Longitudinal Modeling of Lung Function in Respiratory Drug Development

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

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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 Biostastics 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

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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 defenitions 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 imporant

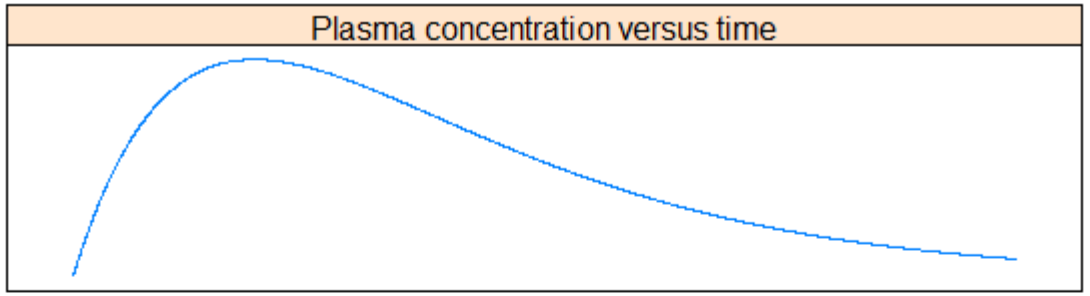
PK-PD MODELING

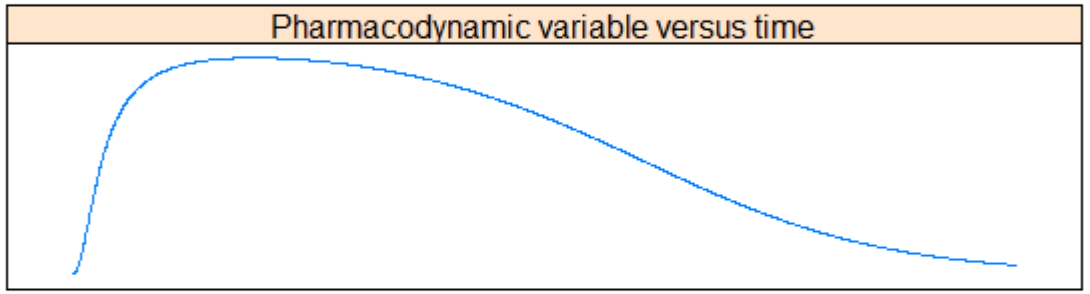
PK-PD modeling

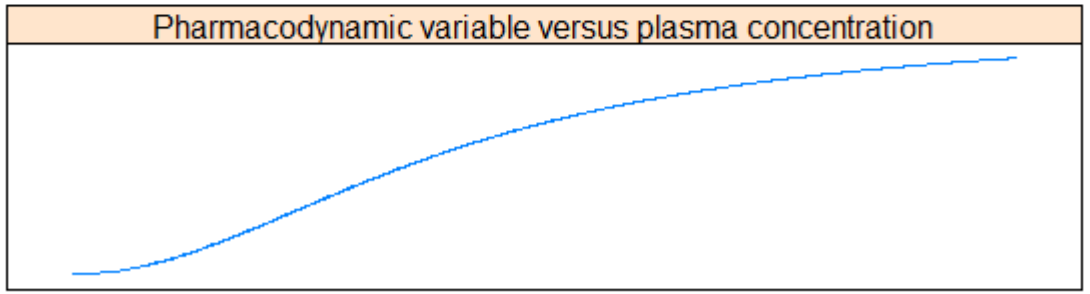
Described in layman's terms

- 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







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

- Key Reference: P. Jacqmin et al., Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. J Pharmacokinet Pharmacodyn 2007; 34: 57-85.

*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:

  - LAMA developed by Novartis: K. Wu et al., Population pharmacodynamic model of the longitudinal FEV1 response to an inhaled long-acting anti-muscarinic in COPD patients. Journal of Pharmacokinetics and Pharmacodynamics. 38:105-119, 2011.

  - LABA developed by Pfizer: J. C. Nielsen et al., Longitudinal FEV1 dose-response model for inhaled PF-00610355 and salmeterol in patients with chronic obstructive pulmonary disease, Journal of Pharmacokinetics and Pharmacodynamics. 2012: 39:619-634.

A CLINICAL TRIAL EXAMPLE

A common design in phase II

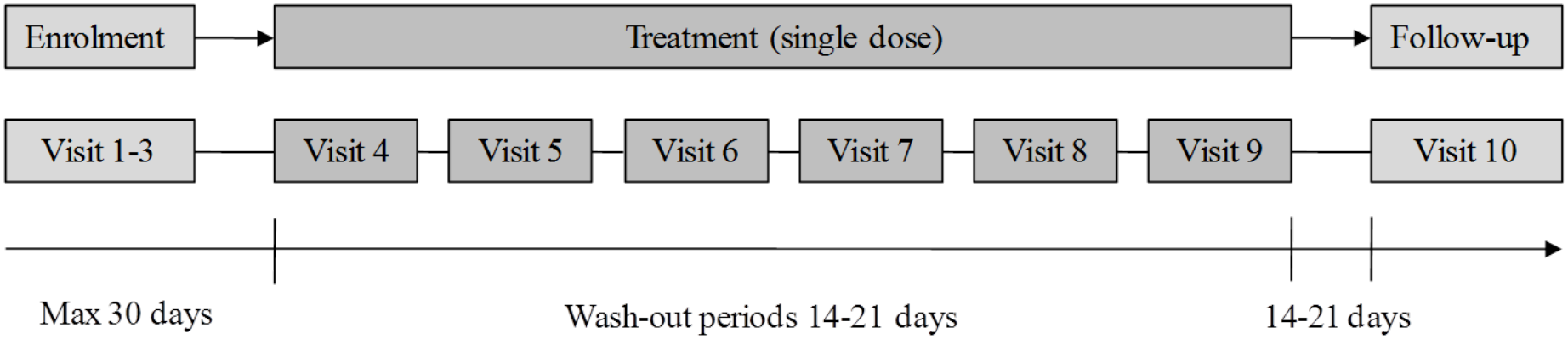
Used frequently for clinical trials in both asthma and COPD

- 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

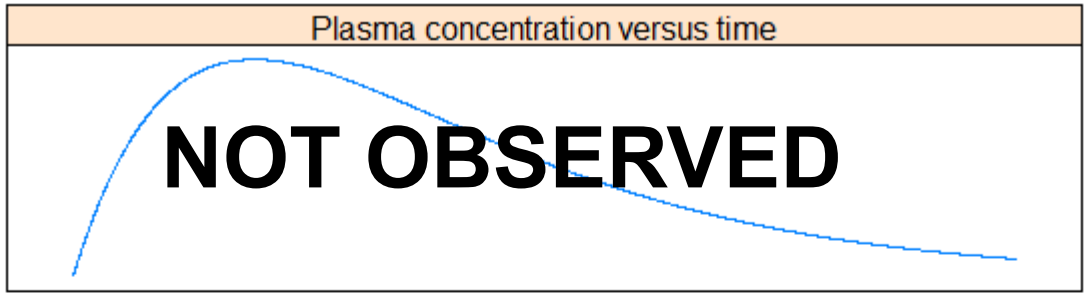


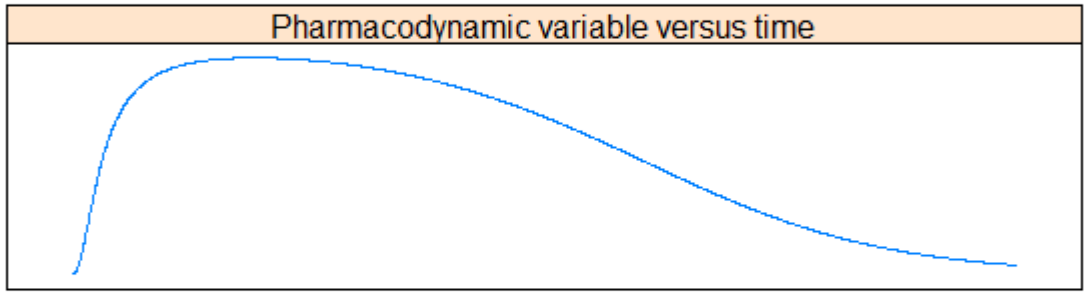
- Cross-over design
  - Important with appropriate wash-out between treatment periods
  - Number of periods may vary, six in this case
- In the beginning of each period, each patient receives a single dose
  - A total of six single doses per patient
  - Three doses of the experimental drug, two active 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

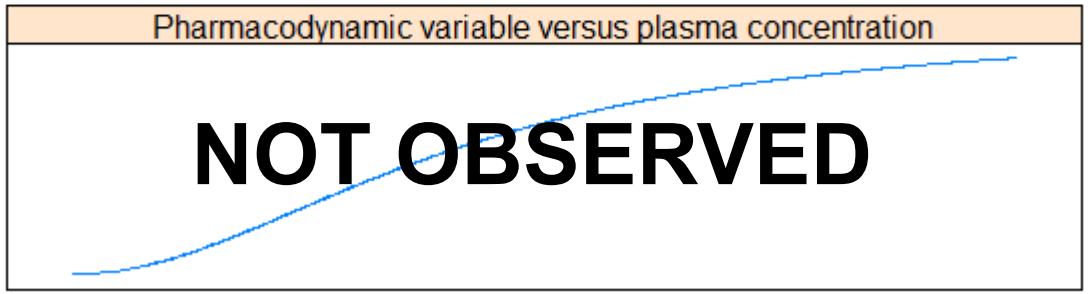
Motivation for using KPD model for SDXO study

- 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







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

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

t denotes time after dose
ct denotes clock time

Drug effect model

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

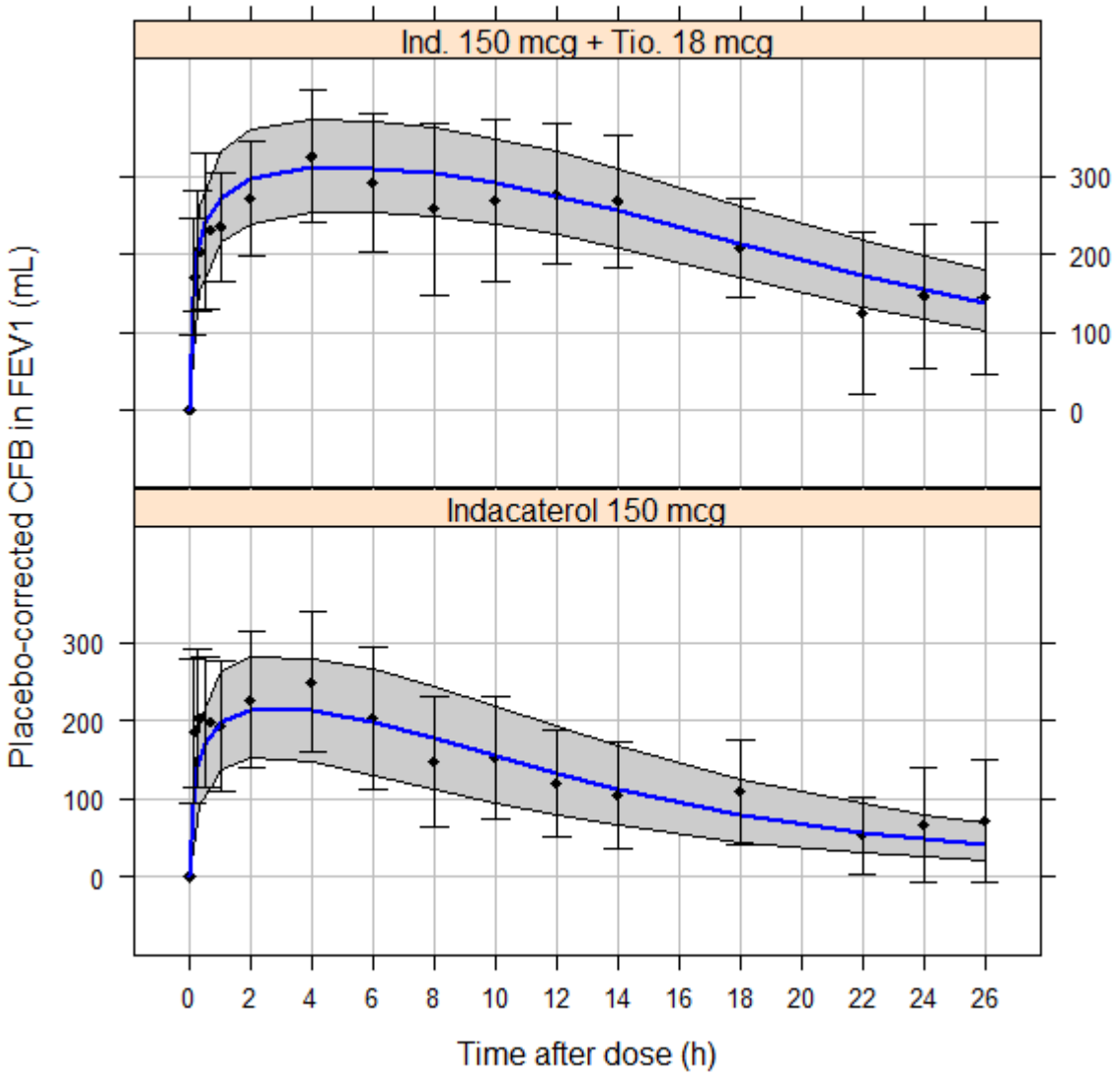
$$E(t) = \frac{E_{\max}}{1 + \exp(\log(EA_{50})) / A(t)}$$

$$= \frac{E_{\max}}{1 + \exp(\log(EA_{50})) / (D \times \exp(\log(k)) \times t \times \exp(-\exp(\log(k)) \times t))}$$

D **denotes dose**
log(*k*), log(EA_{50}) and E_{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

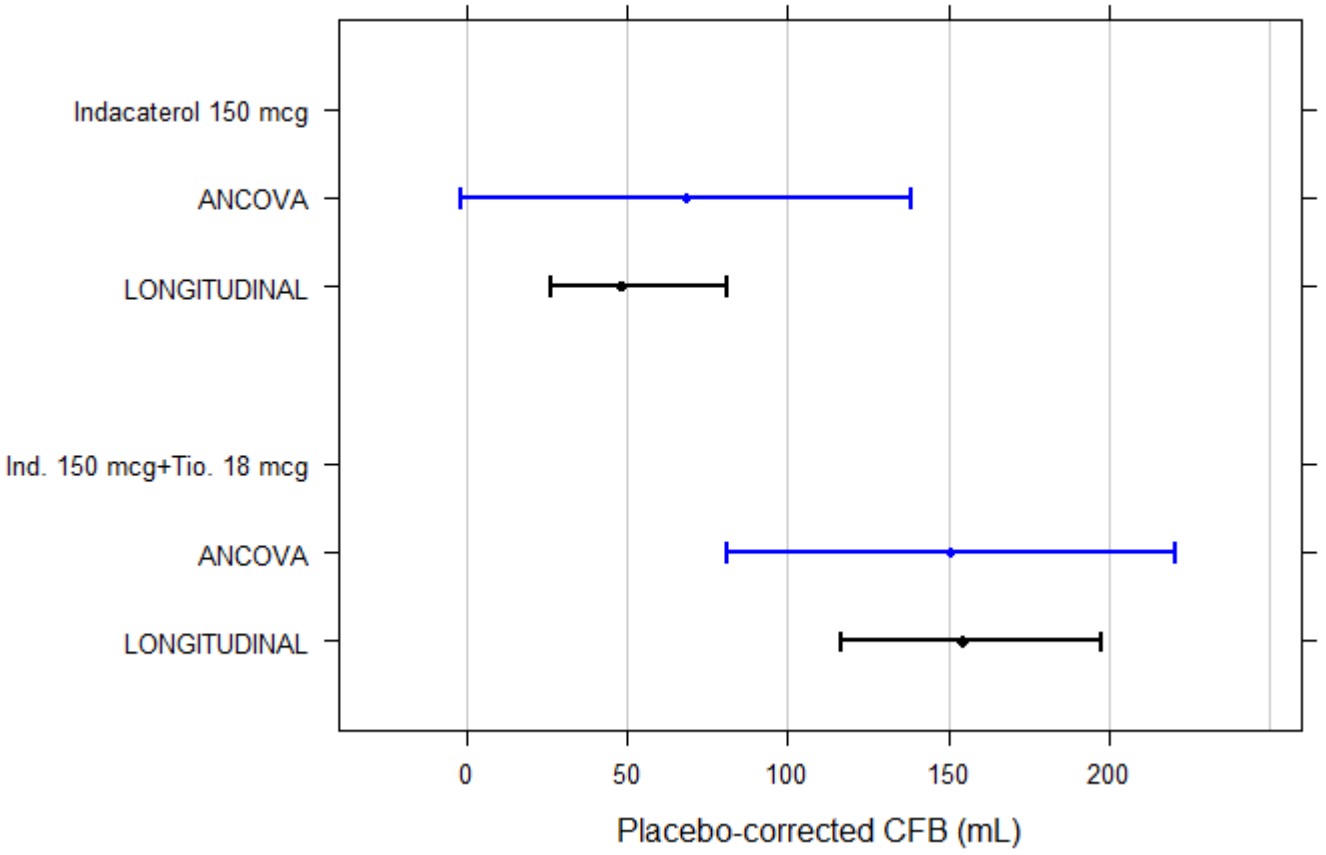
Ind. = Indacaterol

Tio. = Tiotropium

Predicted efficacy after 24 hours

Primary efficacy varable used for decision making

Mean predictions and associated 2-sided 95% CI



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

LABA developed by Pfizer: J. C. Nielsen et al., Longitudinal FEV1 dose-response model for inhaled PF-00610355 and salmeterol in patients with chronic obstructive pulmonary disease, Journal of Pharmacokinetics and Pharmacodynamics. 2012: 39:619-634.

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