Regulatory Population Pharmacokinetics / Pharmacodynamics
Workflow - The Pharsight Approach

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Outline of Talk

Why do POP PK/PD?

Regulatory Population PK-PD Modeling & Simulation Workflow

- Dataset construction including QC and QA activities
- Model Build-Up and Discrimination for Regulatory Population PK/PD Analysis
- Covariate Analysis
- Model Validation (Bootstrap, Predictive Checks, Case-Deletion Diagnostics...)
- Population PK Report & ICHE3 Clinical Study Report
  - Compliant with Population PK Guidances (FDA and EMEA)
  - Quality Controlled and Quality Assured
Population PK/PD Modeling: What is it?

Characterization of the distribution of probable PK/PD outcomes (parameters, concentrations, responses, ...) in a population of interest.

- **Modeling fixed effects**: Discovering & describing predictive relationships between potential explanatory variables (covariates) and PK/PD outcomes.
  - The usual independent variables: time, dose, etc.
  - Effects of patient demographics, concomitant meds, disease, etc.
- **Modeling random effects**: Quantifying unexplained variation in PK/PD outcomes.
How is this different from what I’ve been doing all along?

Maybe it isn’t, or

Maybe it represents a significant change in perspective!

- Explicit consideration of inferences about an entire population of interest rather than just summarizing the results from a small collection of individuals that participated in a study.
- Unit of interest changes from the individual in a study to the population that may receive the drug.
- Notion of PK/PD parameters changes from a single value to a probability distribution that varies as a function of explanatory variables.
Population PK/PD Modeling in Drug Development: When can I use it?

Permits analysis of a wide range of data including sparsely sampled observational data:

- Conventional PK studies with densely sampled data.
- Observational data from clinical efficacy/safety trials in patients.
- Sparsely sampled preclinical PK & TK studies.

Analysis of data pooled from multiple studies of different types; that is, a meta-analysis:

- Combine sparsely-sampled patient studies with densely-sampled data from healthy volunteers.
- Combine data from multiple species to develop models for interspecies scaling.
Role of Population PK/PD Modeling in Drug Development: Why do it?

Characterization of PK/PD in the patient population of interest.

- Identify influential covariates that may warrant some action, e.g., labeling, dose adjustment, contraindication, design of future trials.
  - Patient characteristics
  - Disease effects, e.g., renal or hepatic dysfunction
  - Drug-drug interactions
- Quantify unexplained variation.
  - Relevant to assessing safety risks (e.g., at a specific dose what fraction of patients might reach concentrations associated with a high incidence of adverse events?) and determining whether dose individualization is desirable or unnecessary.
Role of Population PK/PD Modeling in Drug Development: Why do it?

Provide information to optimally treat the individual patient (necessary for drug label) in the patient population

- Design of initial dosage regimens that will ensure that most of the patients will receive a safe and efficacious treatment.
- Use of patient covariates to individualize the initial dosage regimens and increase chance of successful treatment
- Adjust dosage regimens using Bayesian feedback approaches if unexplained variability is large and therapeutic window small
Role of Population PK/PD Modeling in Drug Development: Why do it?

Applications that require a population model with good predictive performance:

- **Drug development**
  - Simulations to optimize clinical trial designs and dosage recommendations.
    - Understand probability distribution of treatment responses in the patient population conditional on treatment strategies, and drug, patient and disease characteristics
    - Understand probability distribution of trial results conditional on trial design and drug characteristics

- **Patient care**
  - Population models are used as informative priors in Bayesian dose adjustment methods (also relevant to concentration-controlled clinical trials and other adaptive trial designs).
Role of Population PK/PD Modeling in Drug Development: Why do it?

Regulatory applications

- Population PK in some form is a de facto requirement
- Population analysis of patient data may be used in lieu of some types of PK trials, e.g., renal impairment or drug-drug interaction studies
- Global Regulatory authorities are becoming increasingly knowledgeable about population analysis.
Regulatory Guidances

- FDA Guidance for Industry: Population Pharmacokinetics, 1999
  [http://www.fda.gov/cder/guidance/5341fnl.htm](http://www.fda.gov/cder/guidance/5341fnl.htm)
- EMEA Guideline: Reporting the Results of a Population Pharmacokinetic Analyses, 2008

Many other Guidances mention use of Population Pharmacokinetics
Typical Population Pharmacokinetics Workflow

Dataset construction

Analytic Report

Clinical Deviations

QA

Locked SAS Dataset(s) (CDISC)

dm.sas7bdat
cm.sas7bdat
ra.sas7bdat
ex.sas7bdat
ex.sas7bdat

Sponsor Data

Pharsight

Sponsor

Work Plan

Protocol

Clinical Study Reports

Analytic Lab

Clinic

Analytic Report

Clinical Deviations

QA

Protocol

Analysis

1. NCA
   - Preclinical
   - Phase I
   - Phase II

2. IVIVC Formulation

3. Regulatory Pop PK, PD Analysis

Reporting

1. Writing
   - Scientific
   - Pharmacological
   - Medical

2. Quality Assurance

3. Formatting

Pharsight
Workflow: Population PK Analysis Part I (Dataset)

1. SAS Dataset(s) from Locked Clinical Database
2. NONMEM Dataset Construction
3. QC
   - Double-Coding
   - Construction/Deconstruction
4. QA
5. NONMEM Dataset Ready for Pop PK/PD Analysis

Locked Clinical Database
Ready for Pop PK/PD
NONMEM Dataset
Analysis
QA Construction/Deconstruction Double-Coding QC
Different Steps to Generate an Analysis Ready Dataset

Understand the design

Read and understand the timeline of the protocol

Schedule of Visits
Schedule of Doses
Schedule of PK/PD observations

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatments / Observations</th>
<th>Time / Event</th>
<th>Active Phase (12Wk)</th>
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<tr>
<td>Active</td>
<td></td>
<td></td>
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<tr>
<td>Phase</td>
<td></td>
<td>Week 1</td>
<td>1</td>
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<tr>
<td>Dose Level 1</td>
<td>Drug, 300 mg over 0.5 Hours</td>
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</tr>
<tr>
<td>Dose Level 2</td>
<td>Drug, 600 mg over 0.5 Hours</td>
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<tr>
<td>Observations</td>
<td>Cp</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
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</tbody>
</table>

Administration data

PK observations data

Randomization data

Demographic and lab data (time independent)

Demographic and lab data (time dependent)

These files are merged to create an analysis dataset

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QC/QA of the Analysis Dataset

SAS Dataset(s) from Locked Clinical Database

Locked Dataset Ready for Pop PK Analysis

<table>
<thead>
<tr>
<th>Pharsight Scientist 1</th>
<th>Pharsight Scientist 2</th>
<th>Quality Control (Comparison)</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Construction of Dataset 1</td>
<td>Deconstruction of Dataset 1</td>
<td>• Comparison of deconstructed Dataset with source SAS files</td>
<td>Verification of Quality Control, Comparison and Reconciliation</td>
</tr>
<tr>
<td>Construction of Dataset 2</td>
<td></td>
<td>• Comparison of the two datasets and reconciliation</td>
<td></td>
</tr>
</tbody>
</table>

Authenticator Print and sign scripts verify ...

Reviewer Comments

QC

QA Comments

QA

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Workflow: PK/PD Modeling Part II (Analysis & Reporting)

Stage I: Dataset
- FINAL QC’ed PK/PD Dataset

Stage II: Analysis
- NLME Engine e.g.: Phoenix NLME, NONMEM
- Grid to enhance time of analysis
- Advanced scripting to ensure reproducibility
- Tables, Figures & Listings (Appendix and In-Text)

Stage III: Reporting
- ICHE3 Report
- Highly customized scripted graphics
- WinNonlin Table Wizard Autopilot

Stage IV: Finalize
- QC Report
- Sr. Review (Approval)
- QA

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Regulatory and Timely POP PK/PD
Pharsight Tools and Facilities to ensure quality and speed

100% QC on all aspects of modeling
Data, models and reporting

Multi-disciplinary Team
Registered RQAP-GLP
Advanced scripted graphics
Advanced dataset assembly (S-Plus)
WinNonlin Table Wizard and Autopilot
Computing Facility (Grid)

Timely analysis and reliable reporting ✓

Stage V: Archive and Share
Pharsight Knowledgebase Server
Model and data storage
Secure Warehouse and convenient sharing with Regulatory agencies ✓
What Tools Do We Use for Population Modeling?

• Traditionally, NONMEM and S-Plus, and on occasion WinBugs

• Pharsight will release a new state-of-the-art population pk/pd modeling product, names Phoenix NLME later this year. It has many advantages over conventional products. This will become our product of choice for population pk/pd modeling due to it’s speed and accuracy, and ease of reporting results. However, if clients prefer a different product be used for a particular project, we will accommodate that request.

• Pharsight’s Scientists are experts in the use of all of the above products
Phoenix NLME Enables Workflows to Facilitate Project Execution and Management
Phoenix NLME Has Powerful Tools For Model Selection
Phoenix NLME Has Powerful Graphics Tools for Reporting and Model Selection
Phoenix NLME Has Powerful Graphics For Assessing Model Performance
Case Study: Population PK/PD to Support NDA Submission
PK Data

PK from PHASE I, II and III studies

Phase I

Phase II

Phase III

Single/Multiple Dose

Single/Multiple Dose

Multiple Dose

Time of exposure

Richness in PK samples
PD Data

Efficacy and Safety from PHASE II/III studies

Phase I

Phase II

Phase III

Multiple Dose

Sparse PK

Three Efficacy endpoints

Two Safety endpoints
## Typical POP PK Model Development Workflow

### Developing the Base PK Model

#### Structural Model

- How many compartments are needed for disposition?
- What input function can describe the absorption?

#### Statistical Model

- What random effects on parameters are needed or supported by the data?
- What residual variability model to use?

#### Deterministic Component

\[
\theta = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix}
\]

#### Disposition function

- One-Two-or Three-compartment
- Non-linearities, target-mediated...

#### Input function

- Between subject variability (BSV) matrix
- Distributional assumption (Log-normal)
  - Full Block
  - Full Diagonal
  - Reduced

#### Stochastic Component

- Residual variability model
  - Additive, proportional, combined

### Between subject variability (BSV) matrix

\[
\Omega = \begin{bmatrix} \Omega_{11} & \Omega_{12} & \Omega_{13} \\ \Omega_{21} & \Omega_{22} & \Omega_{23} \\ \Omega_{31} & \Omega_{32} & \Omega_{33} \end{bmatrix}
\]

### Residual variability model

\[
\Sigma = \begin{bmatrix} \sigma_{11} & 0 & 0 \\ 0 & \sigma_{22} & 0 \\ 0 & 0 & \sigma_{33} \end{bmatrix}
\]
Examples of GOF Plots

Note the smooth predictions at times with no observations

Phoenix NLME generates these very efficiently
Examples of GOF Plots
Covariance needed between Eta’s? (Plot from run with diagonal Omega)
Examples of GOF Plots
Model Building: Adding Covariates
Typical POP PK Model Development Workflow

Developing a Covariate Model: Examples of Covariates

• Demographics
  - Sex, Race, Size (weight, height, BSA, IBW, BMI, ...)

• Lab values
  - Renal function: Serum creatinine
  - Liver: bilirubin, albumin, AST, ALT, ...
  - pheno/genotype

Disease severity, Co-medication, smoking etc.
Summary of Model building

Absorption Model

\[ \Theta = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix} \]

Disposition Model

\[ \Omega = \begin{bmatrix} \Omega_{11} & \Omega_{12} \\ \Omega_{21} & \Omega_{22} \end{bmatrix} \]

Between subject variability Matrix

\[ \Sigma = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ 0 & \sigma_{22} \end{bmatrix} \]

Residual error model

Covariate Model Building

Deterministic Component

Stochastic Component

Base Model
Typical POP PK Model Development Workflow
Developing a Covariate Model: Stepwise Model Building

- Important Covariates (GAM)
- Forward Stepwise Addition
- Graphs of WRES/CWRES and etas vs Covariates: Weight, Sex, CRCL

Repeat until no covariate is significant

Tentative Model With Covariates

Proceed with next step of covariate addition

Test each on PK parameters one by one:
- Weight and Sex on Vd
- Weight, Sex, CRCL on CL

Keep the most Significant

Model + Covariate
Typical POP PK Model Development Workflow
Developing a Covariate Model: Backward Elimination

1. **Covariate Model Building**

2. **Backward Deletion**

   - Remove covariates one by one by reverse order:
     - Weight and **Sex** on Vd
     - **Weight**, Sex, CRCL on CL

3. **Repeat until no covariate can be removed**

4. **Final Model With Covariates**

5. **Proceed with Model Validation and Evaluation**
Typical POP PK Model Development Workflow

Developing a Covariate Model: Multiple Covariates on a Parameter

$$TVCL = \theta_{CL} \cdot \left( \frac{\text{WEIGHT}}{75} \right)^{0.75} \cdot \left( \theta_{CL,\text{SEX}} \right)^{\text{SEX}} \{L/h\}$$

Blue denotes population parameter
Red is a patient specific covariate
Black is a constant - usually the mean or the median are used

Usually a linear multiplicative model with no interactions is used.

This parameterization is easily interpretable

TVCL is the clearance for a subject with median weight with SEX=0

It is always useful to have a realistic typical patient when we have multiple covariates on a single parameter
Examples of Graphs to Aid Covariate Model Building

Explore collinearity between covariates
Summary of Model building

Absorption Model
\[ \Theta = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix} \]

Disposition Model

\[ \Omega = \begin{bmatrix} \Omega_1 \\ \Omega_2 \\ 0 \\ 0 \\ \Omega_3 \end{bmatrix} \]

Between subject variability Matrix

Residual error model
\[ \Sigma = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{bmatrix} \]

Covariate Model Building

Base Model

Deterministic Component

Stochastic Component

Final Model With Covariates

Model Evaluation
Model Discrimination, Evaluation and Diagnosis
Model Evaluation/Diagnosis?

- Assumption Checking
- Evaluation Methods
- Parameters
- Predictive Performance
- Sensitivity Analysis
What Can We Evaluate?

- The different parts of the model
  - Structural PK-PD model
  - Covariate-parameter relationships models
  - Random effect models
  - Residual variability model
- The performance of model-based inferences
  - Parameter estimates & confidence intervals
  - Hypothesis tests
  - Predictions/simulations with model

- Explore the data (EDA)
- Follow the objectives
- Keep the model plausible
- Understand and check the assumptions and limitations
- Define useful decision making criteria
- Diagnosis can include a set of plausible models
How Can We Evaluate?

- **Assumption Checking**
  - Randomization tests for the p-values
  - Graphics for distributional assumptions (Residuals, empirical Bayesian estimates, ...)

- **Stability/precision of parameter estimates**
  - Validation through parameter prediction errors
  - Log-Likelihood Profile
  - Bootstrap (parametric & non-parametric)
  - Cross-Validation/Leverage analysis

- **Assessment of model performance/properties**
  - Prediction errors (from internal or external test set)
  - Posterior Predictive Check
  - Sensitivity Analysis


What to use in diagnostics?

- **Simulation Based Diagnostics**
  - **Posterior Predictive Checks**
    - Select a statistic of interest that a good model should not miss (e.g. AUC, Cmax, etc) and that can be derived from the raw data
    - Simulate many data sets from the model (with uncertainty, TS2.2)
    - Calculate the statistic from the N simulated data and J Replicates
    - Calculate the statistic from the observed data
    - Compare the statistic from raw and simulated data

\[
\begin{bmatrix}
\theta_1 \\
\theta_2 \\
\theta_3
\end{bmatrix}
\]

\[
\begin{bmatrix}
\Omega_{11} & \Omega_{12} & \Omega_{13} \\
\Omega_{21} & \Omega_{22} & \Omega_{23} \\
0 & 0 & \Omega_{33}
\end{bmatrix}
\]

\[
\begin{bmatrix}
\sigma_{11} \\
0 & \sigma_{22}
\end{bmatrix}
\]

\[
\begin{bmatrix}
\text{Var} \\
\text{Cov} & \text{Var} \\
\text{Cov} & \text{Cov} & \text{Var} \\
\text{Cov} & \text{Cov} & \text{Cov} & \text{Var}
\end{bmatrix}
\]

- Draw N Parameters from the final estimates and Variance Covariance Matrix
- Simulate Data according to the design of the study and compute the statistic of interest
- Compare the statistic from raw and simulated data

**If we ignore parameter uncertainty this reduces to predictive check**
Example of a likelihood profile
Example of predictive check

Drug 1 Men

Drug 1 Women

Drug 2

<table>
<thead>
<tr>
<th>Concentrations and predictions in &quot;mg/L&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
</tr>
<tr>
<td>1.5</td>
</tr>
<tr>
<td>1.0</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>0.0</td>
</tr>
</tbody>
</table>

Vd/F=366 L

Vd/F=208 L

TIME "Hr"

90 % PI

Cobs

PRED

Pharsight
Thank you for your time and attention