Longitudinal Modeling of Lung Function in Respiratory Drug Development

Fredrik Öhrn, PhD
Senior Clinical Pharmacometrician
Quantitative Clinical Pharmacology
AstraZeneca R&D Mölndal, Sweden
Outline

• A brief introduction to (respiratory) drug development

• (P)K-PD Modelling

• K-PD approach to longitudinal modeling of lung function

• K-PD model applied to a clinical trial

• Reflections
Brief presentation

- Born in Kristianstad in southern Sweden
  - the year that Argentina won the FIFA World Cup for the first time
- Keen chess player
- Joined the pharmaceutical company AstraZeneca in 2004
- 8 years within Biostatics group at AstraZeneca R&D Mölndal
  - worked primarily with cardiovascular and metabolic diseases
- Since 2012, pharmacometric modeler within Quantitative Clinical Pharmacology
  - worked primarily with respiratory diseases
- Education: PhD in Biostatistics, University of Bath, United Kingdom
  - Group Sequential and Adaptive Methods for Clinical Trials
(RESPIRATORY) DRUG DEVELOPMENT
Drug development and its phases

• Pre-clinical trials
  - carried out before a drug is tested in humans
  - many different types of activities, but beyond scope of this presentation

• Phase I clinical trials
  - usually in healthy volunteers

• Phase II clinical trials
  - initial assessment of efficacy and safety in patients
  - dose-finding to decide on dose(s) for phase III

• Phase III clinical trials
  - large, pivotal trials to confirm efficacy and safety

• Phase IV clinical trials
  - carried out post approval
Respiratory drug development

Some important aspects

• Disease areas with a high unmet medical need, e. g.
  - Asthma
  - Chronic Obstructive Pulmonary Disease (COPD)
  - Both diseases characterized by impaired lung function

• Important guidelines, e. g.
  - Global Initiative for Asthma (GINA)
  - Global initiative for chronic Obstructive Lung Disease: GOLD
  - In addition, regulatory requirements are key to the design of development programmes

• Key measure of lung function
  - Forced expiratory volume during one second (FEV1)
  - FEV1 is an endpoint accepted by regulatory authorities
  - Other measurement of lung functions exist but FEV1 is typically the primary variable

• Exacerbations
  - Sudden worsening of symptoms
  - Varying definitions exist for both Asthma and COPD

• In a typical phase II clinical trial for asthma or COPD, FEV1 is the primary variable

• Large studies are needed to assess exacerbations, so often not done until phase III or IV

• Drugs are often inhaled, which makes the device used to inhale the drug very important
PK-PD MODELING
PK-PD modeling
Described in layman's terms

- Pharmacokinetics (PK): What the body does to the drug
  - What happens to the drug after it is administered
  - Describes absorption, distribution and elimination of the drug

- Pharmacodynamics (PD): What the drug does to the body
  - How is a response variable affected when a drug is administered

- PK-PD Model: The description of the time course of both PK and PD response after administration of a drug
  - describes the relationship between the drug concentrations and the effect variable

- Developed using non-linear mixed effect models
  - typically with a set of hierarchical variability components
    - variability between subjects
    - variability within subjects over time
    - remaining residual variability
Example of PK-PD relationships

Plasma concentration versus time

Pharmacodynamic variable versus time

Pharmacodynamic variable versus plasma concentration
The K-PD modeling approach

- (P)K-PD modelling without being able to observe the PK profile
  - Assuming underlying PK profile that drives the effect

- Useful when it is not possible to collect PK information
  - Limited PK information, for example in phase III
  - Difficult to measure PK, for example in pediatric studies*

- A certain structure of the PK model is often assumed
  - For example time course described by two parameters
  - Goodness of fit versus number of parameters


*Trials in children
K-PD modeling of lung function

- Motivation for use when modeling bronchodilatory effect
  - PK lung concentrations are assumed to drive lung function
  - Unable to measure PK in the lung of humans
  - K-PD model a possibility

- Other examples in the industry all focusing on lung function:

A CLINICAL TRIAL EXAMPLE
A common design in phase II

Used frequently for clinical trials in both asthma and COPD

• Administer a single dose of a drug
  - Follow the lung function for 24 hours (or the time of the dosing interval)

• Cross-over design
  - Appropriate wash-out between treatment periods

• Referred to as a single dose cross-over (SDXO) design
K-PD model applied to a clinical trial

• A single dose cross-over (SDXO) phase IIa study in COPD patients
  - 6-way SDXO study with 39 randomised patients
  - Three doses of experimental drug, placebo and two active comparators
  - Serial measurements of bronchodilatory (FEV1) effect during 26 hours
  - FEV1, forced expiratory volume during 1 second, was the primary efficacy variable
  - For confidentiality reasons, only results of active controls and placebo will be shown
Study design for the COPD trial

- Cross-over design
  - Important with appropriate wash-out between treatment periods
  - Number of periods may vary, six in this case

- In the beginning of each period, each patient receives a single dose
  - A total of six single doses per patient
  - Three doses of the experimental drug, two active comparators and a placebo

- Typical primary analysis
  - Analysis of covariance model
  - Sample size usually based on a t-test
  - Separate analysis at each time point, or mean/area under curve
Motivation for using KPD model for SDXO study

- Utilisation of all data for prediction
- Common framework to assess all timepoints
  - Primary interest is FEV1 24 hours post dose
  - Peak effect another key variable
- Assessed ability to predict outcome of other SDXO studies
  - Found that the model can adequately describe the data
Observed data for KPD modelling

Plasma concentration versus time

Pharmacodynamic variable versus time

Pharmacodynamic variable versus plasma concentration

NOT OBSERVED

NOT OBSERVED
Model for FEV1 effect over time

\[ FEV_{1}(t) = P(t) + E(t) + RE \]

- \( P(t) \) denotes placebo effect over time
- \( E(t) \) denotes drug effect over time
- \( t \) denotes time after dose
- \( RE \) denotes residual error
Substantial variation throughout the day

- Reasonable to model placebo effect using the sum of cosine functions (24 and 12 hr period)
- Linear term to account for trends
- Has tended to describe placebo data well in SDXO trials
- Details on next slide
Placebo model

\[ P(t) = A + \beta_{BL} \times FEV1_{BL} + \beta_t \times t + \left\{ B_{24} \times \cos\left(\frac{2\pi (ct - C_{24})}{24}\right) + B_{12} \times \cos\left(\frac{2\pi (ct - C_{12})}{12}\right) \right\} \]

\( t \) denotes time after dose
\( ct \) denotes clock time
Drug effect model

\[ A(t) = D \times \exp(\log(k)) \times t \times \exp(-\exp(\log(k)) \times t) \]

\[ E(t) = \frac{\max}{1 + \exp(\log(EA_{50}))/A(t)} \]

\[ = \frac{\max}{1 + \exp(\log(EA_{50}))/\left( D \times \exp(\log(k)) \times t \times \exp(-\exp(\log(k)) \times t) \right)} \]

\( D \) denotes dose
\( \log(k), \log(EA_{50}) \) and \( E_{\text{max}} \) are fixed parameters to be estimated
Different \( \log(k) \) and \( \log(EA_{50}) \) defined for the active controls
Random effects for certain parameters
Observed & predicted bronchodilation in COPD patients

The model is able to describe the response across dose groups over time.

**Key**
- Observed mean data with 95% CI
- Longitudinal model mean predictions
- Model-based 95% confidence bands

Ind. = Indacaterol
Tio. = Tiotropium
Predicted efficacy after 24 hours

Primary efficacy variable used for decision making

Mean predictions and associated 2-sided 95% CI

- Indacaterol 150 mcg
- ANCOVA
- Longitudinal
- Ind. 150 mcg + Tio. 18 mcg
- ANCOVA
- Longitudinal

Placebo-corrected CFB (mL)
Possible extensions

• **Sample size for longitudinal analysis vs ANCOVA**
  - Lower sample size to achieve similar precision
  - Higher precision at given sample size
  - Important to assess robustness to assumptions

• **Optimal sampling times**
  - When to measure FEV1
  - Based on covariance matrix of model parameters

• **Designing the next study**
  - Decide dose levels using prior information from SDXO study
  - FEV1 profile at day 1 and end of treatment
  - Use the model for trials with repeated dosing, see for example
Reflections

• Applied for a phase II clinical trial to model effect after single dose

• Examples in literature of repeated dosing approach

• Novel methods to assess drug concentration in the lung

• More mechanistic approach possible