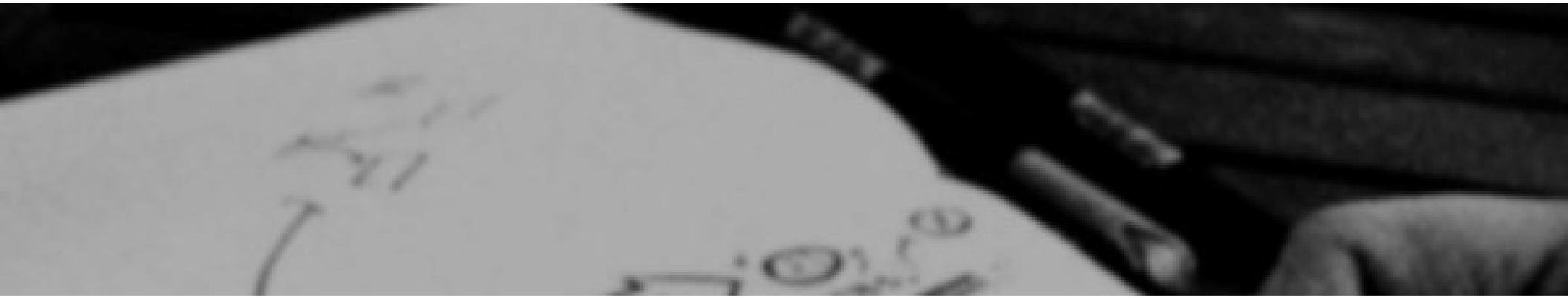
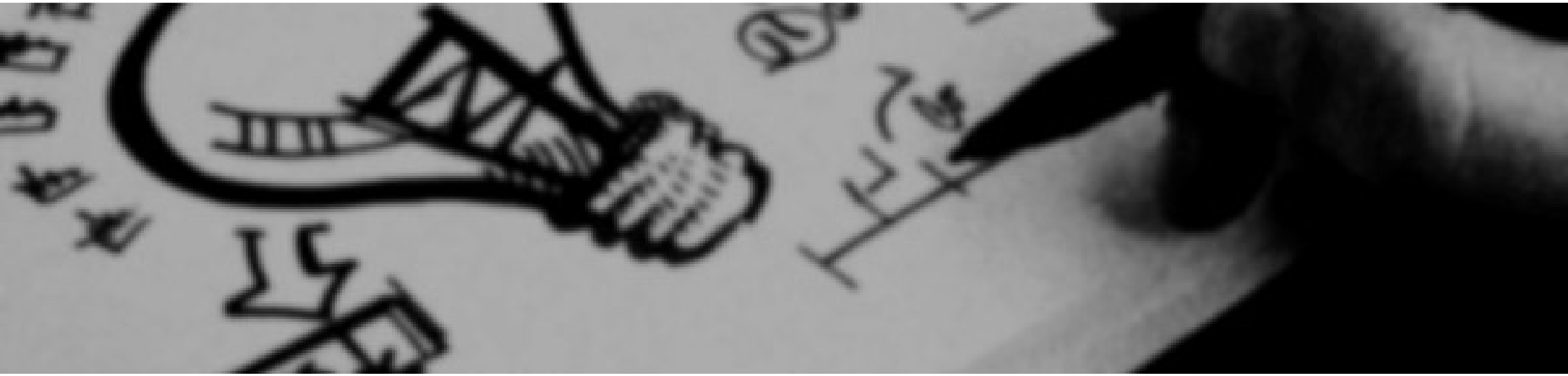


DYNAKIN

REENGINEERING THE DRUG DEVELOPMENT PROCESS



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PK modelling in pharmaceutical development

Prague 22-23 September, 2016

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Outline of the presentation

- Challenges PK analysis to support pharmaceutical development
- Summary of Population PK concepts and applications
- Examples
  - Dealing with data limitations
  - Understanding mechanisms underlying PK profile
  - Use of simulations in pharmaceutical development context

PK analysis to support pharmaceutical development

- Relative bioavailability
  - Same analysis as bioequivalence study: Cmax, AUC
  - Link observations to *in vitro*
- Challenges
  - Limited data and variability of results
  - Cmax and AUC
    - rough estimates, provide little information
    - Variables impacted by many underlying factors
    - Are not independent PK parameters
  - Importance of other criteria can be subjective
    - Analysis not standardized

PK analysis

- Individual approach
  - Non-compartmental (usual) or compartmental
    - individual and average data
  - Standard exponential equations can describe the curves (e.g. $C = Cie^{-kt}$)
- Population modelling approach
  - Studies sources of variability between individuals of a population
    - Population, not limited to sample variability
  - Define mathematical model that describes the data
  - Estimate parameters and variability
  - Assess model fit
  - Explore what explains variability
  - Assess if model fit improved based on statistical criteria
  - Can be predictive under certain conditions(if variability is characterized)

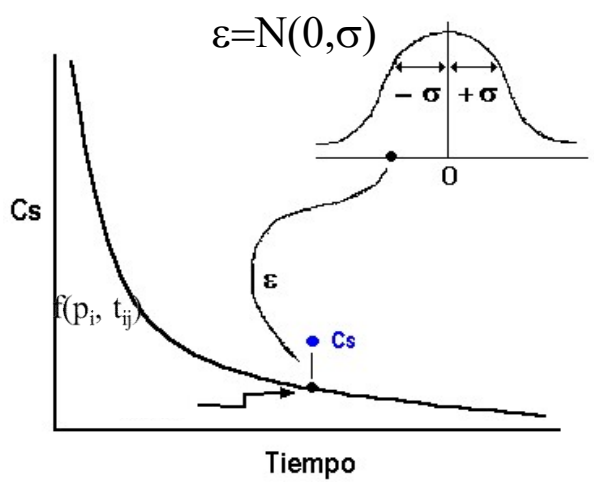
Population analysis

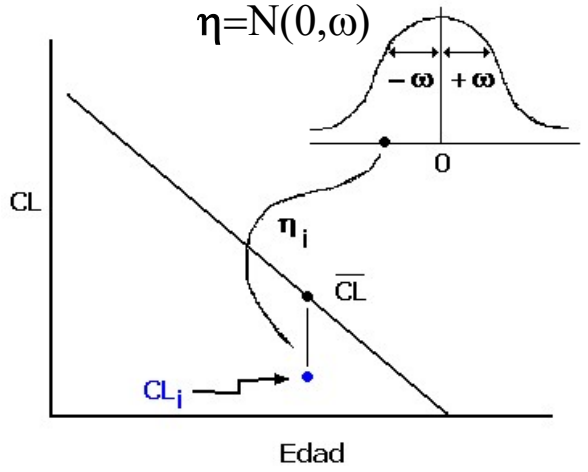
- Two modeling levels
  - Level I: $C_{p_{ij}} = f(p_i, t_{ij}) + \varepsilon_{ij}$ $\quad \varepsilon=N(0,\sigma)$
  - Level II: $p_i = \overline{p} + \eta_i$ $\quad \eta=N(0,\omega)$

f(p,t) is the structural model.

Statistical model for intraindividual variability: ε
Statistical model for interindividual variability: η
σ, ω are standard deviations

Population analysis





$$Cp_{ij} = f(p_i, t_{ij}) + \varepsilon_{ij}$$

$$p_i = \overline{p} + \eta_i$$

RESIDUAL ERROR:

-measurement errors

-model misspecification

INTERINDIVIDUAL ERROR :

-natural variability between individuals (physiology, pathology, etc.)

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Population analysis

- Requires less experimental data to be conclusive
- Can integrate data from different sources
  - Doses, study designs, populations, formulations
  - knowledge integration and knowledge gain
  - With specific considerations and within certain constraints
- Can distinguish what explains the data from random effects
  - Cl, Vd, ka, F…
  - Weight, age, co-medication, disease state…
  - Formulation effects (dissolution, PSD, others…)

Population analysis

- Potential applications
  - Compare doses/products with limited data
  - Population bridging
  - *Determine underlying mechanisms behind profile*
  - PK/PD models for formulation design for hybrids or lifecycle management
  - Simulate to steady state
  - Simulate different scenarios
    - Impact of change in ka on PK profile and average data
    - Impact of change in covariate
    - Fasting to fed conditions (if mechanism is known)
  - Model based evaluation of interactions and application to FDC

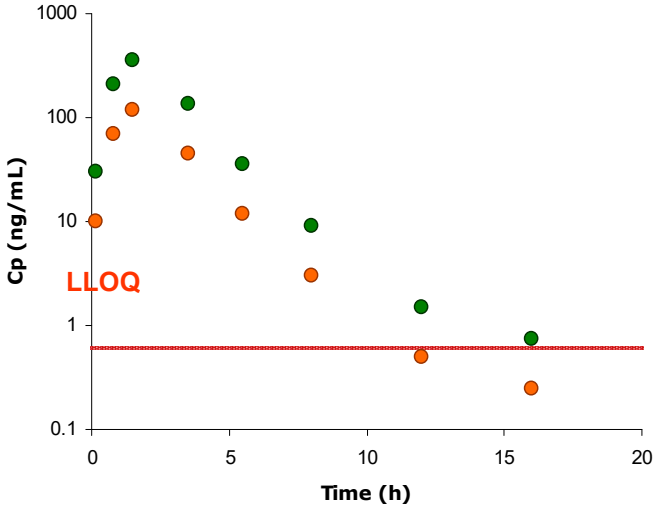
Population analysis

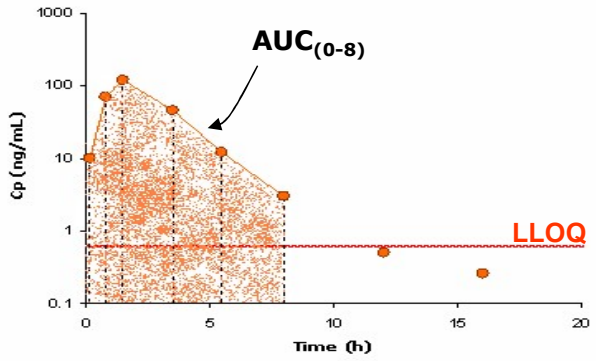
- Models are built for purpose
  - What do we want to know?
  - How certain do we need to be?
  - What are we willing to assume?

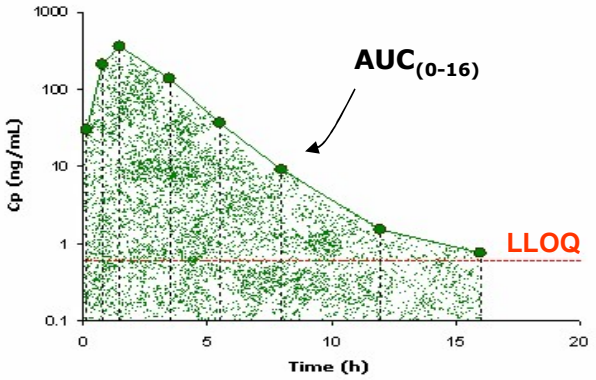
- Possibilities are a function of the quantity, quality and mechanistic understanding of data available

Example 1 dealing with data limitations

Potential applications: Example 1







What is the relative AUC_{0-t} between products?

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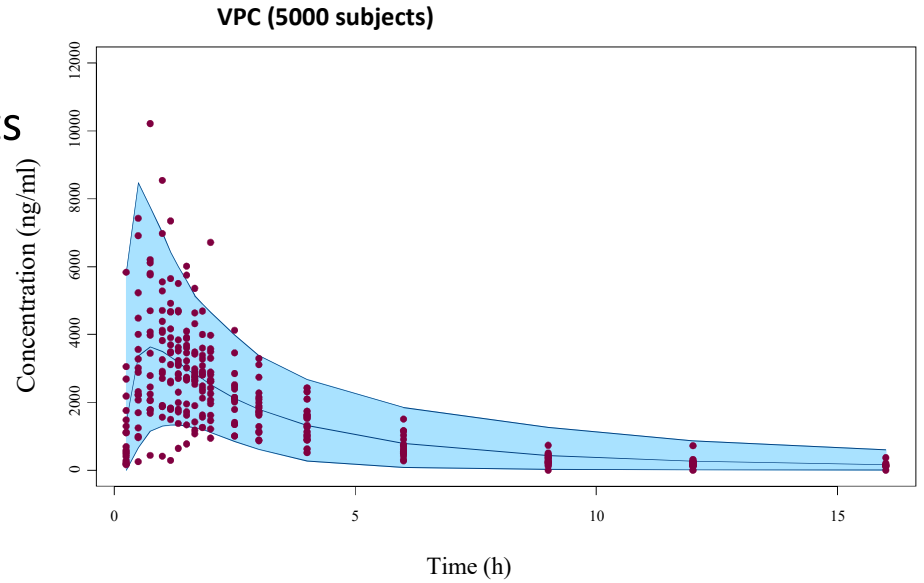
Potential applications: Example 1

- Develop and apply popPK models
  - Confirm appropriate (observations vs predictions)
  - Apply to
    - Overlay 95% CI profiles
    - Calculate $AUC_{0\text{-}t}$ (pop and ind)
    - Additionally, determine if data fits
      - Green vs orange
      - Other studies, literature
    - Explore impact on profile
      - Sensitivity analysis

        (F, ka, other)



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Example 2 understanding underlying mechanisms

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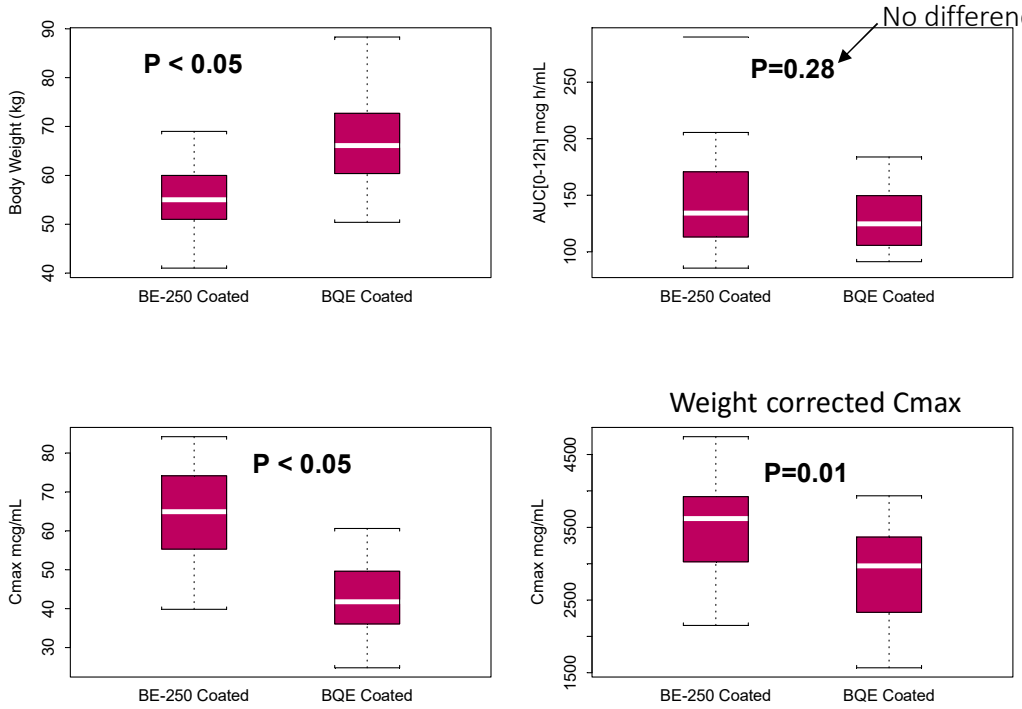
Potential applications: Example 2

- Background
  - Hybrid application, claim faster onset
  - Development of 2 test products
  - Comparison with different brands of reference
  - Two comparative BA studies (BE-250 and BQE)
    - reference data comparable,
    - Test product difference in Cmax between studies
  - Authorities concern: BE study reliable? Safety test product risks of higher Cmax?
- Approach
  - Estimate PK parameters of both studies
  - Model PK and influence of covariates
  - Use model to simulate impact of differences in key covariate and ka
  - Justify concentrations observed or extreme simulations always below safety threshold

Potential applications: Example 2

- Boxplots (red is the interquartile range and whiskers the 95% confidence)
  - p values from separate evaluation presented for informative purposes
- Weights differ between BE-250 and BQE, but AUC does not
- Weight corrected Cmax is barely significant – Weight alone explains almost all of the difference!



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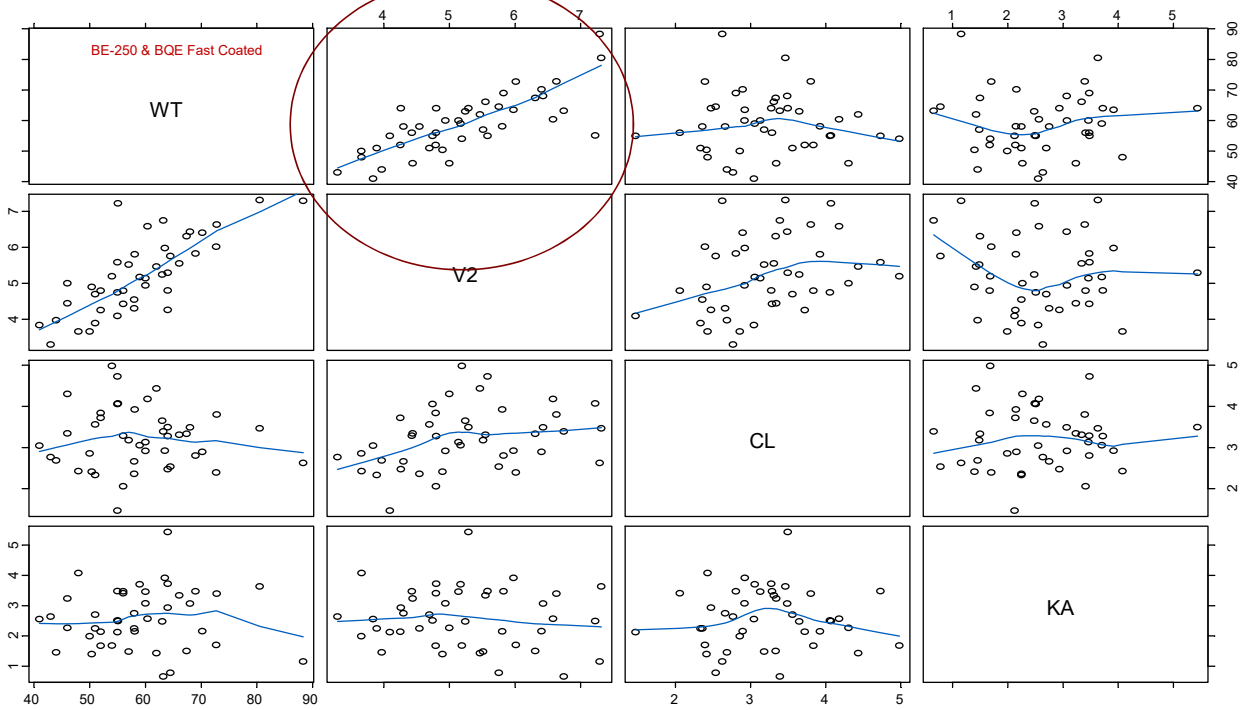
Potential applications: Example 2

- Merged BE-250 + BQE fast coated tablet bi-compartmental model developed
  - Variability in modeled V2 explained completely by WT
  - No relationship with other PK parameters
  - Only difference between studies was WT~V2



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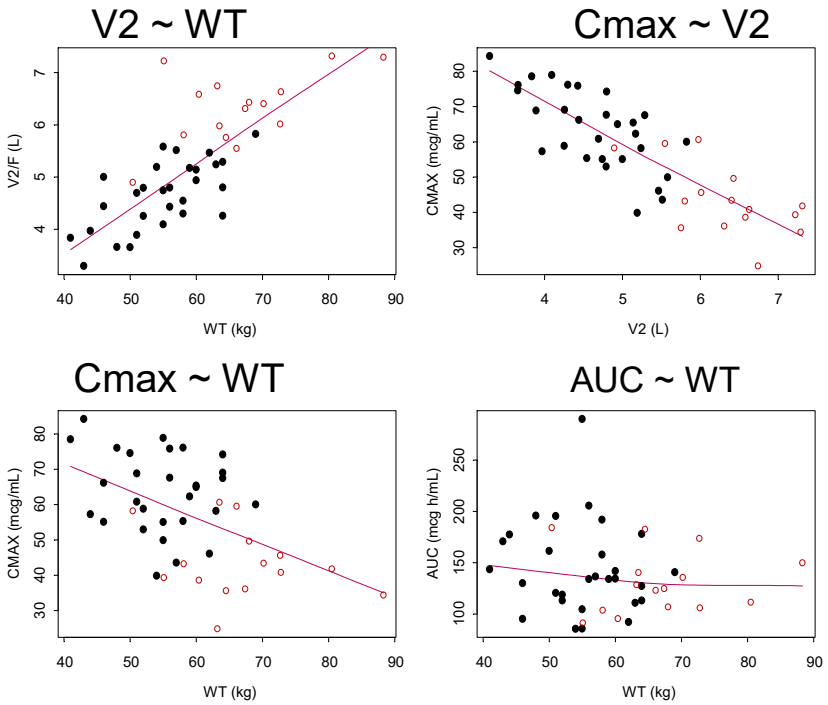
Potential applications: Example 2

- Modeled V2 explains Cmax ~ WT relation



V=5.2 + 5.2*(WT-60)*0.026

(2.6% increase in V per kg increase)

Exposure depends only on dose

Black dots are the BE-250 study

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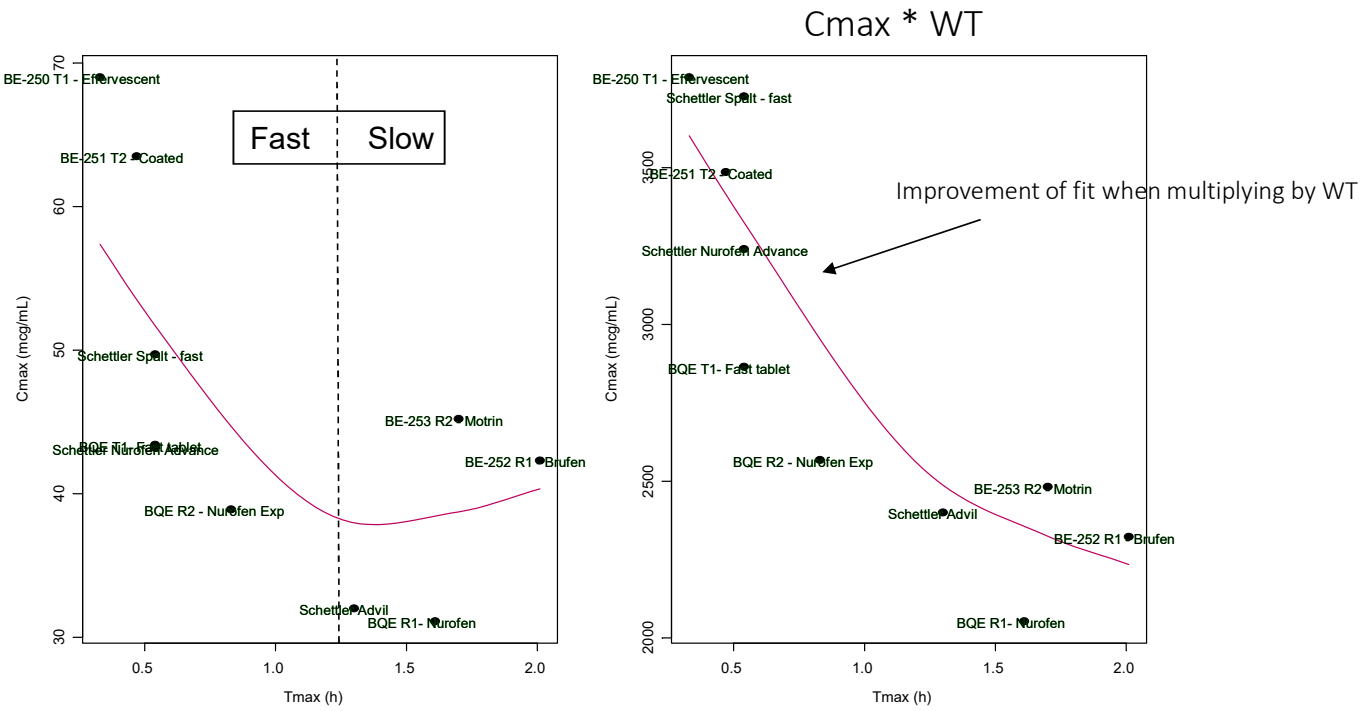
Potential applications: Example 2

- Why not the same for all formulations?



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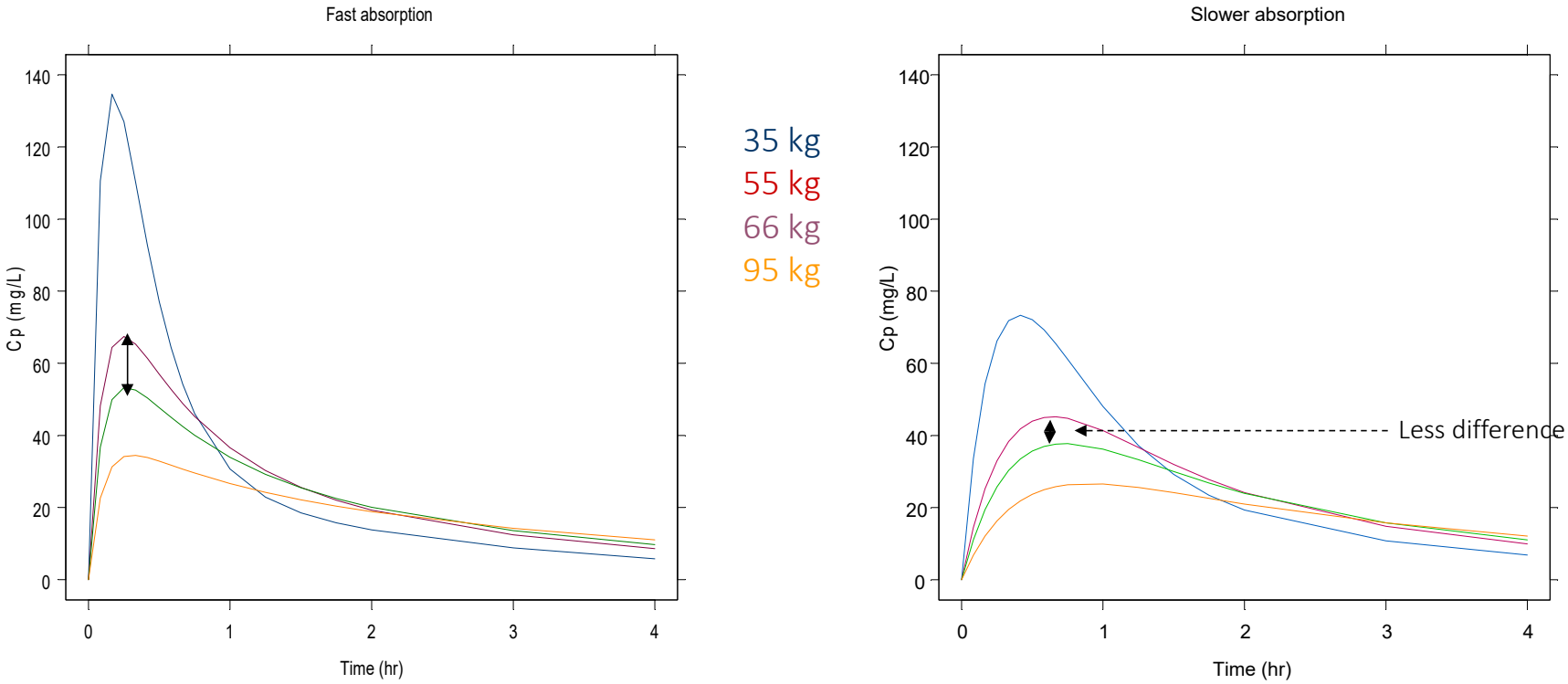
Potential applications: Example 2

- Why not the same for all formulations?



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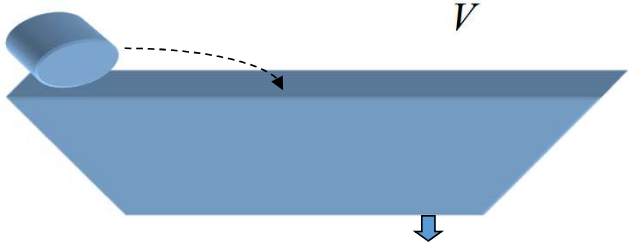
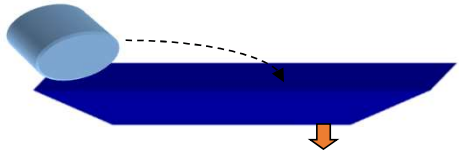
Potential applications: Example 2

- Tub is filled rapidly then at same amount (dose), the starting concentration depends on the size of the tub
- i.v ~ p.o. when ka is greater than 2 h^{-1}

$$C0 = \frac{Dose \cdot F}{V}$$

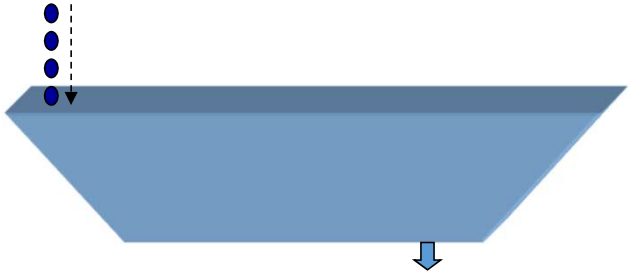


Larger volume = Lower concentration

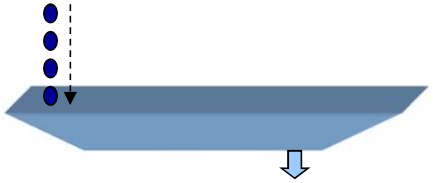


Lower volume = Higher concentration

- Tub is filled slowly then at same amount (dose), the concentration does not depend on the size of the tub to the same extent (**larger influence of ka and ke**)



Larger volume = Same concentration



Lower volume = Same concentration

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Example 3 understanding underlying mechanisms

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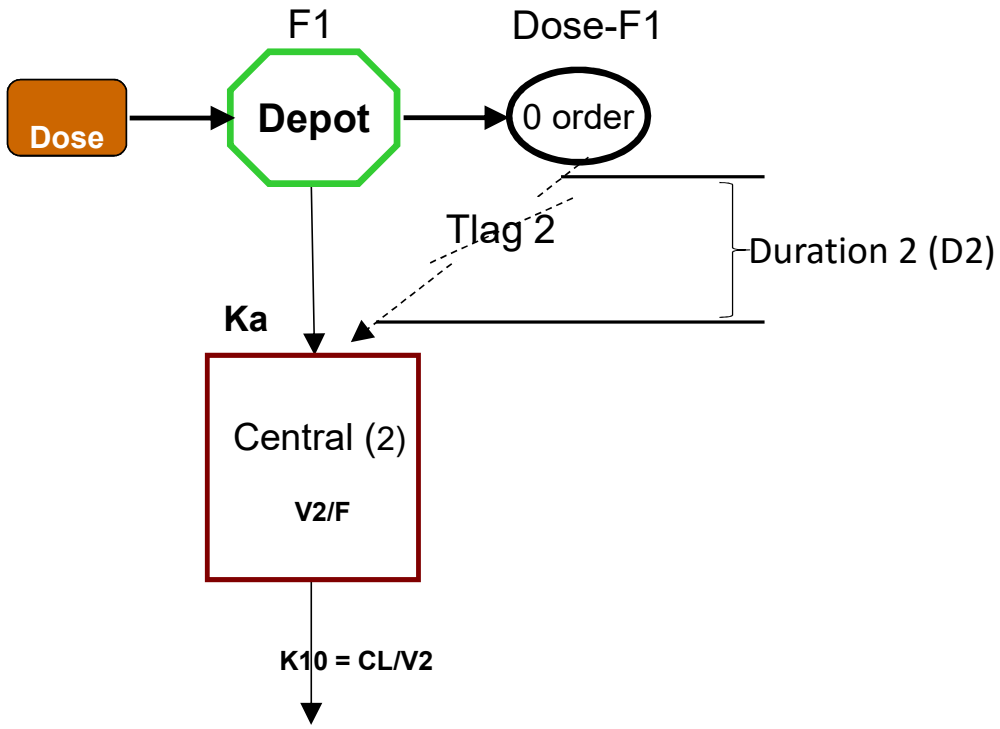
Potential application: Example 3

All results shown are true in form but all values are code-scaled

- Target: develop improved formulation of Drug Z
  - Absorption dependent on pH and solubility
  - Transporter rate limited absorption
  - BCS class III/IV
- In-Vivo and in-vitro data available for 2 tests and one reference product
- In-Vivo convolution method applied ("IVc-PK" model)
  - Modeled from the PK in simultaneous fitting of both dissolution and ADME
  - In vivo absorption PK appears highly complex with multiple peaks
  - Physiological rates of absorption that are both 1st and 0th order combined
  - Concentration dependent transporter saturation

Potential application: Example 3

- Fraction of dose F1 for the 1st order process (ka)
- Remaining dose (Dose-F1) absorbed after a tlag by 0 order (saturated transport)



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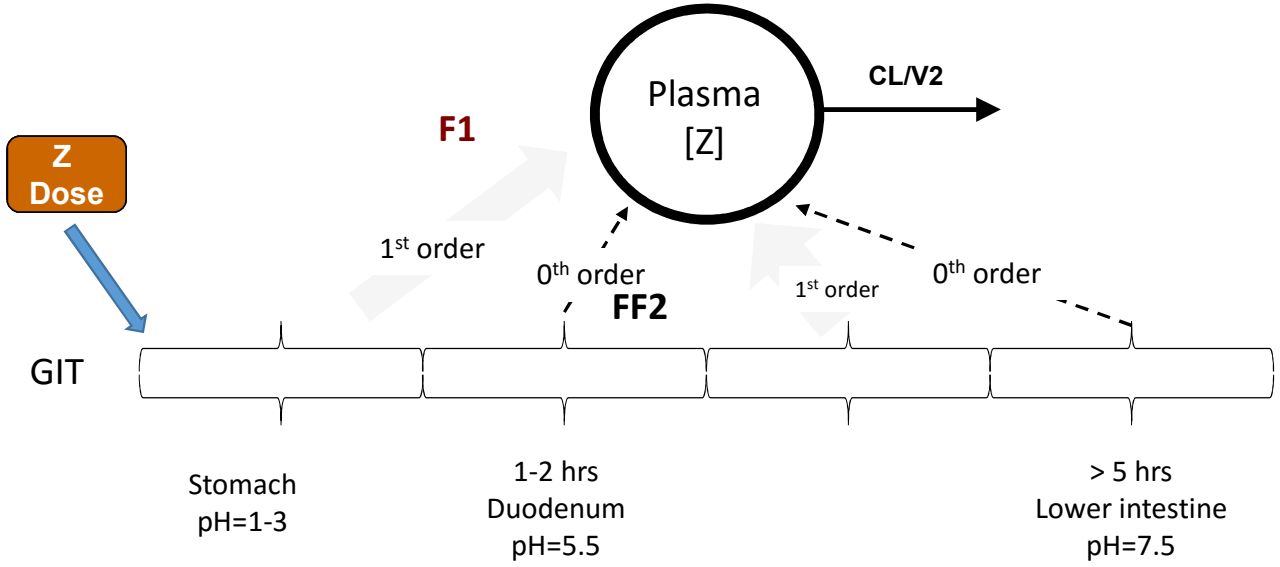
Potential application: Example 3

- Sequential absorption for mono compartmental structure; specific sites of absorption
- Both 0th order processes proceed in parallel (both initiate at 1.3 hours after dose intake)
- Majority of the dose is absorbed prior to saturation (1st order) across the GIT
  - Includes convolution for two in-vivo Weibull dissolution rates (at the transport sites)
  - F1, fraction of dose going to 1st order process (1-F1 goes to the two 0th orders)
  - FF2 proportion reduction in the dose going to the 1st 0th order process



- The model adjusts the position of the arrows and the rates simultaneously
- pH corresponds with time

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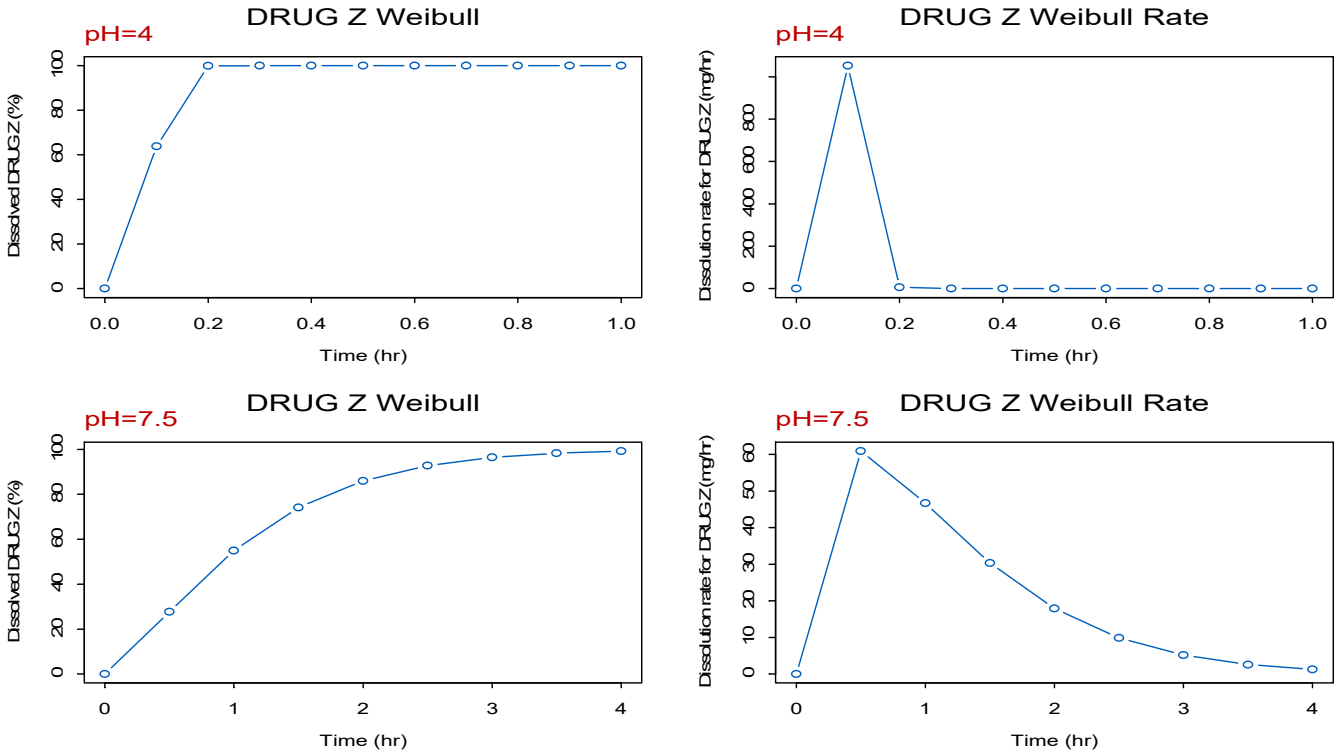
Potential application: Example 3

- Model IVc-PK estimated Weibull absorption profiles and rates at two pH



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Potential application: Example 3

- Custom NONMEM code used for IVc-PK model

```
$SUBROUTINES ADVAN6 TRANS1 TOL=5
$MODEL
 NCOMPARTMENTS=2 NPARAMETERS=11
 COMP=(DEPOT DEFDOSE)
 COMP=(CENTRAL DEFOBS)

$PK
 TVKA  = THETA(1)
 KA    = TVKA*EXP(ETA(1))
 TVCL  = THETA(2)
 CL    = TVCL
 TVV2  = THETA(3)
 V2    = TVV2

 FF    = THETA(4)*EXP(ETA(2))
 FRAC  = THETA(5)*EXP(ETA(3))
 F1    = FF*(1-1/(1+FRAC))
 F2    = FF*(1-F1)

 FRA2  = THETA(6)*EXP(ETA(4))
 FW1   = F2*(1-1/(1+FRA2))
 FW2   = F2*(1-FW1)
 BET1  = THETA(7)
 ALP1  = THETA(8)
 BET2  = THETA(9)
 ALP2  = THETA(10)
 TIM1  = THETA(11)*EXP(ETA(5))
 TIM2  = THETA(11)+THETA(12)

K = CL/V2

 S2  = V2/1000

 IF(TIME.EQ.0.AND.CMT.EQ.1)DOSE=AMT

$DES
WR1=0
WR2=0
IF(TIME.GE.TIM1)THEN
 TT=TIME-TIM1
 WR1 = FW1*DOSE*(BET1/ALP1)*((TT/ALP1)**(BET1-1))*EXP(-(TT/ALP1)**BET1)
ENDIF
IF(TIME.GE.TIM2)THEN
 TT=TIME-TIM2
 WR2 = FW2*DOSE*(BET2/ALP2)*((TT/ALP2)**(BET2-1))*EXP(-(TT/ALP2)**BET2)
ENDIF
GUT = A(1)
DADT(1) =-KA*GUT-WR1-WR2
DADT(2) = KA*GUT+WR1+WR2-K*A(2)

$ ERROR ….
```

Parameters characterizing the profile of Weibull absorption

Maximum amount dissolved a (complex) function of bioavailabilities and F1 fraction

"Alpha" = time scale (Alpha = 0.1 for pH>5; Alpha = 0.43 for pH>6.8)

"Beta" = shape parameter (Beta = 2.96 for pH>5; Beta = 1.1 for pH>6.8)

"TI"=Time of initiation of absorption at each pH

TI = 1.6 hr for pH > 5

TI = 1.8 hr for pH>6.8

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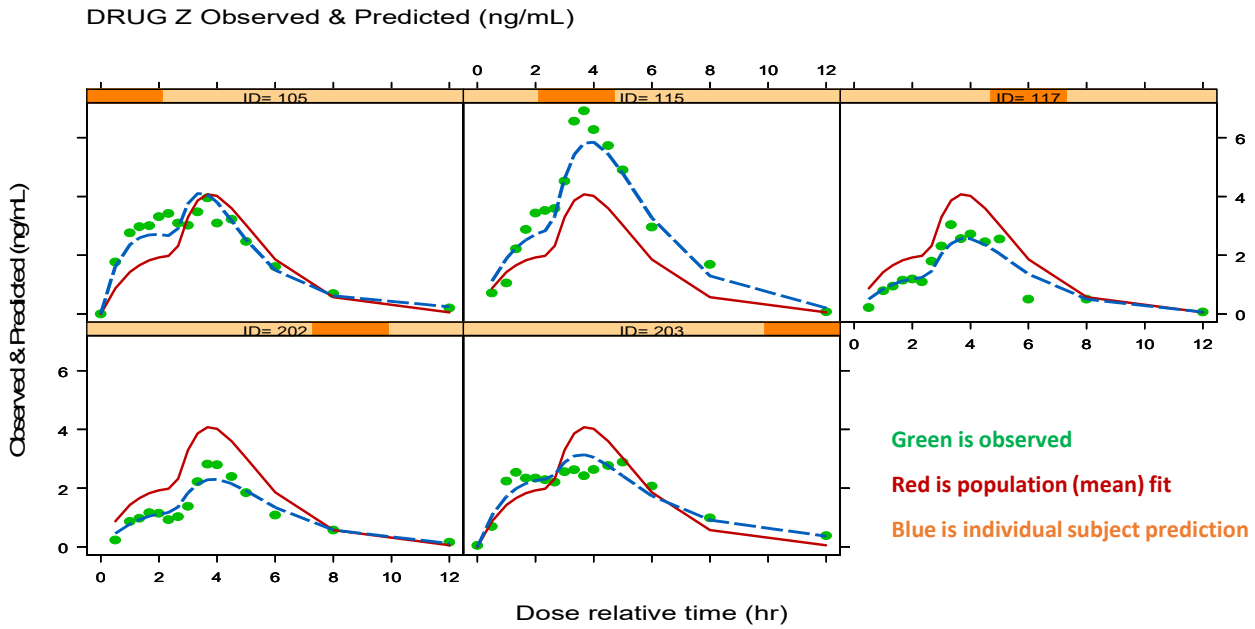
Potential application: Example 3

- Model predictions vs. observed



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Potential application: Example 3

- *In-vivo* expected dissolution is estimated using different pH and times
- Direct correlation with the *in-vitro* profiles
- % of dose absorbed by 0 order different for initial tests and reference
- Formulation can be designed to meet specifications for the desired *in-vivo* PK

- Results of subsequent pilot study fit with modelled expectations

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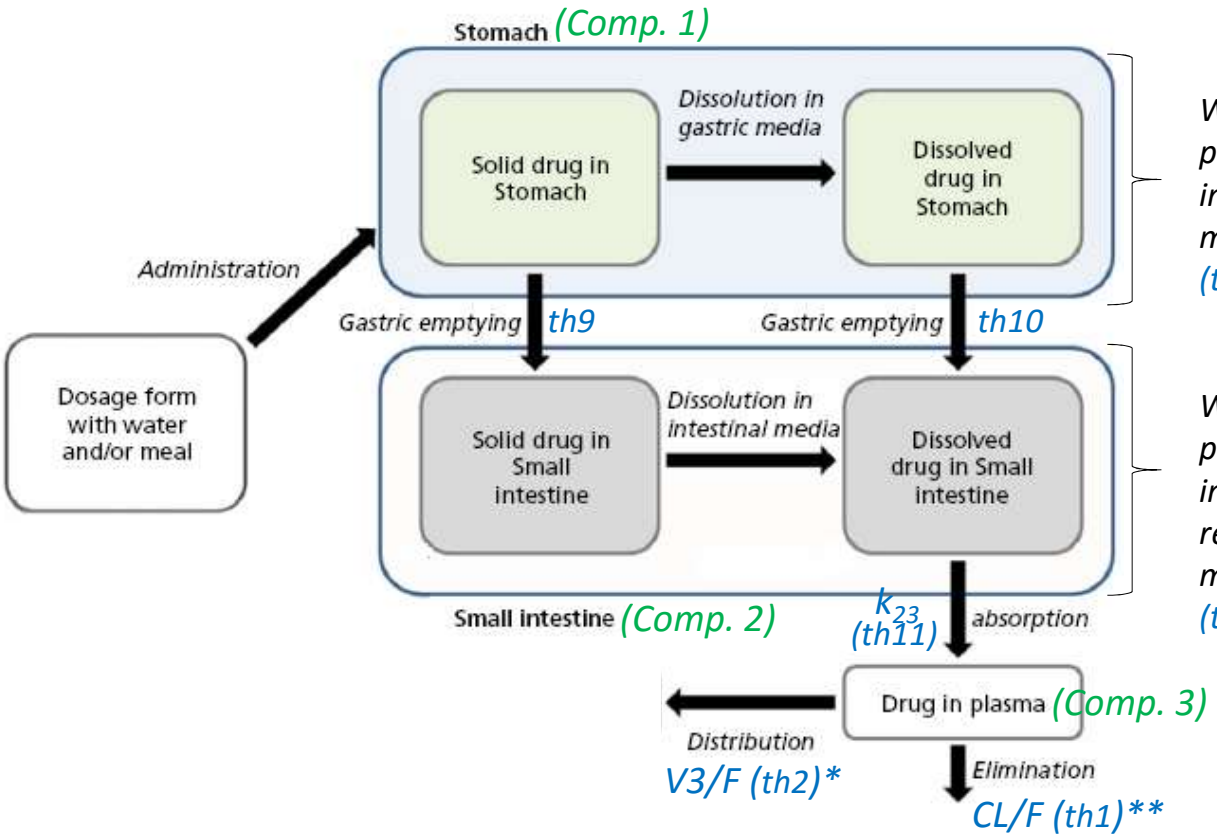
Example 4 understanding underlying mechanisms

- IVIVc two-dissolution-site model– structural model adapted from Otsuka et al. (2015)



* In this case PK best described by one-comp 1st order absorption model

** F (systemic bioavailability after oral administration) is estimated as an additional model parameter I.V. from literature

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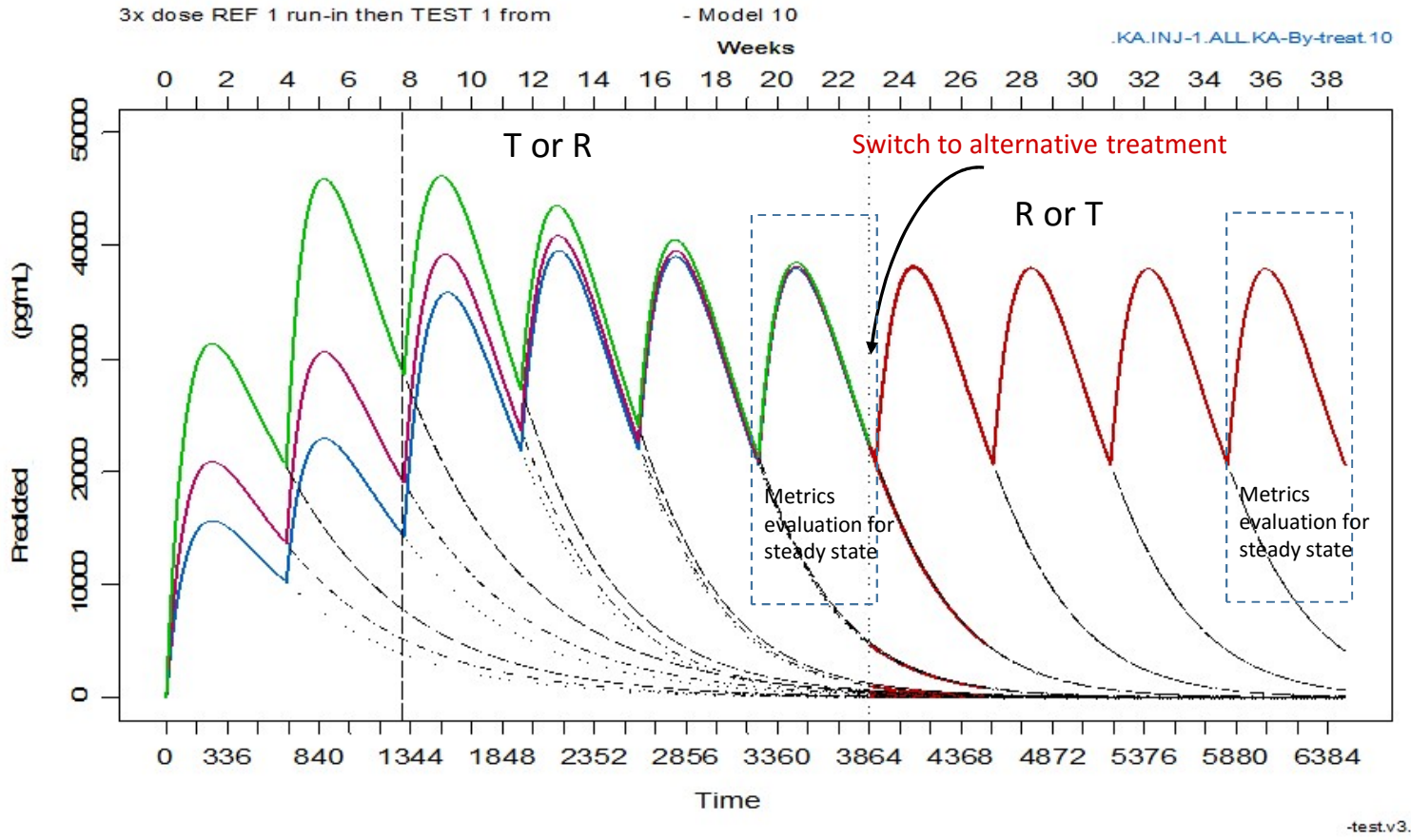
Simulations

Simulations

- Develop and validate popPK models
- Simulate effect of changes in parameters
  - How does a change in ka affect the profile
- Simulate different study possibilities
  - SS with different run-ins (e.g. patient studies)
  - Parallel designs with un-even covariates (e.g. co-medications)
- Different approach depending on use of simulation
  - Simulate single population profile
  - Simulate T and R 95 %CI overlay (e.g. n of 5000)
  - Use population samples to simulate several studies (e.g. 100, 1000, 10^6)

- Theoretical PK of multiple dose with cross-over and different dose run-ins



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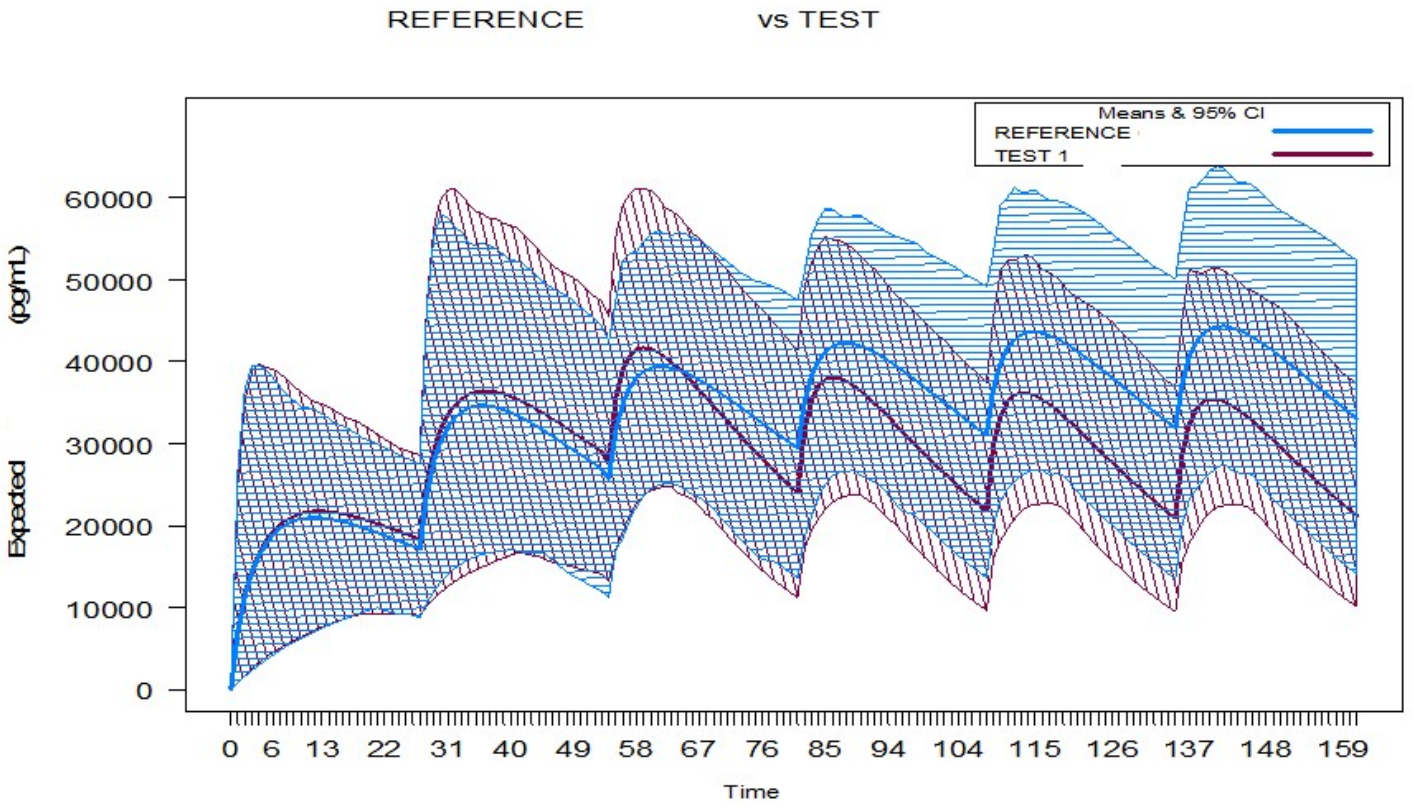
- Steady state simulations using final complete model
  - *Running* period: 2 doses of X mg, Y mg or Z mg, REFERENCE product. (patient proportion 4:3:1)
  - Study Period: 4 doses of Y mg, REFERENCE or TEST 1



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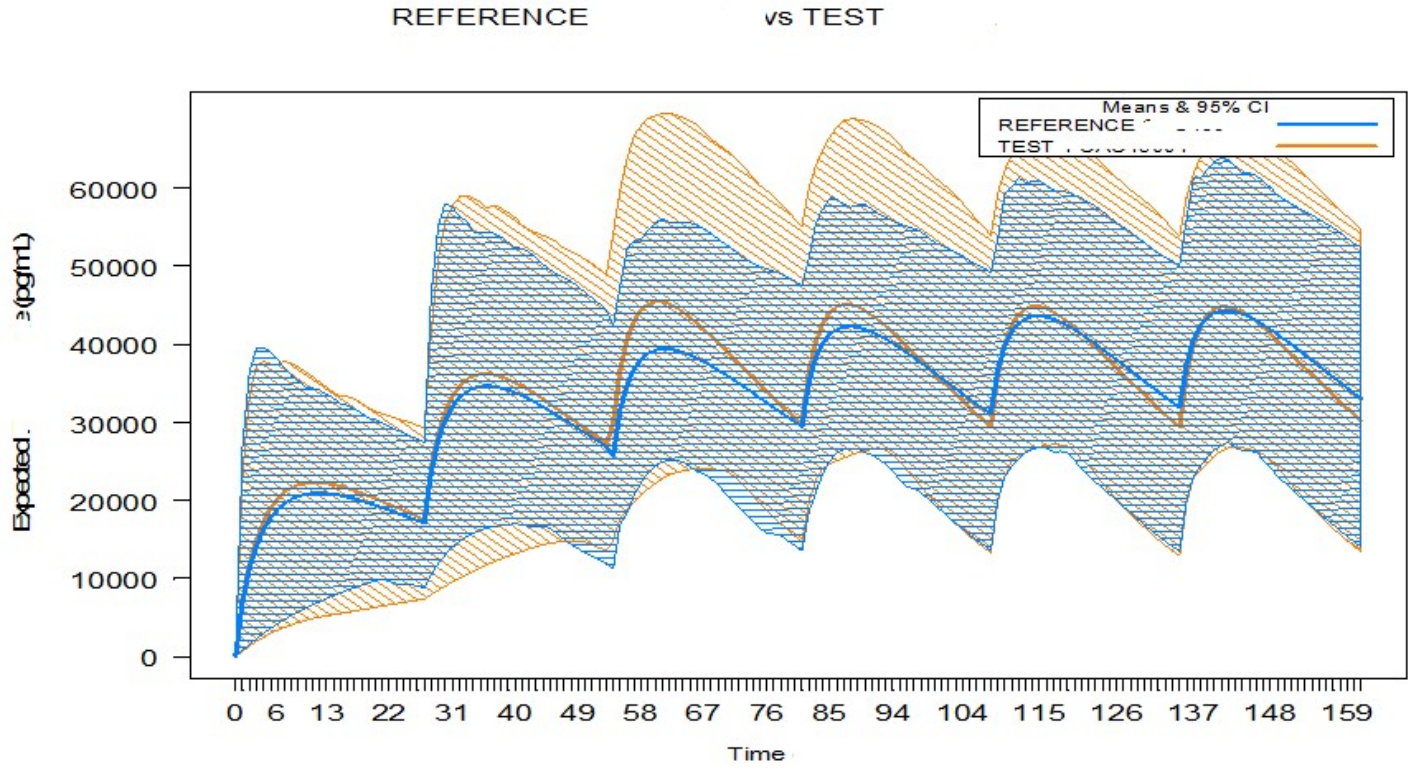
- Steady state simulations using final complete model
  - *Running* period: 2 doses of X mg, Y mg or Z mg, REFERENCE product. (patient proportion 4:3:1)
  - Study Period: 4 doses of Y mg, REFERENCE or TEST 2



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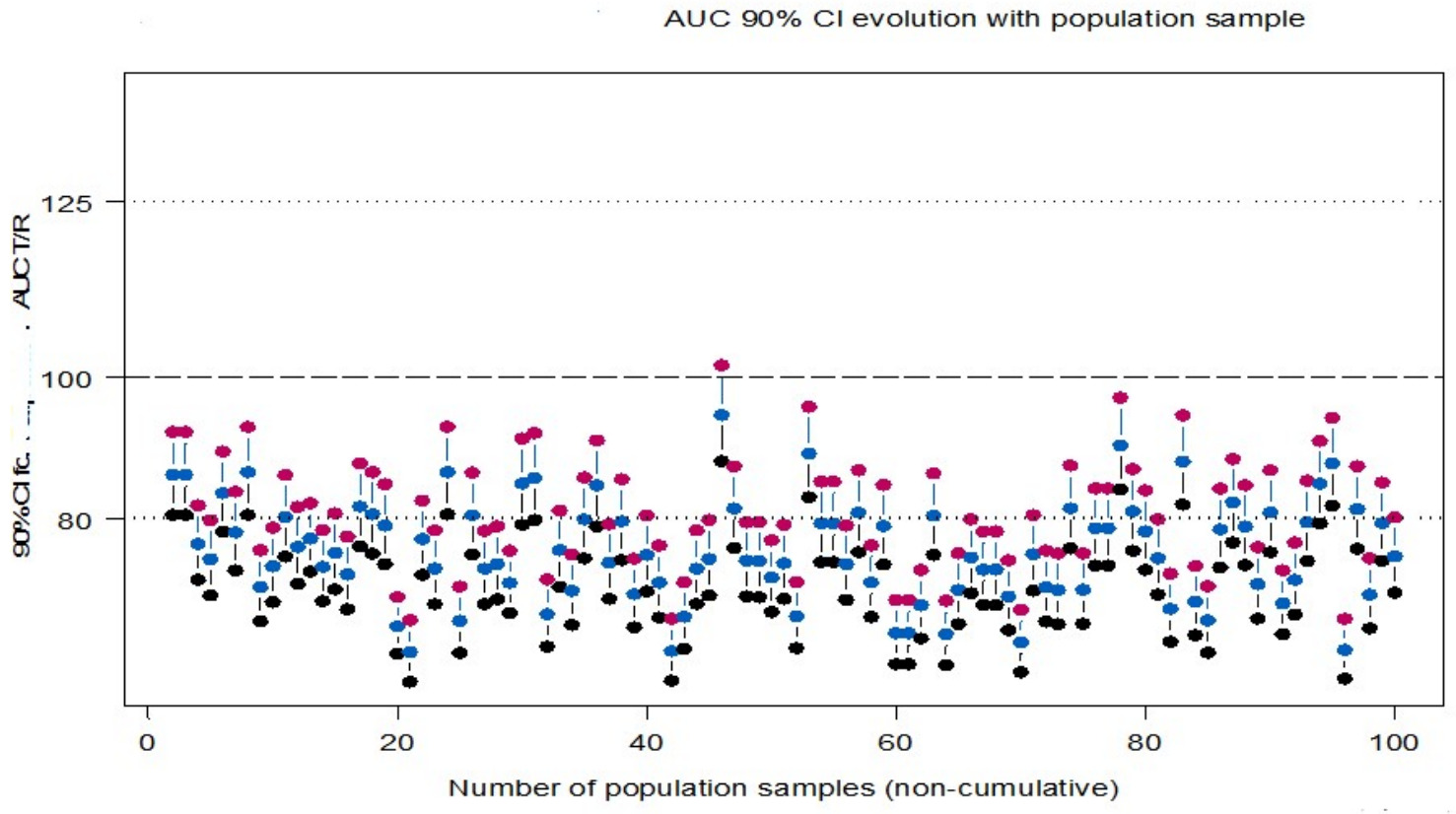
- Simulation of multiple studies
  - AUCss
  - Test 1/ Reference



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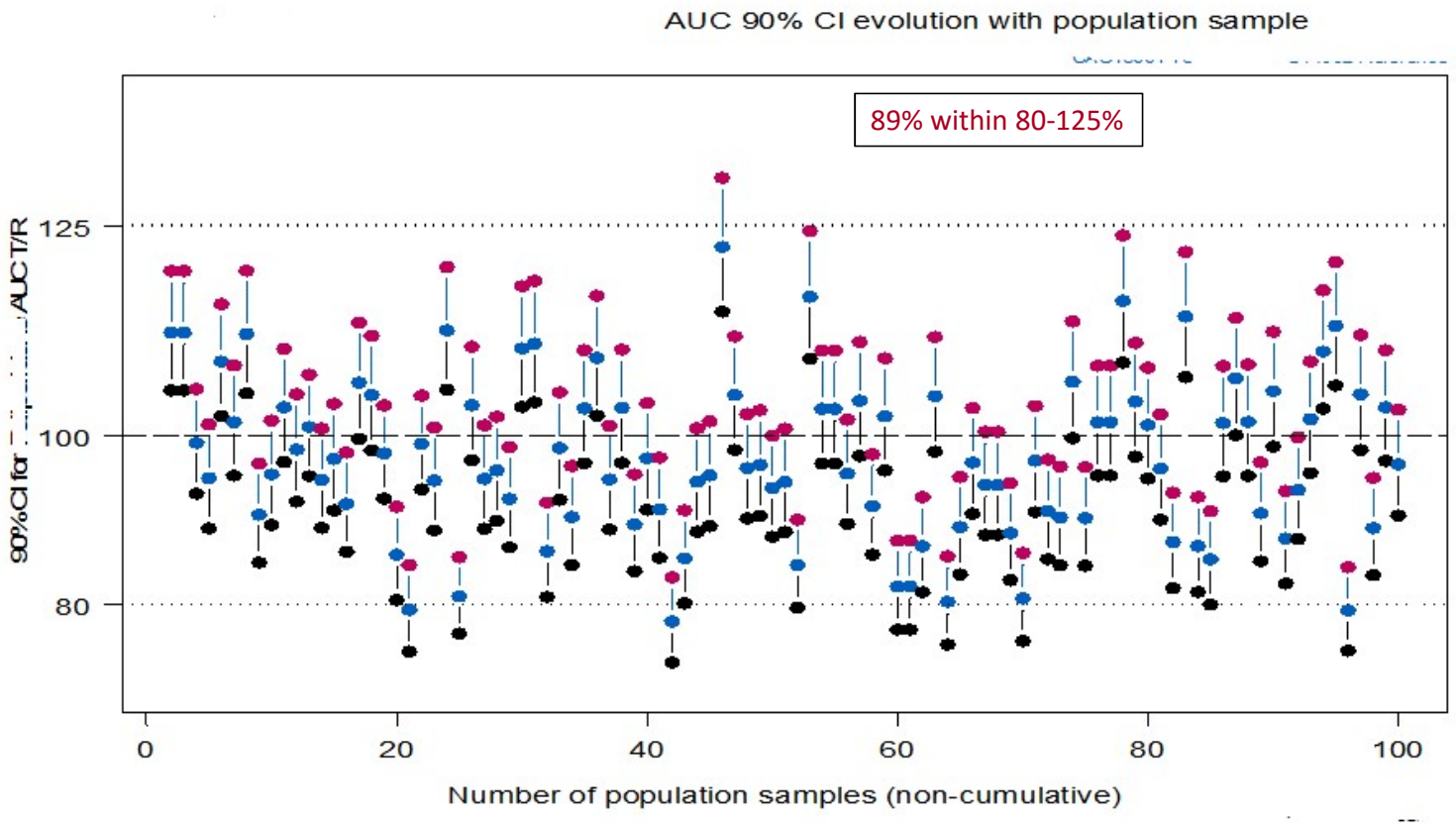
- Simulation of multiple studies
  - AUCss
  - Test 2/ Reference



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Concluding points

- Pop PK methods are a complementary tool for pharm development
  - Can use standard experimental data (e.g. pilot, dissolution,etc.)
  - Descriptive model to understand processes behind observations
  - Distinguish what can be explained (fixed) from what cannot (random)
  - Can test if data fits with galenical hypothesis

- Pop PK simulations supplement risk assessments
  - Simulate what would happen if
    - Different study design, larger sample size,….
    - 100, 1000, 10^6 BE studies were conducted
    - Change in formulation *within studied frame*

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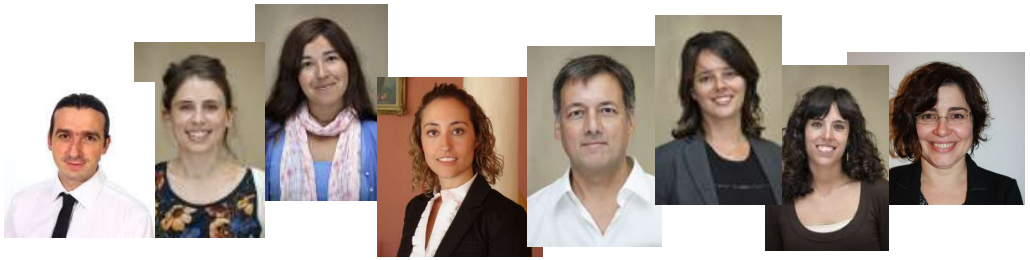
Thank you for your attention!



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