Confirmatory Phase III Population Pharmacokinetic Analysis

Chuanpu Hu, Ph.D.
Honghui Zhou, Ph.D.
Pharmacokinetics,
Modeling and Simulation
B.I.O.
Johnson & Johnson
Outline

Why use confirmatory POP PK?
- More appropriate than exploratory, at least for a primary objective in Phase III

Implement confirmatory POP PK in phase III
- (Minor modification, new example)
- Necessary, potentially even in earlier phases

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Choosing POP PK Model Components

<table>
<thead>
<tr>
<th>Structural</th>
<th>• # of compartments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random effects</td>
<td>• OMEGA BLOCK()</td>
</tr>
<tr>
<td></td>
<td>• EPS (hybrid, power)</td>
</tr>
<tr>
<td>Covariates</td>
<td>• Which parameter(s)?</td>
</tr>
<tr>
<td></td>
<td>• Power, additive (?)</td>
</tr>
</tbody>
</table>

Exploratory analysis: **searching for best fits** (FDA, EMEA guidance)

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Some Quotes on Exploratory Analysis

“Torture the data long enough and they will confess to anything.”

• (Is water boarding torture?)

“Treasure your result of exploratory data analysis, for you will not see it again.”

“The journey of a thousand miles begins with a single step but you will not get far with stepwise regression.”

“Stepwise regression: regression certainly, and many steps but wise?”

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Contrast: Standard (Confirmatory) Statistical Analysis Plan

Use only 1 pre-specified model

• Even though best model is unknown, e.g., whether to adjust for sex, weight, etc.

Alternative “what if” scenarios addressed by sensitivity analyses

• Few cases, results treated accordingly (perhaps with lighter weights)
## Exploratory vs. Confirmatory

<table>
<thead>
<tr>
<th></th>
<th>Is model “likely?”</th>
<th>Unbiased parameter estimates?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generate new hypothesis?</td>
<td>Interpretable p-value?</td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td>Yes</td>
<td>No (selection bias)</td>
</tr>
<tr>
<td><strong>Confirmatory</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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POP PK at phase III: What is Important?

- Is model likely?
  - No
    - Sparse sampling design cannot support complex model
    - No future plan to confirm new hypotheses

- Generate new hypothesis?
  - Yes

- Unbiased parameter estimates?
  - Yes
    - Important for labeling, covariate-based dosing adjustment
    - Main focus: covariate effect on CL

Interpretable p-value?

Confirmatory approach is more suitable!

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**Confirmatory Approach: Primary analysis**

**Base model (structural + random effects)**
- Use phase I/II model to simulate under phase III design, to find the best identifiable model
- 1 simulation usually enough

**Covariate model**
- Use **full model** (with all covariates) on CL
  - Unless mechanistic knowledge indicate otherwise

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Confirmatory Sensitivity analyses

(1) Allometric
- \( CL \sim \text{weight}^{0.75}, \ V \sim \text{weight} \)

(2) Linear mixed effect model
- \( \log(\text{conc})_{ij} = \text{Dose} \ \text{TI} \ \text{Cov1} \ \text{Cov2} \ldots \ \text{CovN} + \eta_i + \varepsilon_{ij} \)
- TI: time indicator (adjusting for time, 0 – 4 categories)
- Analyzing covariate effects on average observed exposure

Exploratory analysis could be a sensitivity analysis

Guard against alternative scenarios, e.g., influence of inaccuracies in time recording
Deciding on Covariate-based Dosing Adjustment

<table>
<thead>
<tr>
<th>In principle, no different than exploratory approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess covariate effect using model estimate and CIs</td>
</tr>
<tr>
<td>• Continuous covariate effect evaluated as ratio between the predicted CL at 25% and 75% percentiles</td>
</tr>
<tr>
<td>Deciding a threshold beyond which dosing adjustment would be needed</td>
</tr>
<tr>
<td>• Knowledge on therapeutic window needed – however this is usually not explicit</td>
</tr>
<tr>
<td>The BE 80-125% criterion can be considered as a lower bound</td>
</tr>
<tr>
<td>• Used here for illustration purpose only</td>
</tr>
</tbody>
</table>

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Preplanning: Confirmatory Approach

Base model: simple may be fine
- Only a “feel good” factor when fitting is good (?)
- Likely not crucial for covariate effect assessment

Covariate list may need trimming to ensure enough power

Trimming criteria are situation specific, but for a nominal proposal:
- At least 20 subjects per covariate category
- Remove covariates having correlations > 0.5 – 0.75, based on pharmacological rationale

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Preplanning: Exploratory Approach

Should be done, however easy (incentive!) to ignore, as most evaluations focus only on “final” model

“Validated” models may not be good enough

- No practical way to account for model exploration, therefore interpretation dubious
- Use of mixed effect models vary, “overall” criteria may not be useful for the specific use

Helpful to have a confirmatory mindset – refrain from exploration with no power

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Application Example – A Phase III study

Study characteristics

- Subcutaneous dosing
- ~600 patients, 3400+ concentration observations
- 16 covariates in the dataset: weight, age, concurrent disease, comed, etc.

Considerations before analysis begins

- Established a priori covariate order
- Covariates with <20 patients dropped from consideration
- For LME model: 4 time indicator categories
  - Week 4 trough, Week > 4 trough, early non-trough, late non-trough

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Base model (pre-specification)

Previous POPPK model developed from phase I/II data

- 2-compartment model with 1st order absorption
- Full var-cov matrix for between-subject variability on all 5 structural model parameters
- Additive + proportional within-subject variability

1 simulated dataset using previous POPPK model with current study design considered for base model

Simple exploration shows only 1-compartment model with 1st order absorption could be identified

- var-cov matrix for between-subject variability on (CL, V)
- Weight effect on (CL, V)

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Allometric model estimate and 90% CI

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Regression model estimate and 90% CI

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Confirmatory Analysis Conclusions

Primary analysis
- Weight may be considered relevant (25% effect on CL)

Sensitivity analysis
- Might suggest sex, concurrent disease 1, 3, and baseline disease score 3
- However Borderline average effects, wide CI

Conclusion:
- Weight may be considered relevant (25% effect on CL)

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Exploratory model estimate and 90% CI

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Main results quite similar between confirmatory and exploratory analysis

• More generally, likely sufficient power with common phase III analyses

Exploratory had explicitly >50 NONMEM runs documented

• Many undocumented ones, required much deliberation time over which models to adopt at different stages

Confirmatory used <10 NONMEM runs

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How Convincing Is 1 Example?

Simulation study may be natural to ask, however

- Existing simulations already showed potential biases of exploratory approach
- Confirmatory analyses are unbiased, as long as assumptions are met
- Practical situations vary, many mechanism not easy to postulate
  - e.g., how dosing/sampling error occur

Example result consistent with expectations and serves as illustrations

- Confirmatory approach applied to several phase III examples (6 and ongoing), # subjects ranging from 500 to 3,000
- Consistent results observed, more so with larger sample cases

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Summary on Confirmatory Analysis

Many benefits

• Forces careful analysis planning
• Many fewer model runs
• Conceptually more accurate and interpretable results
• Fits phase III main objective

Should be conducted routinely, at least in phase III

• Keep selection bias in check, even if exploration wanted