Model Integrated Equivalence for BE Assessment of Long Acting Injectables: *In Silico* Continuation to Steady state

Best Practices for Utilizing Modeling Approaches to Support Generic Product Development

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Model Based BE for LAI

Plan

- Background presented in last year presentation of November 2021
- PK approaches for LAI and Types of model-based BE
  - In silico continuation BE
  - Virtual BE
- Examples of LAI and Model-Based BE programs using *in silico* continuation (not "virtual BE")
- Program steps
- Validation of PPK models
  - Of the individual fit, necessary for "in silico continuation"
  - Of both individual fit & population predictions, necessary for "Virtual BE"
- Current main issues
- Conclusions

Model Based BE for LAI

Other types of products where it is useful

STATE OF THE ART

Table 2 Situations in which model-based bioequivalence assessment should be advantageous or prioritized

Scenarios	Examples	Advantages
Drugs with complex PKs that may violate assumptions of NCPT analyses: • Nonlinear PK • Not eliminated from the sampling compartment • Endogenous homeostatic feedback mechanism	• Drugs with nonlinear PK and/or those that are not eliminated by renal excretion or hepatic metabolism (e.g., iron products)[67] • Endogenous products with an unstable baseline due to homeostatic feedback mechanisms (e.g., Levothyroxine in healthy volunteers) or with high baseline values relative to the observed C_{max}	Model directly incorporates and addresses characteristics that are not related to the formulation performances allowing a more robust assessment of BE. In the case of iron products, this approach seems to require a much lower sample size compared to NCPT analysis[67]
Biosimilars	• Peg-filgrastim • Rituximab • Adalimumab	• Model can help identify PK differences that could be due to the formulation and/or to the biologic. • Model should allow better interchangeability assessment[71]
Study population does not allow extensive blood samples to be collected	• Pediatric studies • Patient studies[66]	Allows study to include fewer samples, and at various times after dose administration (do not need to be either after single dose or at steady state)
Systemic drug exposure not detectable	• Extremely low bioavailability drug and/or analytical limitations (e.g., alendronate sodium in the past)[63,65] • Product for which PD parameters can be obtained without corresponding PK data[60,64]	Differences in formulation performances can be extracted from another medium (e.g., urine) or with PD measures only[60]
Topical, locally acting dermatological products besides corticosteroids	• Skin stripping data[65]	Comparison of rate and extent of exposure at the site of activity (skin) can be obtained, circumventing the need for large and indiscriminative equivalence studies with clinical end points
Complex modified release products	• Long-acting modified release products, including injectables • Multiphasic modified release products • Transdermal formulations (e.g., nitroglycerin)[57,58]	The diverse release mechanisms can be compared between two formulations, robustly differentiating them from behavior that is drug related
Situations where sample size needed to pass equivalence limits (e.g., 80–125) would be unfeasible for an ethical, financial and/or technical reason	• Clinical equivalence study with variability in clinical end point response that is too high	Using smaller sized clinical study(ies), simulations of studies with different and greater sample sizes could be used for equivalence assessment

BE, bioequivalence; C_{max}, peak plasma concentration; NCPT, noncompartmental; PD, pharmacodynamic; PK, pharmacokinetic.

scenarios proposed in **Table 2**, model-based approaches have already shown their usefulness.[60]

HOW TO ASSESS BIOEQUIVALENCE USING MODEL-BASED APPROACHES?

The essence of this approach, when it applies to drugs that act systemically, consists in the development of a population PK model that simultaneously fits data from both test and reference products. Model parameters related to formulation performances, such as absorption rate constants (Ka_{test} and Ka_{ref}) and a relative bioavailability parameter (F_{rel}), would be fitted to allow differences in rate and extent of exposure, whereas all other model parameters describing the drug's systemic processes such as distribution and elimination (volumes of distribution and clearances) would be identical for both formulations. The model parameters that are indicative of formulation performances can then be compared statistically in a manner analogous to the comparison of the AUC and C_{max} metrics with ln-transformed T/R ratios and 90% CIs. Finally, as mentioned earlier, the model-based results also in terms of fitted or predicted C_{max} and AUCs can then be subjected to the same statistical comparisons.

The use of K_a as a potential end point for assessing bioequivalence is interesting because it is purely representative of the absorption rate. In contrast, as explained previously, C_{max} derived by NCPT analysis is a function of various processes, therefore, it does not only reflect rate. However, the K_a on its own may be a parameter that is too discriminative for bioequivalence comparisons. **Table 3** presents potential metrics for bioequivalence that could be used for different types of systemically acting products and compares them to metrics that could be determined by NCPT methods. As previously noted, K_a can sometimes be too discriminative as a bioequivalence metric, and it should, therefore, be considered in conjunction with the fitted or predicted C_{max}.

Figure 2 illustrates potential bioequivalence metrics for different types of products and for various approaches. Parameters that could be compared to assess bioequivalence are those in red, and parameters in green represent product-specific parameters that may or may not be different for each formulation.

- Liposomal products

- Oncology products administered via different dosing cycles

- Implants that deliver active ingredient over a very long time

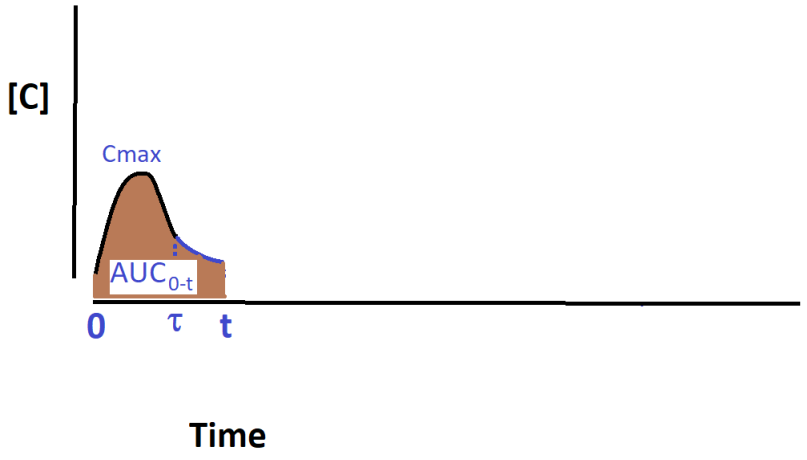
Ref.: Seng Yue C, Ozdin D, Selber-Hnatiw S, Ducharme MP. Clin Pharmacol Ther 2019;105(2):350-362.

Model Based BE for LAI

PK Methodologies

Noncompartmental ("Observed" PK)

- "observed" Cmax
- "Observed" AUC_{0-t}
  - Only fitting is kel (or λz) leading to calculation of AUC_{o-inf}



Big Issues with LAI SD PK studies

- Often in Patients: impossible to find a sufficiently large number of them starting therapy within a moderate time frame
- Parallel design as once therapy is started, it cannot stop (no washout possible). Sample size becomes HUGE (>200) as driven by Inter-CV and not Intra-CV

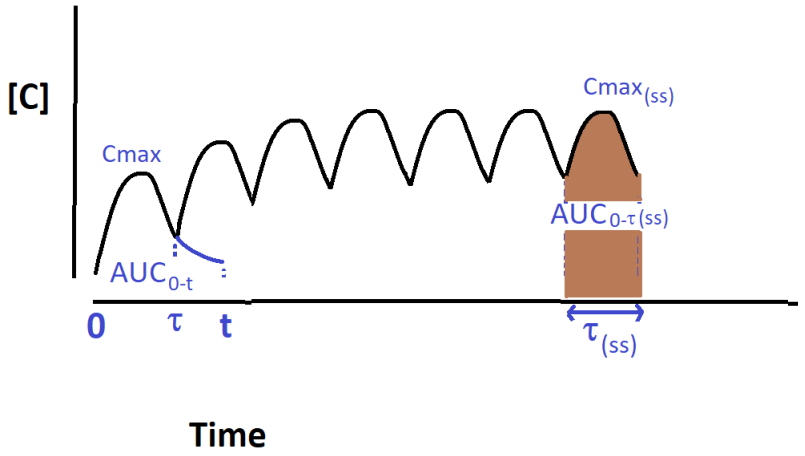
→ Almost Impossible to do SD studies

Model Based BE for LAI

PK Methodologies

Noncompartmental ("Observed" PK)

- "observed" Cmax(ss)
- "Observed" $AUC_{0-\tau\,(ss)}$



Big Issues with LAI SS PK studies

- Need to demonstrate SS achievement. It may t
  to 2 years for some products
  - Parallel: huge sample size (>200)
  - Crossover: need to allow time for sufficient washout while on other therapy and then attain SS again. Study duration may be 3-5 years without even being able to replicate treatments and allow SABE....

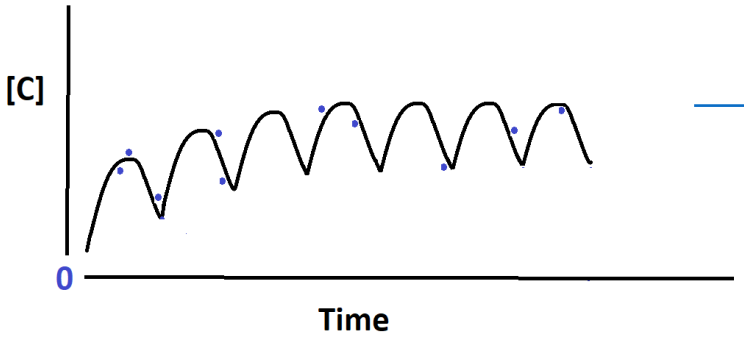
→ Almost Impossible to do SS studies as well

Model Based BE for LAI

PK Methodologies

Population PK ("Fitted" PK)

- Can use data at any time
- Once the data is fitted to a PPK model, you can....

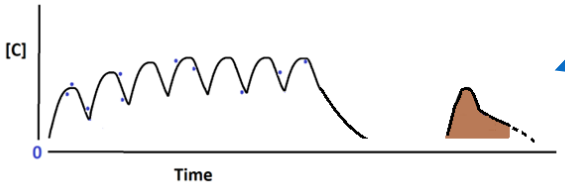


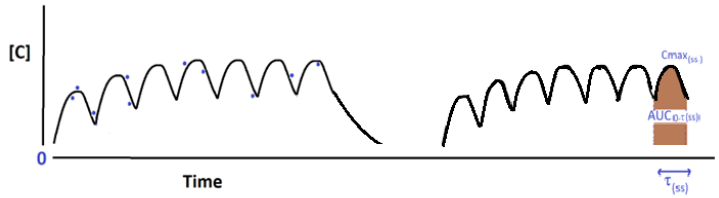
PPK model

Indiv. PK results

Pop. PK results

"continue" dosing *in silico* in the same patients





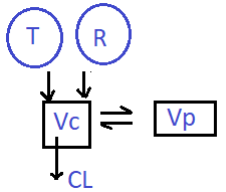
Or, create new patients and simulate "Virtual" studies ("Virtual BE")

Model Based BE for LAI

Results from a PPK analysis

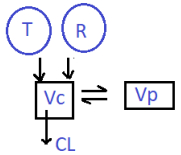
A PPK analysis gives the following sets of results

- Individual fitted results
  - Whether the analysis is conducted with FOCE (NONMEM) or EM (ADAPT5, Monolix, Certara NLME) algorithms, the individual fits are conducted with MAP, and do not have to follow at all the population part of the model, only its structure.



Individual fits

- Population PK results
  - These may or may not follow the individual fitted results. For them to be predictive, the PPK model HAS to include covariates.



Population predictions

- Residual variability
  - This is what is unexplained by the model. Similar to “noise”

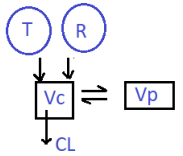
Ref.:
Colucci P, Seng Yue C, Ducharme MP. Chapter 20: Applications of software packages in pharmacokinetics. In: Ducharme MP, Shargel L, eds. Applied Pharmacokinetics & Pharmacodynamics. McGraw Hill, 2022.
Ducharme M, Ponomarchuk O, Bakir D, Ozdin D, Shargel L. Chapter 30: PK and PD in Clinical Drug Development. In: Ducharme MP, Shargel L, eds. Applied Pharmacokinetics & Pharmacodynamics. McGraw Hill, 2022.

Model Based BE for LAI

Two main types of Model-Based BE

1) Continuation "in silico" of dosing to the exact same patients for which we have clinical data, using a standard, conservative and conventional design
   1) BE based on actual clinical patient data
   2) Validation is simpler as one needs to only show that the individual fits are appropriate, not the population part of the model that would be used for simulations
   3) Needs a clinical sample size that will result in 80 or 90% power

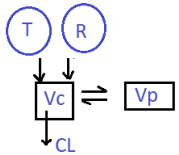
Using a PPK model



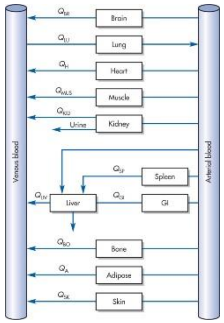
Individual fits

2) Virtual BE (e.g., 1000+ BE studies simulated with simulated patients)
   1) Need a PPK model that is validated for this purpose
   2) In practice, very difficult to validate. A model is never perfect, and often can be very far from being perfect for these complicated drug products.
   3) Clinical sample size can be smaller than the ones needed for 80/90% power

Using a PPK or PBPK model



Population predictions



Model Based BE for LAI

Long-Acting Injectables (LAI) examples

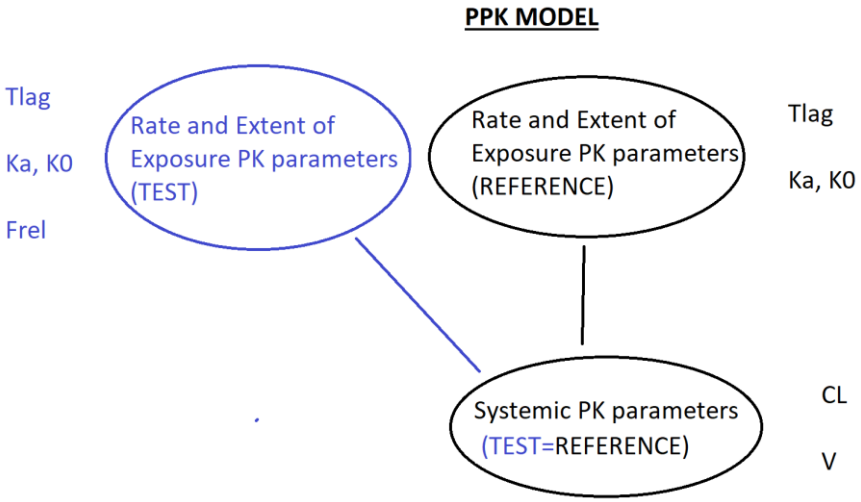
Product	STD (90% power, T/R 0.95)		Model-Based (90% power, T/R 0.95)	
	Design, length	Total n	Design, length	Total n
Invega Sustenna	SS, parallel Pts, 8 mths	~360 (ICV <60%)	RT, TR, cross, pts, 2 mths & +	~52 (ISCV<40%)
	SS, cross, pts, 16 mths if no w/o	~52 (ISCV<40%)	RTRT, TRTR cross, pts, 4 mths & +	>24 (SABE)
Invega Trinza	SS parallel, pts, 18 mths & +	~360 (ICV <60%)	RRTT, TTRR, cross, pts, 12 mths &+	~52 (ISCV<40%)
	SS, cross,Pts, 36 mths if no w/o	~52 (ISCV<40%)		>24 (SABE)

RED: arguably Not feasible

Model Based BE for LAI

Crossover vs. parallel

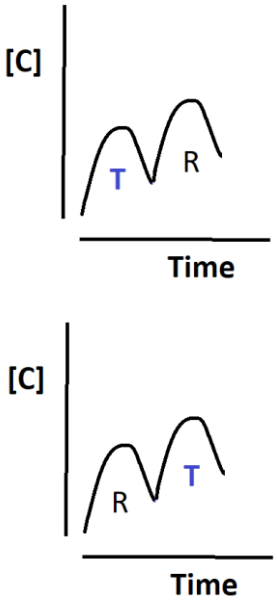
Population PK ("Fitted" PK)



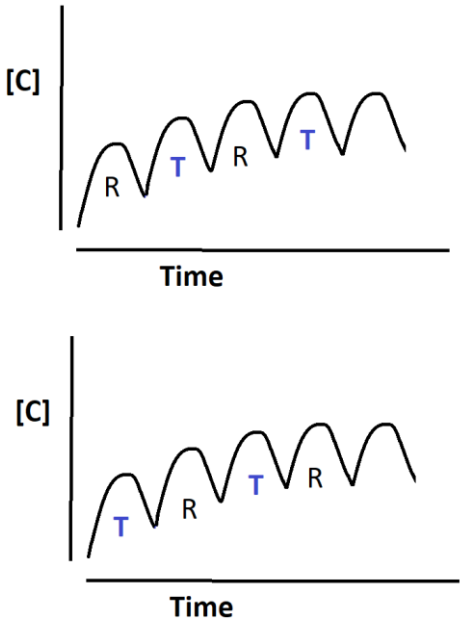
Crossover much preferred and needed

STUDY DESIGN

2-way, Cross, ABE



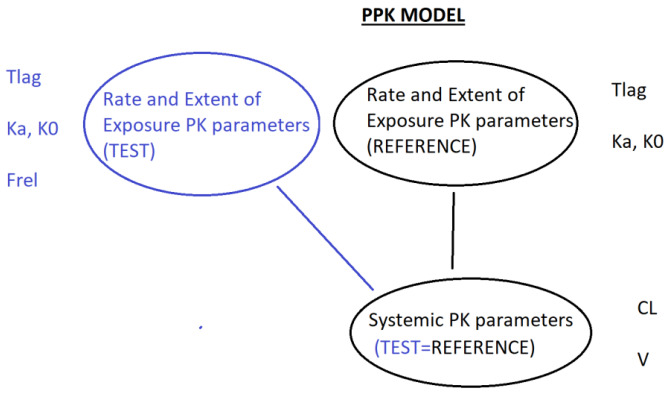
4-way, Cross, SABE



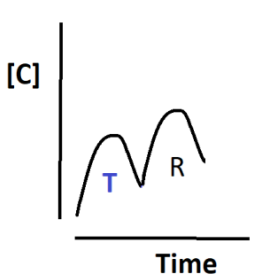
Model Based BE for LAI

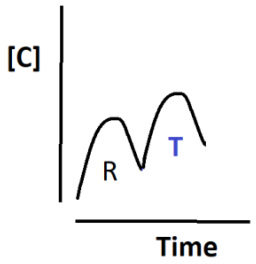
PK Methodologies

Population PK ("Fitted" PK)

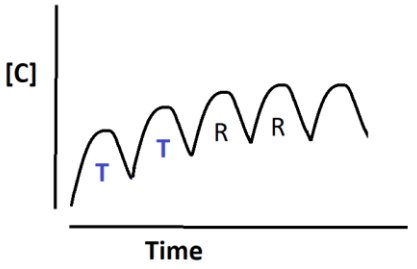


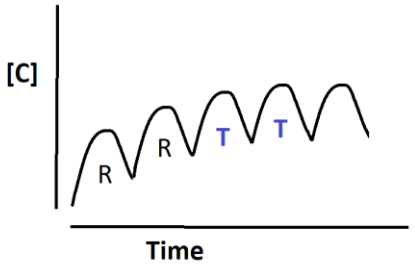
For some products, more than 1 dose will be needed if the absorption half life is too long versus the dosing interval





VS.

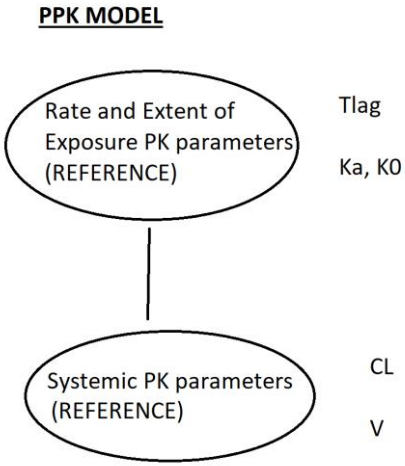




Model Based BE for LAI

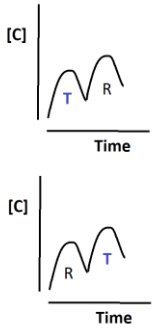
PROGRAM STEPS

1) Need a validated PPK model for the Reference product



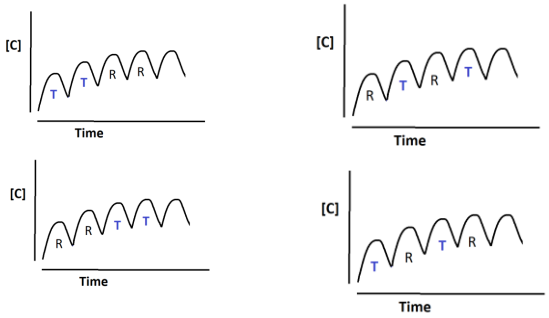
For a 2-way (ABE) study design, need a PPK model without Inter-Occasion Variability (IOV), but with a residual variability that is ideally 15-20% (i.e., 80-125%, 90% CI limits)

1. Population PK parameter means
2. Inter-CV of all PK parameters
3. Low Residual variability



For a 4-way (SABE) study design, need a PPK model that also includes Inter-Occasion Variability (IOV)

1. Population PK parameter means
2. Inter-CV of all PK parameters
3. IOV for some or all PK parameters
4. Low Residual variability

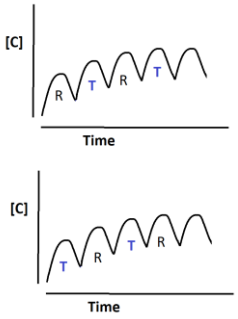


If there is no PPK model (or if it is deficient), a PILOT study, conducted minimally with only the Reference product will be needed to create one

Model Based BE for LAI

PROGRAM STEPS

2) Prove *a priori* that Proposed Study Design can be successful and discriminative



PPK model with IOV and low Res Var

↓

Simulate 1000s studies with T/R ratios of 95% and 79.99% (~80%)

↓

Show that with T/R ratio of 95%, the power obtained is as it is supposed to be (80 or 90%)

↓

Show that with T/R ratio of 79.99%, the alpha error is less than 5%

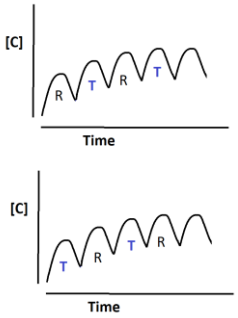
Yes → Submit study design synopsis, Analysis plans, and all reports and models to US FDA

No → Change and improve Study Design

Model Based BE for LAI

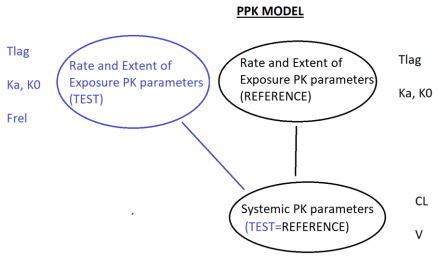
STEPS

3) Once Plan is approved, conduct study, assess BE



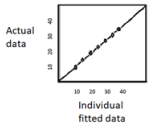
Example of a 4 month, “4 way”, 2 sequences study in n=24 patients (SABE)

Fit ALL individual data to the PPK model



Get ALL of the individual PK parameters in every patient (interested in individual results, not the population ones)

Internally validate the individual results



PK parameter	T/R and 90% CIs		Agreement
	“Observed” from NCPT	Model “Fitted”	
Cmax	X (Y to Z%)	A (B to C%)	√
AUC	X (Y to Z%)	A (B to C%)	√

“Continue” in silico all the individual patients and have them receive single doses of the T and the R products with washout, and determine in these exact 24 patients, the BE results according to the criteria specified in the approved plan (minimally, Cmax and AUC0-t)

Model Based BE for LAI

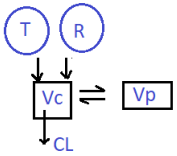
Validation of PPK models

Needs to be "FIT for Purpose" for BE, and is based on what needs to be addressed:

If a **discriminative** Clinical PK Study is really needed:

- Needs to be appropriate to assess exposure differences at a +/-20% difference (ln scale)

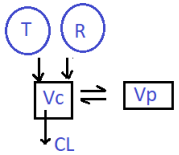
→ A PPK model with residual variability of <25% should be OK, if the "fitted" actual individual results are used to "continue in silico" the same patients.



Individual fits

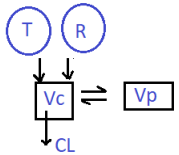
If a clinical PK study **does not need to be as discriminative**:

→ If between ~33-50% is acceptable, then virtual BE may be appropriate, maybe with PPK, as PBPK usually cannot be validated at such a criteria

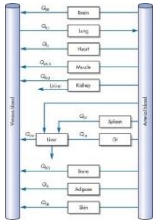


Population predictions

→ If +/-50% or more is acceptable, then virtual BE should be PK with either PBPK or PPK as they should be able to be Validated to that level of precision

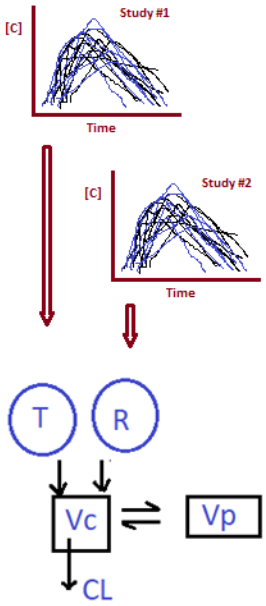


Population predictions



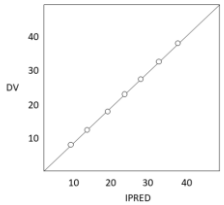
Model Based BE for LAI

Validation of PPK models



Results #1 Individual FITTED PK results

PK parameter	T/R and 90% CIs		Agreement
	"Observed" from NCPT	Model "Fitted"	
Cmax	X (Y to Z%)	A (B to C%)	✓
AUC	X (Y to Z%)	A (B to C%)	✓



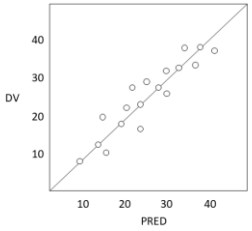
Results #2

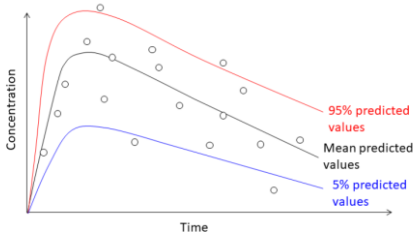
Residual Variability (in %)
(what is unexplained by the model and the fits)

➡ Number has to be lower than what the PPK model has to address

Results #3

Population PREDICTED PK results





These two sets of results are pertinent for the **"continuation"** approach with complete sample size

These two sets of results are pertinent for the **"Virtual BE"** approach with incomplete sample size

Ref.:

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Model Based BE for LAI

Current Issues

- Availability of a PPK model in the literature with IOV and Low Residual Variability

- Necessity of absolutely validating the model BEFORE conducting the pivotal study
  - Establishing Innovative study design with available model despite issues
  - Validating or Improving model using pivotal study

Model Based BE for LAI

Summary of a Program

1) Model-based BE necessary for many LAI products
2) Decision on the type of Model-Based BE that will be pursued
   a) Complete clinical sample size in patients
      - Continue dosing in silico in the same patients with a PPK model
   b) Limited sample size in patients
      - Virtual BE
3) Finding an innovative Model-Based study design?
   a) Need a PPK model
   b) Validate model
   c) Compare multiple model-based designs to a standard conventional (but often unfeasible) design in terms of power and alpha errors
   d) Propose Model-based clinical design
4) Submit proposal with future PK Analysis Plans to FDA as part of Product Development Meeting
5) Conduct the pivotal clinical study, the model-based BE analysis and submit

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Thank you!