Is Confirmatory PK/PD Modeling Possible?

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Outline

- PK/PD modeling – why, how
- Exploratory vs. confirmatory: when to use which?
- Difficulties of confirmatory PK-PD modeling
- A confirmatory approach in phase III population
  PK
    - Objective
    - Available information
    - Method
- Possible extensions
Model-based Drug Development (MBDD)

• Builds a model to predict probability distribution of trial outcome, given trial design
• Based on knowledge of the drug, patient and disease characteristics
• Integrates literature, pre-clinical and clinical information of NCE and related compounds
• Quantifies uncertainty in trial outcome due to model uncertainty and patient variability
• Provides quantitative rationale for selecting trial strategies
Demand of MBDD is Rising

- FDA critical path list for drug development
- As drug development becomes more challenging, more information is demanded from data
- Learn – confirm paradigm:
  - Generate hypotheses at early stage
    - MBDD crucial
  - Confirm at late stage
PK/PD

- Usually serves as a critical component of Model-based Drug Development
- Using scientific knowledge of drug
- PK: exposure – time profile
  - Dose - Exposure
- PD: using mechanistic knowledge of drug action
  - Exposure – Response
- PK/PD:
  - Dose (Regimen) – Response (Time Course)
How Drugs Work

- **PK**: What the body does to the drug
- **PD**: What the drug does to the body
A mechanistic view of PK and PD

Jusko et. al., JPB  23: 5, 1995

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PK/PD Data and Model Estimation

- Differential equation based structural models
- Typically multiple exposure/response measurements per subject
  - Nonlinear mixed effect models
- Model choices ideally mechanistically based, however information is uncertain
- Dominant analysis approach: extensive exploratory, searching for best fit among
  - Structural model (# of compartments in diff. eqn.)
  - Random effect forms
  - Covariate effects on parameters (fixed effects)
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?”
## Exploratory vs. Confirmatory

<table>
<thead>
<tr>
<th>Approach</th>
<th>Is model “likely?”</th>
<th>Unbiased parameter estimates?</th>
<th>Interpretable p-value?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploratory</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Confirmatory</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
In Practice

- PK and PD data contain useful information – how best to analyze in light of existing uncertainties?
- An Illustration in POP PK:
POPs PK at phase III

- Powerful, well recognized
  - FDA, EMEA guidance in place
- Main objective: assessing covariate influence on exposure
  - Labeling and potential covariate-based dosing adjustment decisions
- (Typical exposure measures: AUC and Cmax)
- Phase III study PK: sparse sampling
  - Few samples per subject, large # subjects
What Can Phase III Sampling Estimate?

- Not good:
  - Complex structural model
  - Cmax

- Good:
  - Average exposure (AUC, or CL)
  - Simple structure models, e.g., 1-compartment
  - Average main PK parameter estimates (CL, V)
  - Covariate influence on CL
Known Problems that May Affect Exploratory POP PK

• Selection bias
  – Theory: linear regression model selection leads to over-estimated covariate effects (Harrell, Regression Model Strategies, 2000)
    • Potentially over-adjustment on dose
  – Simulations
    • Ribbing & Jonsson, J/PK/PD 2004: POP PK covariate model selection
Contrast: 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)
Idea for Confirmatory Phase III POP PK

- Main objective: covariate-based dose adjustment for labeling
  - Covariate effect on CL is main focus
- Usually not enough power to support exploratory schemes anyway (GDF concept: Ye JASA 1999)
- Use full model assessment for CL only, not any other parameters
- How to specify base model (1 or 2 compartment, What random effects)?
Pre-specify Base Model

• Prior POP PK model usually available, built from phase I/II data
  – Usually more extensively sampled, thus more complex than phase III data can support
• Combine this with phase III study design (i.e., dose/sampling scheme)
  – Use simulated study data to select identifiable base model
• Unlikely to influence covariate model estimates; however needed to maintain confirmatory nature
Confirmatory Phase III POP PK Proposal

• Pre-specify analysis of phase III POP PK
• Structural model
  – Use phase I/II model to simulate under phase III design, to find the best identifiable model
    • 1 simulation usually enough
  – Pre-specify
• Covariate model: use full model (with all covariates) on CL
• 2 – 3 additional sensitivity analyses, to guard against alternative scenarios, e.g., influence of inaccuracies in time recording, and assess robustness
  – Exploratory analysis could be a sensitivity analysis
Sensitivity Analysis (a)

- Mechanistic Rationale in literature to suggest
  - $CL \sim \text{weight}^{0.75}$, $V \sim \text{weight}$
- Fix this relationship in base model
- Use full covariate model for rest of the covariates
- Gives a sense of robustness on
  - Covariate effect on $V$
  - Influence of other covariates
Sensitivity Analysis (b)

- Linear mixed effect (LME) model:
  \[
  \log(\text{conc})_{ij} = \text{Dose} \times T I \times \text{Cov1} \times \text{Cov2} \ldots \times \text{CovN} + \eta_i + \epsilon_{ij}
  \]
  - TI: time indicator (adjusting for time, 0 – 4 categories)

- Assesses covariate effect on average exposure (closely related to CL)
- Use full covariate model
- Examine robustness to
  - Structural model
  - Dosing/sampling time inaccuracies
Analysis Characteristics

• LME model analysis:
  – A step function approximation to structural model
  – Less efficient ⇔ more robust
    • May be expected to produce a lower bound on covariate effects
  – Easy (!) to implement
  – Results may be down weighted, if losing too much efficiency (wide CI)
• Confirmatory analyses need planning!
Preplanning: Confirmatory Analyses

- Base model assumptions
  - A “feel good” factor? Simple choice may be fine
  - 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
Preplanning: Exploratory Analyses

• Should be done, however
  – Easy (incentive) to ignore, as most evaluations focus only on “final” model
• “Validations” used in practice instead, however
  – 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 assessment
• Helpful to have a confirmatory mindset – refrain from explore options with no power
Deciding on Covariate-based Dosing Adjustment

- In principle, no different than exploratory approach
- Assess covariate effect using model estimate (and CIs)
- Deciding a threshold beyond which dosing adjustment would be needed
  - Knowledge on therapeutic window needed – however this is usually not explicit
- The BE 80-125% criterion can be considered as a lower bound
  - Used here for illustration purpose only
Application Example – A Phase III study

• 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
Base model

• 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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Regression model estimate and 90% CI

Covariate effect on CL

- weight
- sex
- methotrexate
- comed 1
- comed 2
- disease duration
- disease 1
- disease 2
- disease 3
- disease 4
- baseline score 1
- baseline score 2
- baseline score 3

0.8 1.0 1.2 1.4 1.6
Confirmatory Analysis Conclusions

- Weight may be considered relevant (25~30% effect on CL)
- Sensitivity analysis also might suggest sex, concurrent disease 1, 3, and baseline disease score 3
  - Borderline average effects, wide CI
- Conclusion:
  - Weight may be the only potentially relevant covariate, with 25% effect on CL
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Covariate effect on CL

- weight
- baseline score 3
- immune response
- smoking

Exploratory model estimate and 90% CI
Application Example Result Summary

• Main results quite similar between confirmatory and exploratory analyses
  – More generally, likely sufficient power with common phase III analyses
• Each traditional analysis documented explicitly 50+ models
  – Other analyses go into hundreds
  – Many undocumented ones, required much deliberation time over which models to adopt at different stages
• New proposal: <10 models used
• Advantage of confirmatory analysis: much less work, theoretically more accurate result
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 POP PK: Current Experience

• 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
• Reasonable for phase III
• Should be usable for phase II
Future Extension to PK/PD

- Certain exposure-response models are commonly used, e.g., Indirect Model
- Same approach applicable to phase 3 analysis
  - Need prior PK/PD model from phase 2
- Benefits of confirmatory PK/PD analysis
  - Results more interpretable, unbiased
  - Reduced analysis time
Extension to PK/PD – Current Difficulty

• PD endpoints vary – less standard
• PK/PD modeling less frequently conducted than (POP) PK
• Less experienced analysts
• Nevertheless, could aim to conduct whenever possible
Future

- FDA encourages innovation
- Resistance: “modeling is an art”
- Transform M&S from ad hoc processes to a rigorous, standardized paradigm helps to facilitate MBDD
- A formal paradigm could enable
  - Easier acceptance across different disciplines
  - Better planning
  - Eventually, fully integrating MBDD into drug development

- In 5 years (?)
  - Confirmatory POP PK for phase II-III
  - Confirmatory PK/PD for phase III
Future - Ideal (?

- Standard (confirmatory) analysis plan for POP PK and PK/PD in all phases
  - Using all information from earlier studies, same class of compounds, etc.
- Exploratory analysis specified as sensitivity analysis
  - More frequent, and carry more weight in earlier phases
Summary Thoughts

• Learn – confirm paradigm
  – Exploratory analysis has its benefits, especially at early stage

• All stages can benefit from confirmatory analyses
  – Even when exploratory, having a confirmatory mindset can help to keep exploration within reason (power of data)
When a new idea comes ...

IN MY SPARE TIME I CAME UP WITH AN IDEA FOR YOUR PROJECT.

YOUR IDEA IS SO GOOD THAT IT MAKES ALL THE WORK I DID FOR THE PAST YEAR A MISERABLE MISTAKE.

YOU'RE WELCOME. I CAN'T LET YOU LEAVE THIS CUBICLE ALIVE.

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