

Karthik Venkatakrishnan, Ph.D
Evaluating Clinical Pharmacologic Variability in Drug Discovery, Development, Regulation and Utilization

1. Identify sources of variability
2. Quantify (estimate) effect
3. Assess clinical significance
4. Guide risk management and prescribing

Huang SM and Lesko LJ. Journal of Clinical Pharmacology. 44: 559-569, 2004
Drug-Drug Interactions

• A clinically significant drug-drug interaction (DDI) occurs when the therapeutic or toxic effects of a medication are altered by administration with another drug.

• Mechanistic Classification
  – Pharmacokinetic Interactions
    • Drug X alters the absorption (A), distribution (D), metabolism (M) or elimination (E) of Drug Y resulting in altered blood/target organ levels leading to potential effects on efficacy and/or safety
  – Pharmacodynamic Interactions
    • Drug X alters the pharmacologic effect (efficacy and/or safety) of Drug Y without affecting its pharmacokinetics
Pharmacogenomic Variation

- Genetic polymorphisms can alter the activity and/or expression of molecular determinants of pharmacology (PK or PD), thereby influencing the therapeutic and/or toxic effects of a medication

- Examples of Molecular Mechanisms
  - Single Nucleotide Polymorphisms
    - Coding Regions (Synonymous vs. Non-synonymous)
    - Noncoding regions (e.g., Promoter/Enhancer; Intronic)
  - Insertions and Deletions
  - Copy Number Variation (CNV)

- Categories of Pharmacogenomic Variation
  - ADME Pharmacogenomics
    - Germline genomic variation -- drug metabolizing enzymes/transporters
  - Target Pharmacogenomics
    - Germline variation -- drug targets/pathways relevant to efficacy or safety
    - Somatic variation in cancer genome (Oncology)
    - Genetic variation in microbial genome (Infectious diseases)
Clinically Important Drug Metabolizing Cytochromes P450
Selected examples of Clinically Significant Substrates, Inhibitors and Inducers of CYP3A

CYP3A Inhibitors
- Ketoconazole
- Itraconazole
- Voriconazole
- Posaconazole
- Ritonavir*
- Clarithromycin*
- Verapamil*
- Diltiazem*
- Erythromycin*
- Fluconazole
- Grapefruit Juice*†

CYP1A2
- CYP2B6
- CYP2C8
- CYP2C9
- CYP2C19
- CYP2D6

CYP3A Substrates
- Midazolam, Alprazolam, Pimozide, Quetiapine, Nifedipine, Simvastatin, Atorvastatin, Cyclosporine A, Tacrolimus, Sirolimus, Sildenafil, Everolimus, Vincristine, Docetaxel (~50% of clinically used small molecule drugs are metabolized by CYP3A)

CYP3A Inducers
+ PXR/ CAR activators
- Rifampin
- Carbamazepine
- Phenytoin
- Phenobarbital
- St. John’s Wort

*Mechanism-based inactivator (time-dependent inhibitor)
†Intestine-selective CYP3A inhibitor
Examples of CYP3A Inhibition DDI

Effect of Ketoconazole on Triazolam vs. Alprazolam PK

**Triazolam**

- $C_{max}$: 2.1-fold $\uparrow$
- AUC: 14-fold $\uparrow$
- $t_{1/2}$: 6-fold $\uparrow$

**Alprazolam**

- $C_{max}$: 1.1-fold $\uparrow$
- AUC: 4-fold $\uparrow$
- $t_{1/2}$: 4-fold $\uparrow$

*Greenblatt DJ et al., Clin Pharmacol Ther. 64: 237-47, 1998*
Examples of CYP3A Induction DDI

Midazolam – Rifampin Interaction

Cyclosporine A – St. John’s Wort Interaction

Effect on Dose requirement

Kharasch ED et al., Clin Pharmacol Ther 76:452-66, 2004
CYP2D6 Genetic Polymorphisms

• CYP2D6 is one of the best characterized drug-metabolizing enzymes with clinically important genetic polymorphisms

• Multiple alleles result in a spectrum of activity depending on the specific diplotype in an individual
  – Extensive metabolizers (EM) – “normal” activity (AS 1-2)
  – Intermediate metabolizers (PM) – reduced activity (AS 0.5)
  – Poor metabolizers (PM) – virtually absent activity (AS 0)
  – Ultrarapid metabolizers (URM) – increased activity (AS > 2)

• CYP2D6 allele frequencies differ between racial/ethnic groups resulting in corresponding differences in PM/URM frequencies.
  – PM: 6-10% of Caucasians, 2% of Asians, ~10% of African Americans
  – URM: 1-10% in Caucasians, substantially higher (16-28%) in North African/Middle Eastern populations.
Examples of Clinical Implications of CYP2D6 Pharmacogenetics

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype

• **Codeine**
  - Bioactivated to morphine via CYP2D6 mediated metabolism
  - URMs at increased risk for morphine toxicity; PMs at risk for inadequate analgesia.
  - CPIC guidelines recommend avoiding codeine use in URMs and PMs

• **Pimozide**
  - CYP2D6-mediated metabolism is a major contributor to overall clearance
    • Population PK model-based oral clearance: 55 L/hr in EM and 15 L/hr in PM
  - Pimozide produces concentration-dependent QT prolongation.
  - USPI revised to require CYP2D6 genotyping at doses > 4 mg/d
  - Maximum dose of 4 mg is specified for PMs (vs. 10 mg for IM/EM patients)

*Crews KR et al., Clinical Pharmacology and Therapeutics. 91: 321-6, 2012.*
Drug Transporters

Emerging Molecular Determinants of Drug-Drug Interactions

Zamek-Gliszczynski et al., Clin Pharmacol Ther. 92: 553-556, 2012
Transporter DDI and Pharmacogenomics: OATP1B1 as an Illustrative Example

Pravastatin-Cyclosporine DDI

10 mg pravastatin in patients on CsA-based immunosuppression

10 mg pravastatin in patients with Familial Hypercholesterolemia

10-fold ↑ in AUC
t$_{1/2}$ unchanged

Effect of c.521T>C SNP on simvastatin Acid PK

CC vs. TT: 3.2-fold ↑ in AUC

OATP1B1 c.521T>C SNP and Statin Myopathy
Illustration of Genomewide Association Approach

In strong linkage disequilibrium
With rs4149056 (c.521T>C)

- 80 mg/d simvastatin
- 85 cases with myopathy
- 90 controls

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<tr>
<th>TT/CT/CC</th>
<th>C Allele Frequency</th>
<th>Odds Ratio (95% CI) per C Allele</th>
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<tr>
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<td>No. of cases</td>
<td>No. of controls</td>
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<td>TT/CT/CC</td>
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N=85 N=90

Assessment of Drug-Drug Interactions in Drug Development
Drugs Withdrawn from the U.S. Market due to DDIs (1998-2003)

*Impact on Contemporary Drug Development*

- **Mibefradil**
  - Mechanism-based CYP3A inhibitor and P-gp inhibitor
  - 26 drugs spanning several therapeutic areas contraindicated
  - Withdrawn within a year of approval

- **Terfenadine, Astemizole, Cisapride**
  - Sensitive CYP3A Substrates and HERG inhibitors

- **Cerivastatin**
  - Rhabdomyolysis and fatal drug interactions with gemfibrozil

→ Increased focus on DDI risk assessment in drug discovery and development
→ Experimental *in vitro* models of DDIs to guide clinical risk assessment
→ Mathematical models of *in vitro* to clinical predictions of DDI magnitude
→ Comprehensive regulatory guidances (US and EU) and scientifically guided translation of DDI information into prescribing guidance
→ Strong commitment (academia, industry, regulators) to continually update current opinion based on emerging science

Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Shu-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2012
Clinical Pharmacology

Guideline on the investigation of drug interactions

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Guideline Document Information:
- EMA Guideline (2012)
- Guidance for Industry
- Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations
- DRAFT GUIDANCE
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Guideline on the investigation of drug interactions:
- 21 June 2012
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- Committee for Human Medicinal Products (CHMF)

Guideline Document Details:
- Draft Guidance
- Final
- June 2012
- CPMF/RWP/560/95/Rev. 1 Corr
- Committee for Human Medicinal Products (CHMF)

Guideline Document Keywords:
- Interaction, guideline, metabolism, inhibition, induction, transport, enzyme, transport proteins, transporter, absorption, food, distribution, PK/PD, herbal, SMPC

References:
CYP Inhibition DDI Risk Assessment: Case Study

Effects of terbinafine on CYP2D6 and CYP3A4/5 activities in human liver microsomes

- Terbinafine vs. CYP2D6: \([I]/[K_i] >> 1\)
  - Interaction Likely
  - In a clinical DDI study, terbinafine increased AUC of the CYP2D6 substrate desipramine by ~ 5-fold

- Terbinafine vs. CYP3A: \([I]/[K_i] < 0.1\):
  - Remote possibility of interaction
  - In a clinical DDI study, terbinafine did not affect the AUC of the CYP3A substrate midazolam

**CYP2D6**
- IC\(_{50}\) 0.041 \(\mu\)M

**CYP3A**
- IC\(_{50}\) >300 \(\mu\)M

*In vitro data from J Pharmacol Exp Ther. 316:336–348, 2006*
Translation to Therapeutics – Scenario 1

Patient on a stable dose of Metoprolol for hypertension, requiring systemic antifungal therapy for onychomycosis.

Metoprolol clearance is primarily via metabolism by CYP2D6

↑ metoprolol exposure can result in bradycardia and decreased cardioselectivity of β-blockade

Terbinafine is a CYP2D6 inhibitor

Itraconazole is not a CYP2D6 inhibitor

Consider Itraconazole instead of Terbinafine
Consider Terbinafine instead of Itraconazole

Patient on a stable dose of Simvastatin for dyslipidemia, requiring systemic antifungal therapy for onychomycosis.

Simvastatin clearance is primarily via metabolism by CYP3A4

Terbinafine is not a CYP3A4 inhibitor

Itraconazole is a strong CYP3A4 inhibitor

↑ simvastatin exposure can result in ↑ risk of rhabdomyolysis

→
Recent Scientific Advances in the Quantitative Predictions of Clinical DDIs from In Vitro Data

- Example of application to Cabazitaxel
  - Produced CYP3A inhibition \textit{in vitro}
  - \( \frac{C_{\text{max}}}{K_i} > 0.1 \) -- DDI risk with CYP3A substrates could not be dismissed as unlikely
  - PB-PK model-based simulations predicted <1.1-fold increase in midazolam exposure
  - Model-based predictions concluded lack of clinically relevant CYP3A inhibition to support labeling without need for a clinical DDI study

\textit{Fahmi et al., Drug Metab Dispos., 37(8):1658-66, 2009}
\textit{Zhao et al., Clin Pharmacol Ther 89:259-6, 2011}
Study Design and Data Analysis Considerations

- Ensure adequate number of subjects to estimate DDI magnitude or genotype effect (e.g., AUC ratio) with adequate precision.
- Inference based on interpretation of 90% confidence intervals of DDI magnitude rather than p-values.

<table>
<thead>
<tr>
<th>Study</th>
<th>(\text{AUC}_I/\text{AUC}_C) Geometric Mean Ratio (90% CI)</th>
<th>p-value</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>A</td>
<td>0.91 (0.85, 0.98)</td>
<td>&lt;0.05</td>
<td>Not clinically significant</td>
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<tr>
<td>B</td>
<td>1.15 (0.60, 2.2)</td>
<td>&gt;0.1, NS</td>
<td>Inconclusive</td>
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</table>

- Considerations in design of PG-PK association studies
  - Frequency of genotypes of interest (e.g., EM vs. PM sub-populations)
  - Expected effect size (e.g., from \textit{in vitro} drug metabolism data)
  - Prospective genotyped cohorts vs. Retrospective Analysis
  - Integration of genotype as a covariate in population PK analyses
  - Informative PK sampling schemes
Determinants of Clinical Significance of a Drug-Drug Interaction

1. Interaction Magnitude
2. Therapeutic Index of Object/ Victim Drug

Scenario 1
- Interactions Not Clinically Significant
- Toxic
- Not effective

Scenario 2
- Clinically Significant Interactions
- Toxic
- Not effective

Adapted from Greenblatt DJ and Shader RI, Pharmacokinetics in Clinical Practice, 1985
Scenarios/ Examples Illustrating Applications of Concepts in Drug Development Settings
Scenario 1: PB-PK Model-Based Risk Assessment
Investigational Agent Entering First-In-Human Clinical Development in a Patient Population Likely to be on Multiple Concomitant Medications

In Vitro Metabolic Phenotype

Venkatakrishnan K et al., Clinical Pharmacokinetics 49(11): 703-727, 2010
Scenario 1: DDI Risk Management in Clinical Development

Investigational Agent Entering First-In-Human Clinical Development in a Patient Population Likely to be on Multiple Concomitant Medications

- Excluded concomitant medications in FIH trial
  - Strong and moderate inhibitors and inducers of CYP3A
  - Strong inhibitors and inducers (e.g., heavy smoking) of CYP1A2

- Simulations support lack of need for excluding CYP2D6 PMs

- DDI simulations and risk assessment to be updated using observed clinical PK in FIH study
  - Will guide ketoconazole DDI study design (e.g., NME dose selection) based on
    - Projected magnitude of DDI and associated inter-subject variability
    - Clinical safety profile and Therapeutic Index in Phase 1
**Scenario 2: Integrating DDI Results with PK/Safety Relationships**

*CYP3A Substrate NME with potential for dose-related QTc prolongation*

- PK/QTc model-predicted $\Delta$QTcF at $T_{\text{max}}$ at the highest Phase 2/3 dose – 0.8 ms (95% CI: 0.4 - 1.2)
- Ketoconazole DDI study showed ~2-fold increase in NME exposure
- PK/QTc model-predicted $\Delta$QTcF at $T_{\text{max}}$ at the highest Phase 2/3 dose under strong CYP3A inhibition – < 2 msec – << 5 ms ICH E14 threshold
- Enabled conclusion that clinically significant QT prolongation is unlikely over the proposed Ph 2/3 dose range even in the context of a DDI with a strong CYP3A inhibitor
Translating Clinical DDI Results to Prescribing Guidance

Illustration with Everolimus (Afinitor®)

Sensitive CYP3A4 substrate
Recommended Dosage in multiple oncology indications* = 10 mg QD
* Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC

- Avoid strong CYP3A4 inhibitors.
- Use caution with moderate CYP3A4 inhibitors, reduce dose to 2.5 mg.
- A dose increase to 5 mg may be considered, depending on tolerance.
- Avoid strong CYP3A4 inducers.
- If required, consider dose increase in 5 mg increments to a maximum of 20 mg

Kovarik JM et al., Biopharmaceutics and Drug Disposition 27: 421-6, 2006
Afinitor® United States Prescribing Information (Revised 08/2012)
Integrated Approach to DDI and PGx in Drug Development

Other sources of PK or PD variability

Pharmacogenetic Variability
DME’s, transporters, PD targets

Pharmacokinetic DDI
Inhibition/induction of CYPs, transporters, etc.

RESPONSE

DOSE

EXPOSURE

Target Proteins

Clearance Mechanisms

ADME Proteins

INFORM LABELING

Assess clinical significance via PK/PD integration (E-R for efficacy and safety)

Extend mechanism-based inference of DDI risk to other drugs

In vitro metabolism studies
In vitro DDI risk assessment
Human ADME study
Clinical DDI studies
PG-PK Association
Population PK

IDENTIFY MOLECULAR DETERMINANTS
RATIONALIZE CLINICAL STRATEGY
ELIMINATE UNNECESSARY STUDIES
INFORM STUDY DESIGN

Venkatakrishnan K. In Encyclopedia of Drug Metabolism and Drug Interactions, 2012.