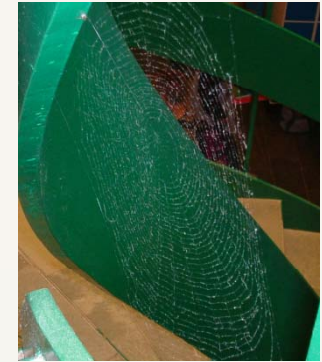




VNIVERSITAT  
ID VALÈNCIA

## Area 1. WP2

# Modelling and Biosimulation in the Authorisation Process of Medical Products



# Assessment of bioequivalence: parent drug or metabolite?

*Assoc Prof. Marival Bermejo*

*Depto. Ingeniería: Área de Farmacia y Tecnología Farmacéutica*

*Facultad de Farmacia.*

*Universidad Miguel Hernández de Elche*

*España*

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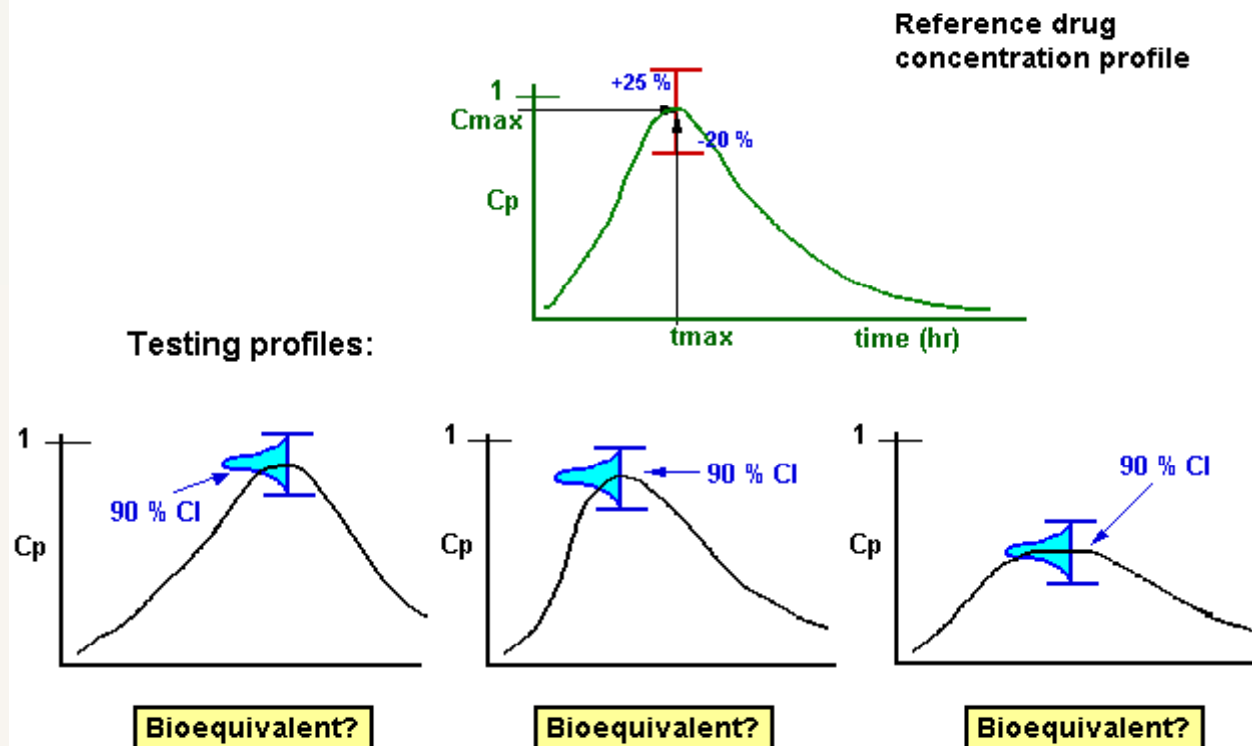
*BioSim*  
EU NETWORK OF EXCELLENCE

# Objective

- To use computer simulation approach to solve gaps in regulatory guidances regarding bioavailability (BA) and bioequivalence assessment (BE). **Drugs with active metabolites.**
- To improve/refine/redefine the current requirements/recommendations about the design and data analysis in the BE studies, based on the outcomes of the simulations.

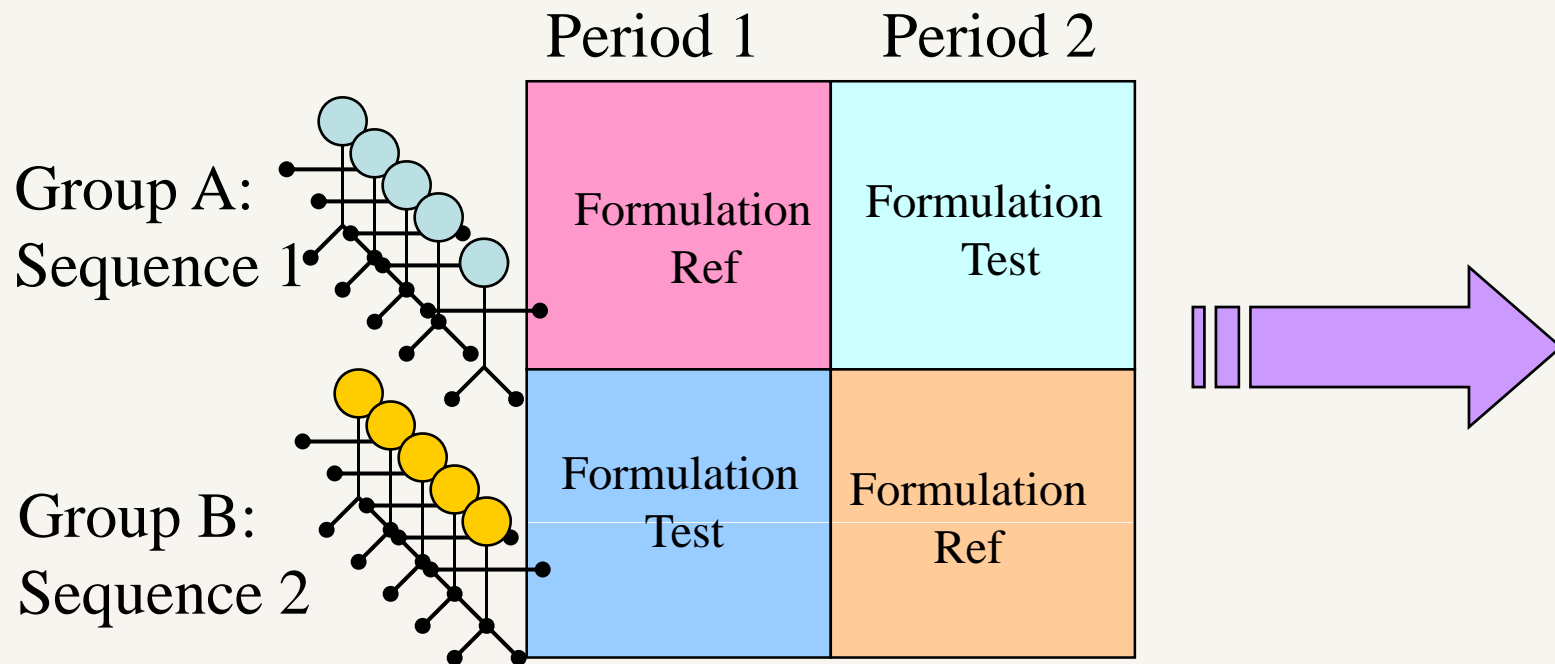
# Bioequivalence studies: comparative clinical trial between two drug products containing the same drug that use a PK endpoint as a surrogate of therapeutic equivalence.

Example of Testing Cmax Bioequivalence:



# BE Study design

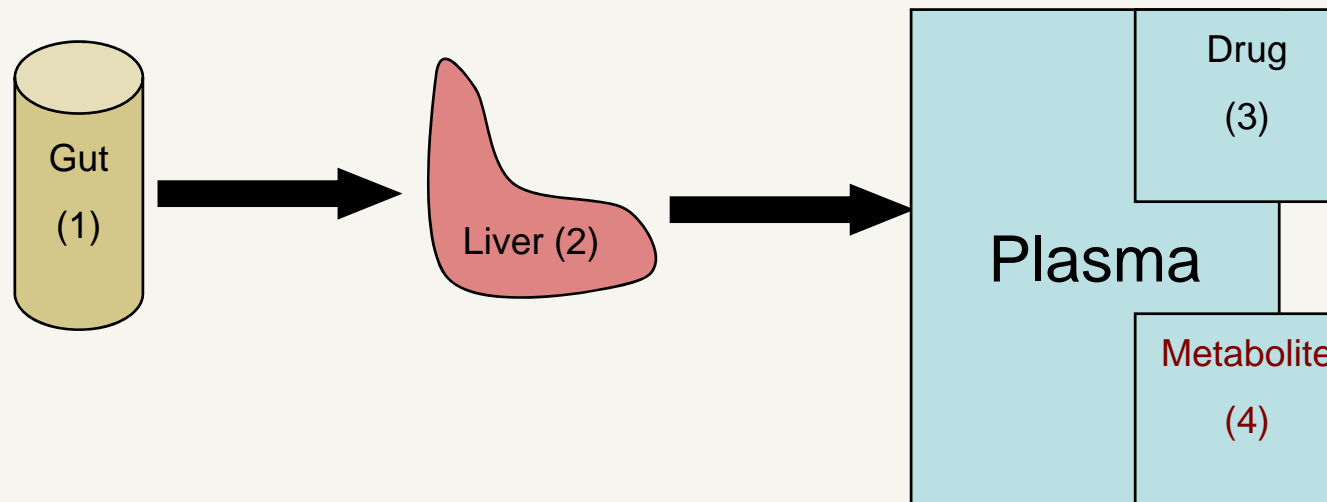
## Two Way Cross-Over Design



***If the drug has metabolites.....***

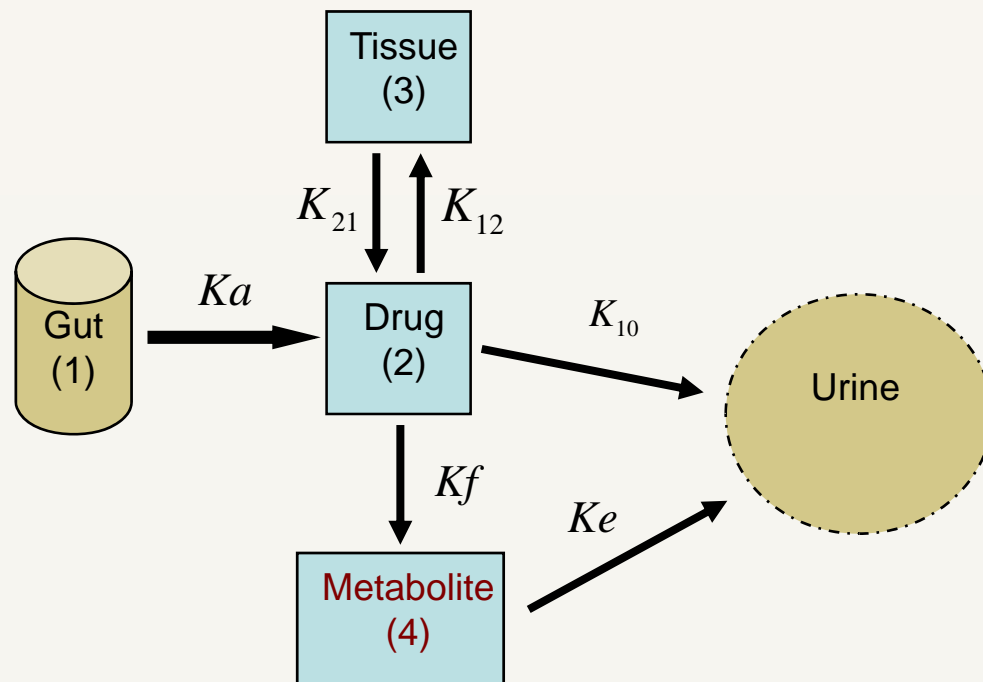
***Question:***

***Which is the best analyte to compare the formulations?***



## Criteria to be considered

- Activity of the specie
- Intra-subject variability of the specie
- Consumer risk and producer risk of the analytes



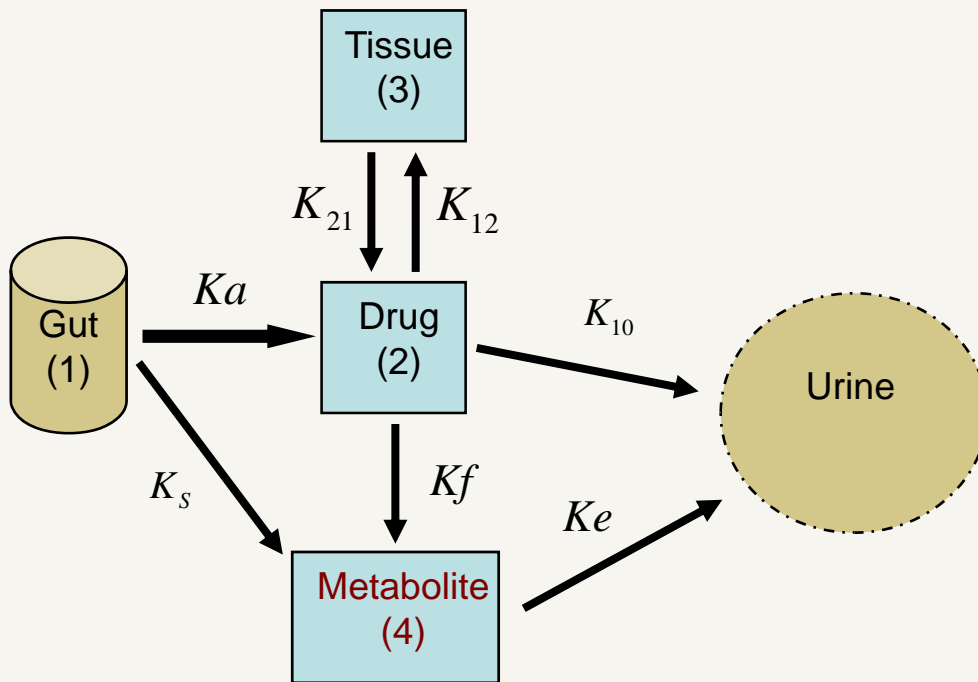
### Scenarios in the simulations

- $F=1$  for both Test and Reference
- Linear Kinetics
- $K_f > K_e$  and  $K_f < K_e$
- Different CV % was added to  $K_a$ ,  $K_f$  and  $k_e$

### Issues

- Empiric model
- It does not take into account extent of absorption
- It does not take into account first pass effect
- It just considers 90% CI width for choosing drug or metabolite.

Chen ML, Jackson AJ, Pharm Res. 1991 Jan;8(1):25-32.



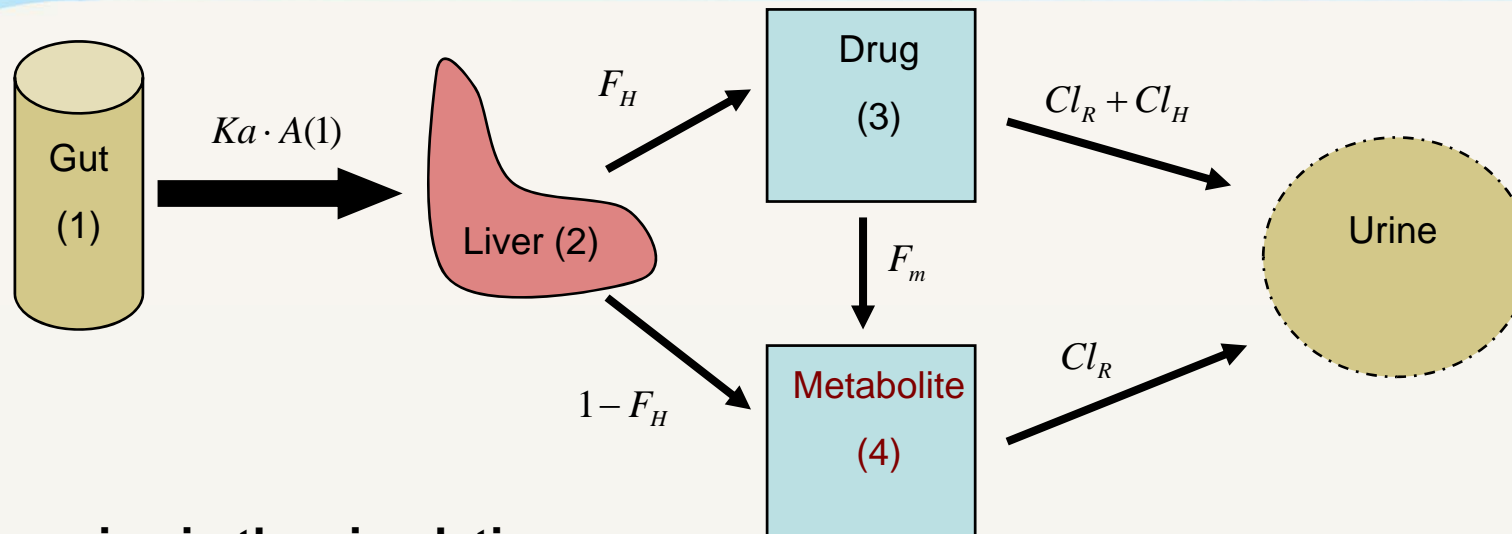
### Issues

- Still too empiric
- It does not take into account extent of absorption
- It just consider 90% CI width for choosing drug or metabolite.

Chen ML, Jackson AJ, Pharm Res. 1995 May;12(5):700-8.

### Scenarios in the simulations

- $F=1$  for both Test and Reference
- $K_a/K_s = 3$  and  $K_a/K_s = 1.5$
- $\text{IntraCV}_{K_a} > \text{IntraCV}_{K_s}$  and  $\text{IntraCV}_{K_a} < \text{IntraCV}_{K_s}$



## Scenarios in the simulations

- $F_{rel}=1$  and  $F_{rel}=0.75$
- $Ka_T/Ka_R=1$  and  $Ka_T/Ka_R=0.75$
- Several Intrasubject variabilities
- $F_m=0.75$  and  $F_m=0.25$

## Issues

- There are overparametrization.  $Cl_H$ ,  $F_H$ ,  $Cl_{int}$  and  $F_m$  should not be independent.

Jackson AJ, Pharm Res. 2000 Nov;17(11):1432-6.

## Regulatory differences between FDA and EMEA

According to the EMEA, if **metabolites significantly contribute to the net activity** of an active substance and the **pharmacokinetic system is non-linear**, it is **necessary to measure both parent drug and active metabolite** plasma concentrations and **evaluate them separately**.

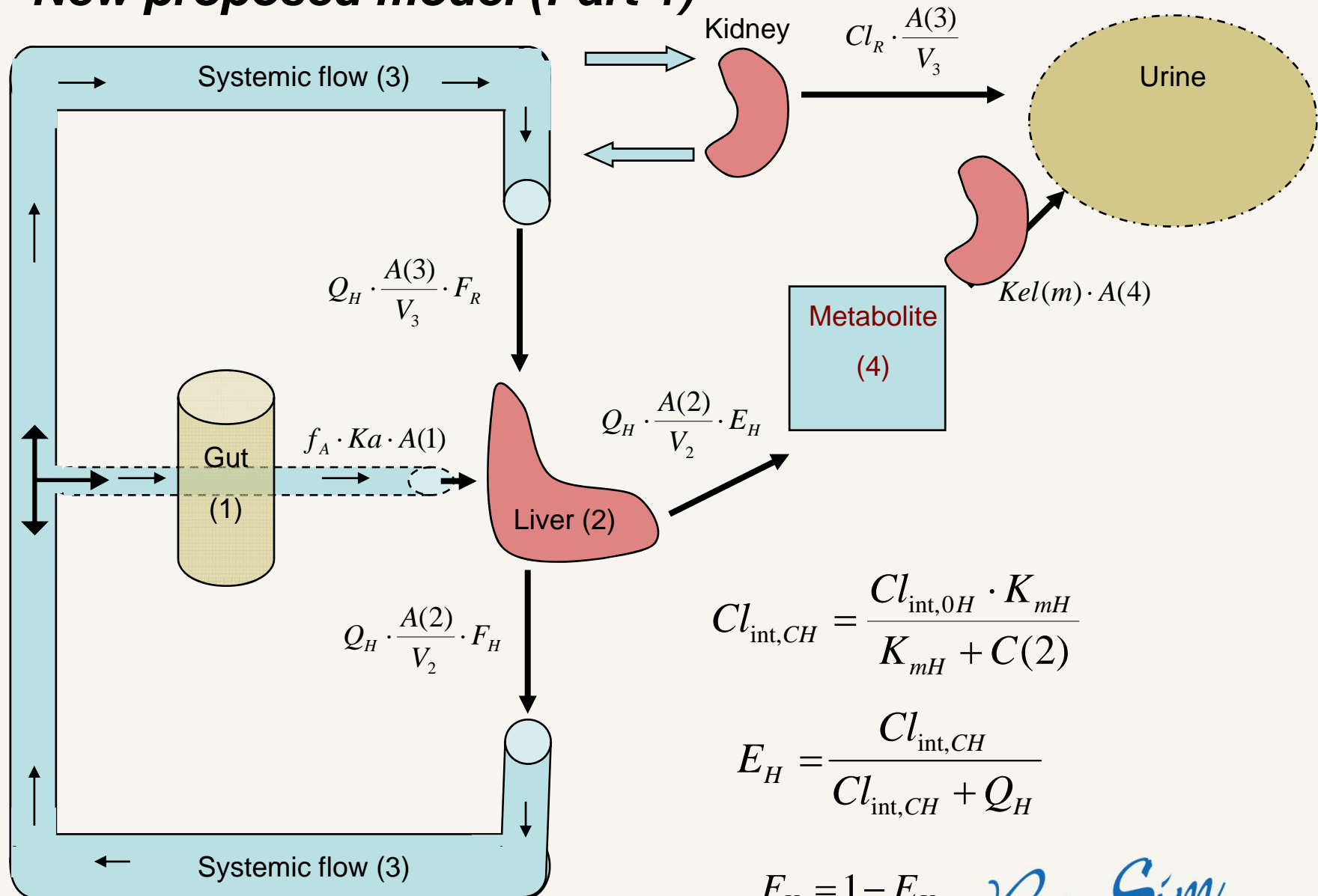
For the FDA, if the metabolite **contributes meaningfully to safety and/or efficacy** and is formed as a result of gut wall or other presystemic metabolism, FDA **recommends that the metabolite and the parent drug be measured**. That is regardless all the processes are linear.

# Regulatory differences: FDA and EMEA

## Questions

- should not we use the specie that gives more accurate results? (no matter the activity)
- Is it theoretically possible that parent drug ratios are inside the BE limits (e.g. 80-125 %) and the metabolite ratios are outside?.
- Could the non-linearity in parent drug be amplified (or attenuated) in the metabolite?
- Could the metabolite be BE but not parent drug, so metabolite not representing dosage form performance? Is this relevant or not?

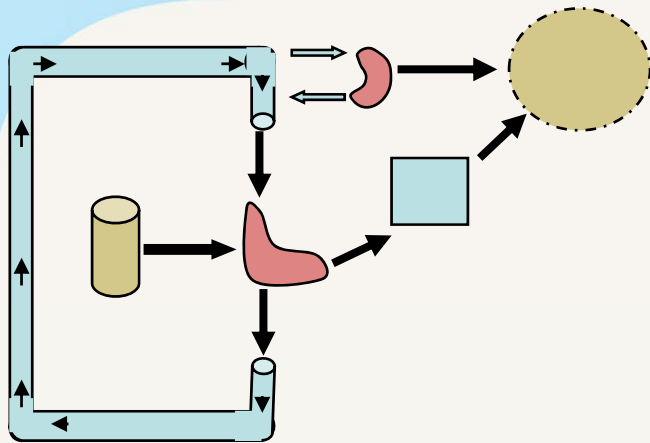
- New proposed model (Part 1)**



$$Cl_{int,CH} = \frac{Cl_{int,0H} \cdot K_{mH}}{K_{mH} + C(2)}$$

$$E_H = \frac{Cl_{int,CH}}{Cl_{int,CH} + Q_H}$$

$$F_H = 1 - E_{1H}$$



- ***New proposed model***

- Semi-physiological model:
- Plasma compartment, gut, liver, metabolite.
- Intestinal lumen: solid drug, dissolved fraction, luminal degradation.
- The intestinal transit: considered as an operative absorption time (OAT).

- ❑ Once the drug is absorbed, it goes to liver, where it is partially metabolized.
- ❑ This metabolism can be non-linear, depending on the drug concentration in liver.
- ❑ The drug is assumed to be distributed rapidly in 1 compartment and eliminated by metabolism in liver (mainly) and excreted unaltered by renal excretion.
- ❑ Metabolite is assumed to be excreted by renal excretion.
- ❑ **This first model has been extended to accommodate:**
  - ❑ **a peripheral compartment**
  - ❑ **Intestinal first pass effect**
  - ❑ **a second metabolic route**

## Subject generation

Database of 2400\*24 Subjects in Excel assigning:

- ID for each subject
- Study (1 to 2400)

And randomly

- Sequence (0 or 1).

- Period, occasion and formulation:

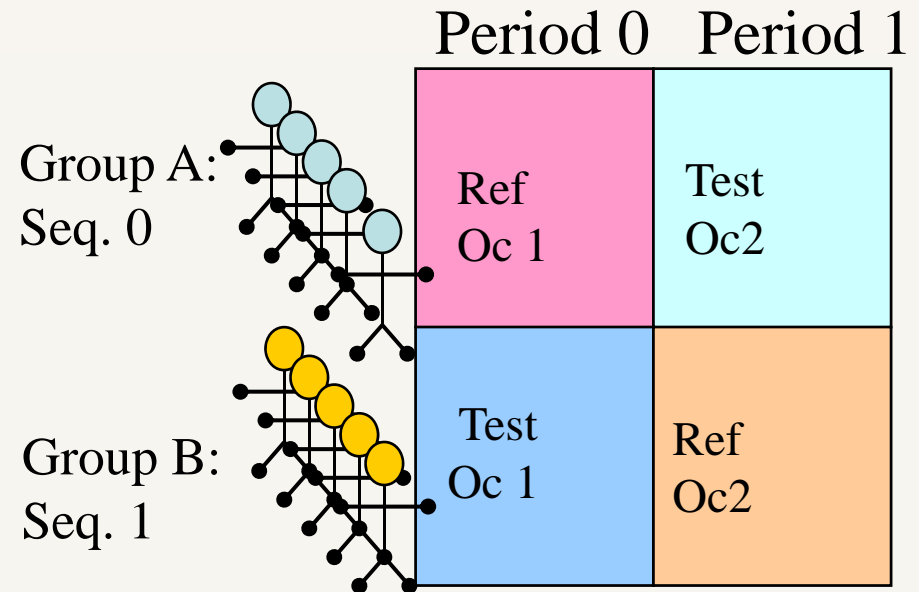
A. in seq =0. Period = 0 Reference. Period = 1 Test

B. in seq= 1. Period = 0 Test. Period = 1 Reference

C. Occasion (OC1 y OC2).

➤ Period = 0. OC1 = 1. OC2 = 0

➤ Period = 1. OC1 = 0. OC2 = 1



## Fixed and Random effects

$$P_t = P_R \cdot E_{\text{seq}}^{\text{seq}} \cdot E_{\text{period}}^{\text{period}} \cdot E_{\text{form}}^{\text{form}}$$

$$P_i = P_t \cdot e^{(\text{EtaIID} + \text{EtaOC1} \cdot \text{OC1} + \text{EtaOC2} \cdot \text{OC2})}$$

$$C_{pi} = f(P_i, \text{Doses}, \text{time}) \cdot (1 + \text{eps})$$

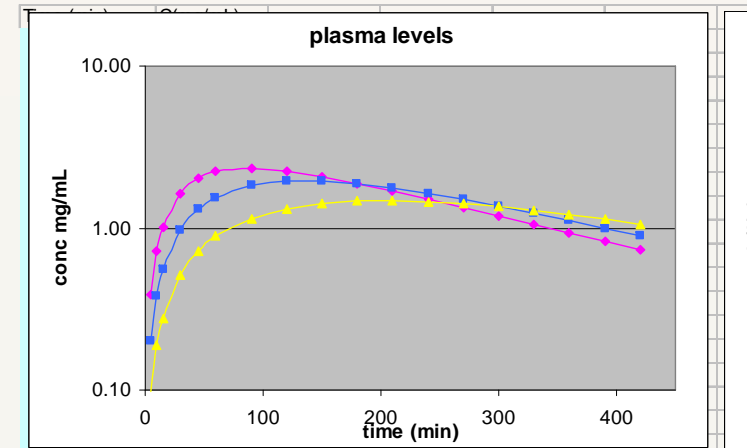
R: Reference

i: subject

## Study designs

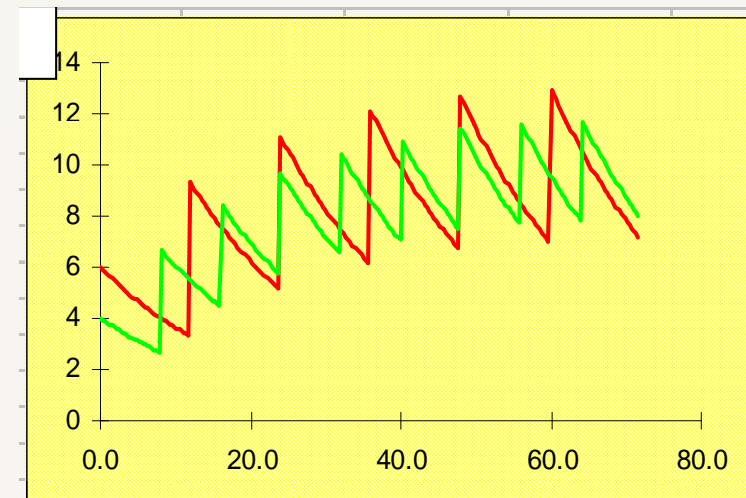
### Single dose

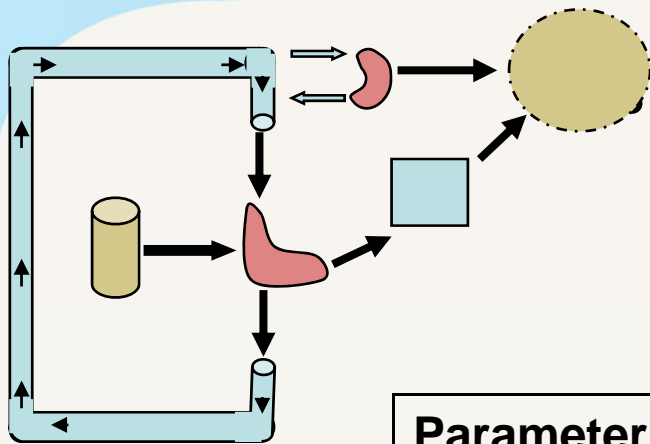
- 24 subjects/study
- 96 scenarios
- 2400 studies/scenario



### Multiple dose

- 24 subjects/study
- 96 scenarios
- 1000 studies/scenario

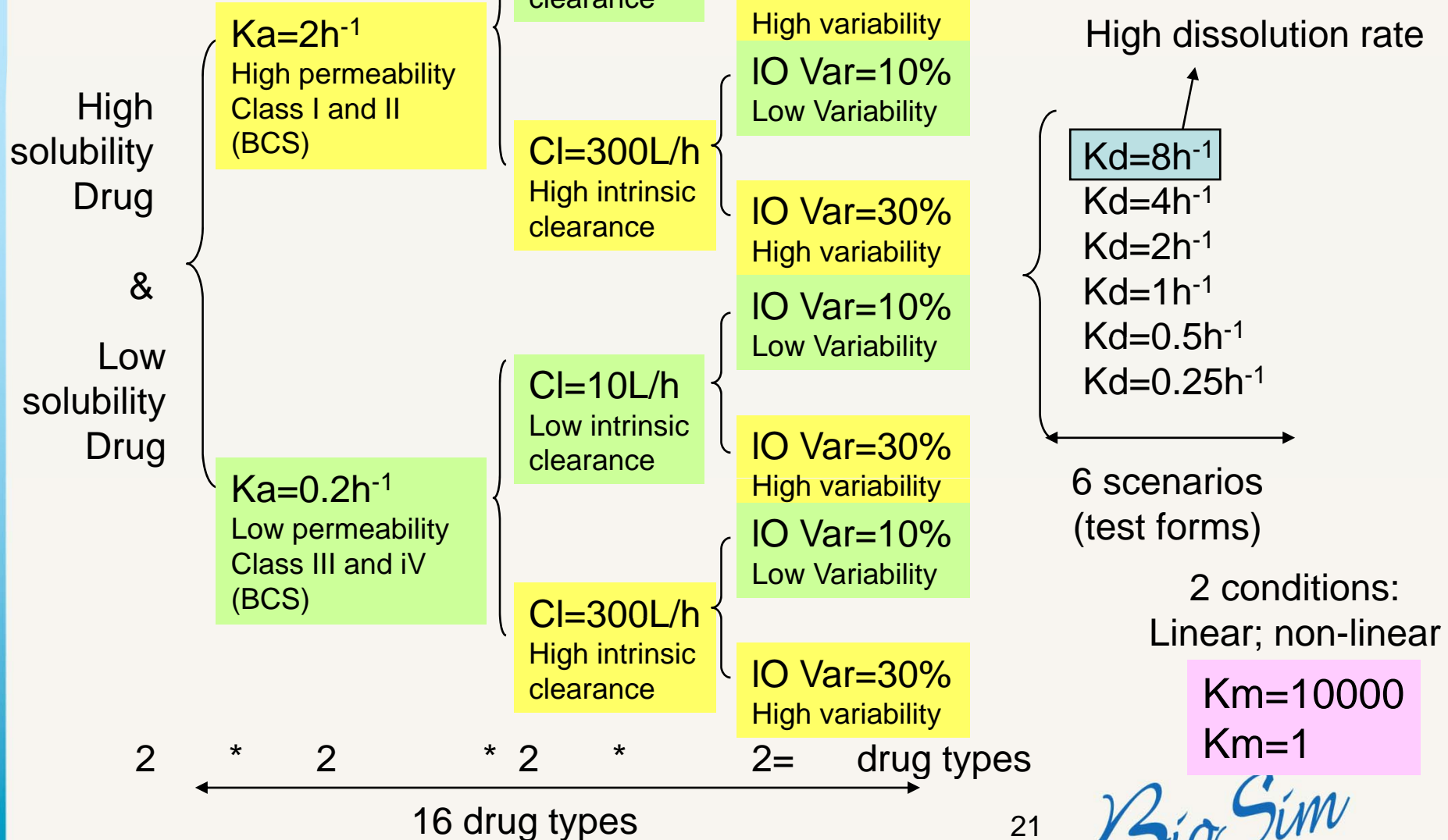




## Average Parameters for simulations

Parameter	Value
OAT (h)	4
Degradation rate in lumen ( $\text{h}^{-1}$ )	0
Dissolution rate for reference form ( $\text{h}^{-1}$ )	8
Renal clearance of PD (L/h)	0.05
Hepatic blood flow (QH) (L/h)	90
Clearance of metabolite (L/h)	20
Hepatic Volume (L)	1
Central compartment volume (L)	40
Metabolite compartment volume (L)	40

# Drug types and Scenarios



# Simulations

- Interindividual variability 20% all parameters.
- Interocassion variability 10% in all parameters( but Clint)
- Interocassion variability of Parent Drug Intrinsic Clearance (Clint) modelled as High 30% or Low 10%.
- Variabilities added with exponential model.

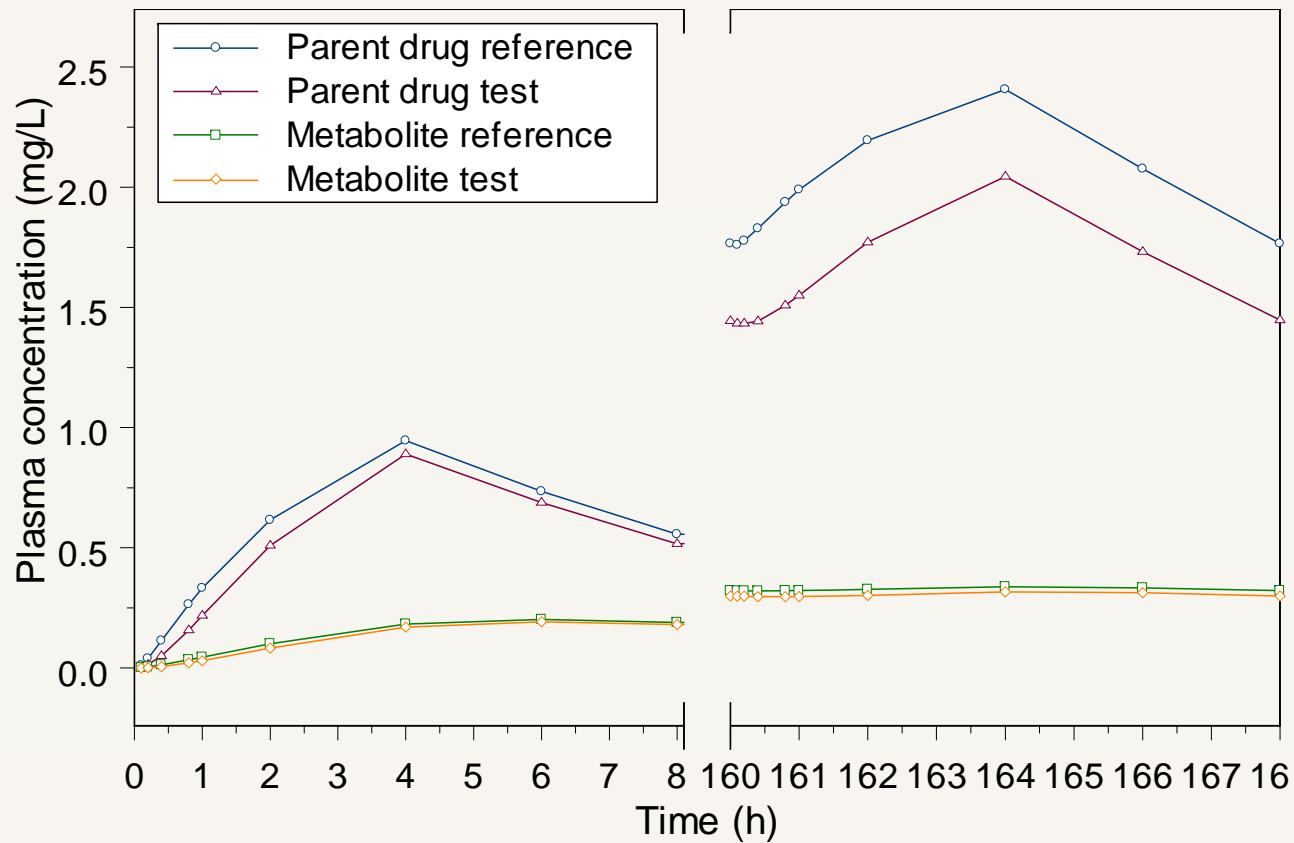
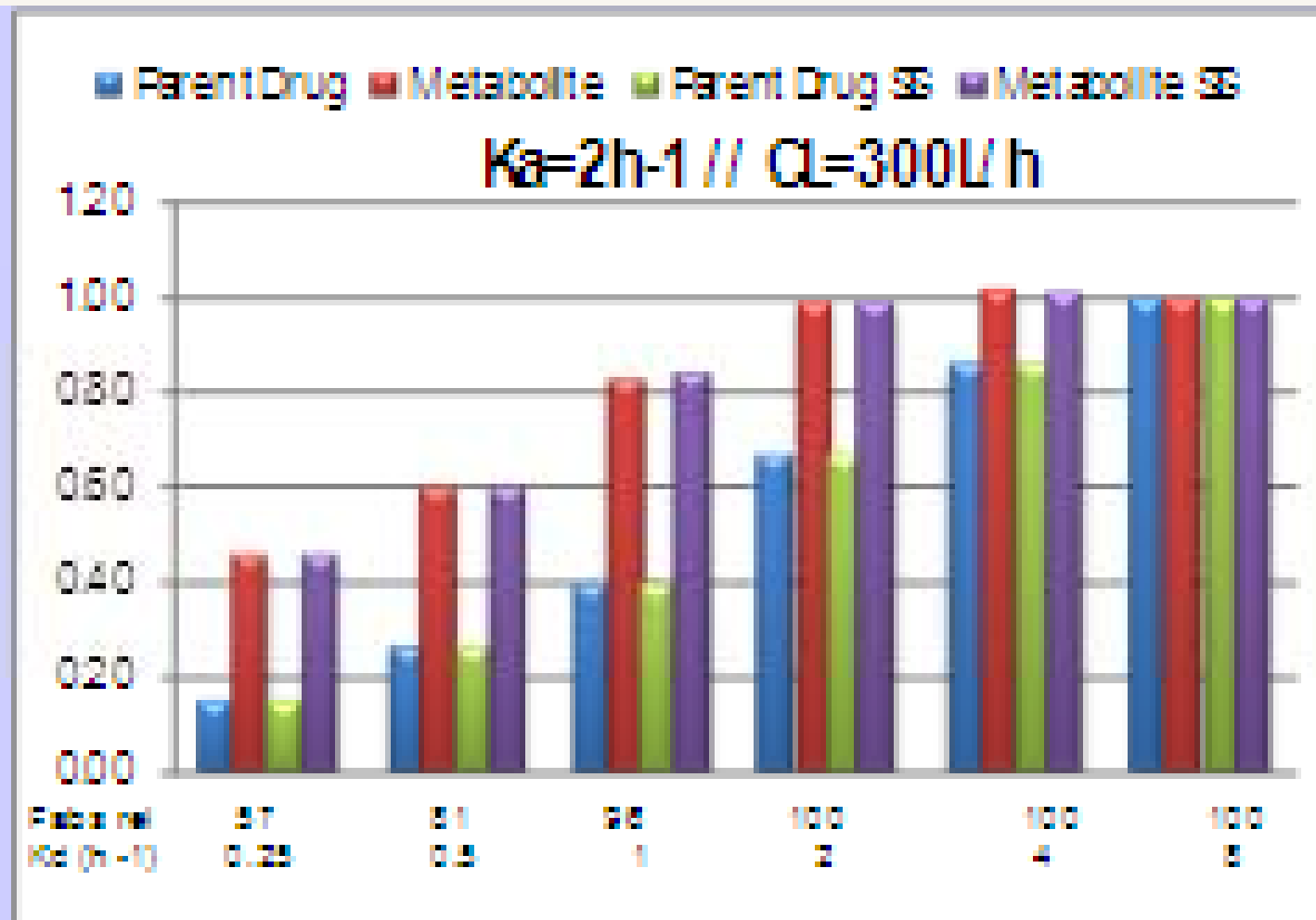
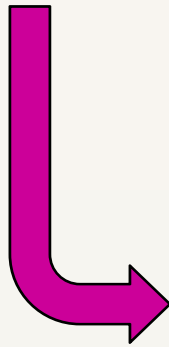


Figure 2: Plasma concentrations of reference and test at single dose (left) and multiple dose (SS) (right) in scenario  $K_a=0.2 \text{ h}^{-1}$ ,  $Cl=10 \text{ L/h}$ ,  $K_m=1 \text{ mg/L}$ ,  $K_d=2 \text{ h}^{-1}$ .

## AUC or Cmax ratios



- Diss rate of test and Fabs rel

# Class 1 and 3 Linear

$K_m = 10000 \text{ mg/L}$

**HIGH PERMEABILITY**

**LOW PERMEABILITY**

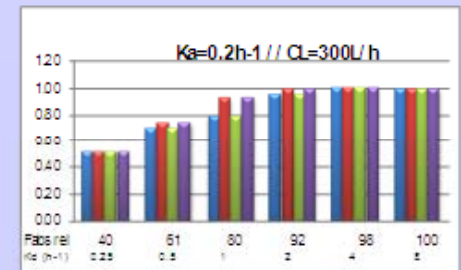
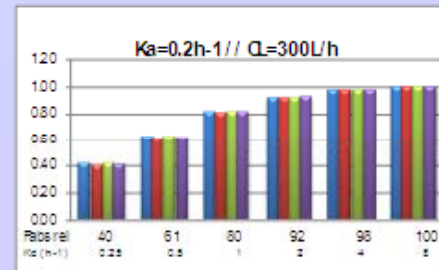
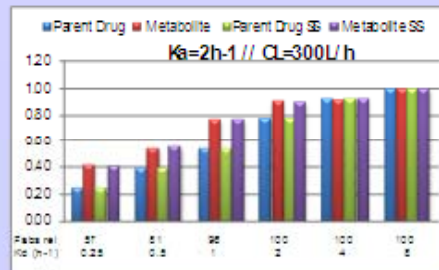
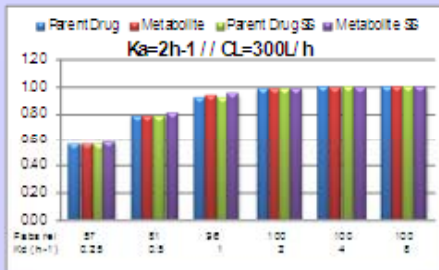
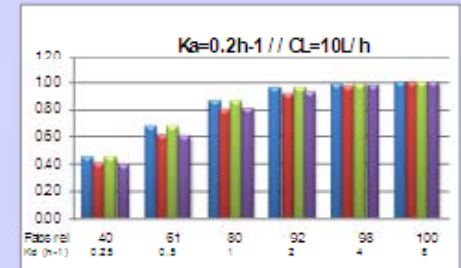
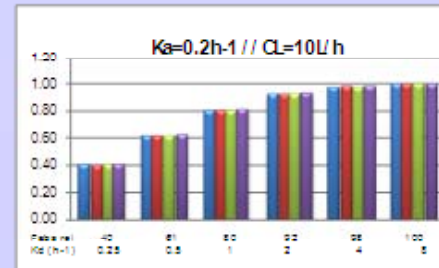
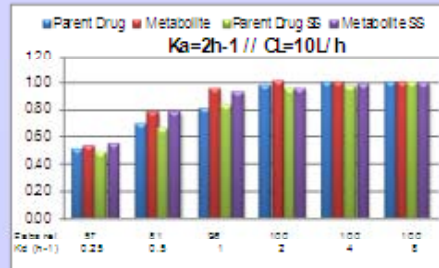
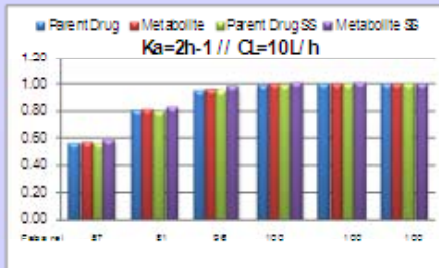
**AUC ratio**

**Cmax ratio**

**AUC ratio**

**Cmax ratio**

LINEAR



**HIGH SOLUBILITY**

■ Parent Drug    
 ■ Metabolite    
 ■ Parent Drug SS    
 ■ Metabolite SS

# Class 1 and 3 non linear

## HIGH SOLUBILITY

■ Parent Drug   
 ■ Metabolite   
 ■ Parent Drug SS   
 ■ Metabolite SS

### HIGH PERMEABILITY

$K_m = 1 \text{ mg/L}$

### LOW PERMEABILITY

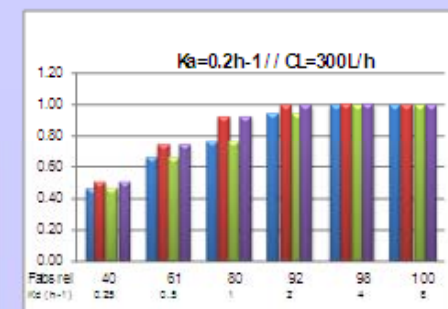
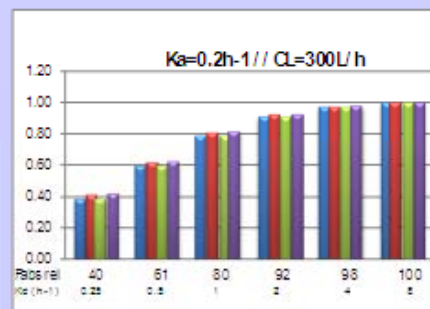
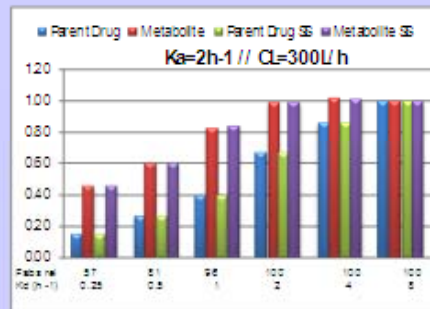
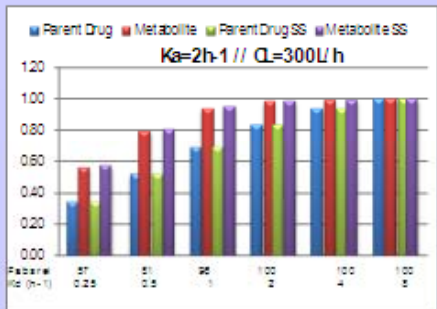
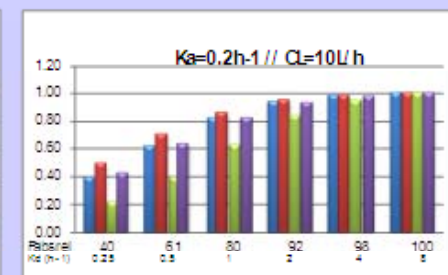
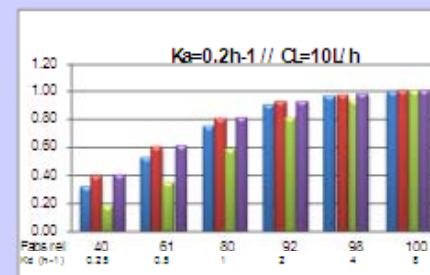
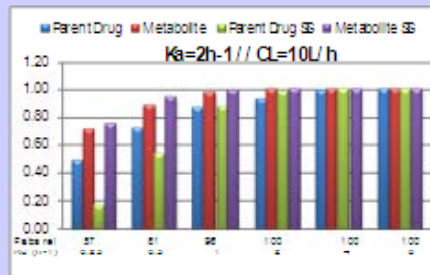
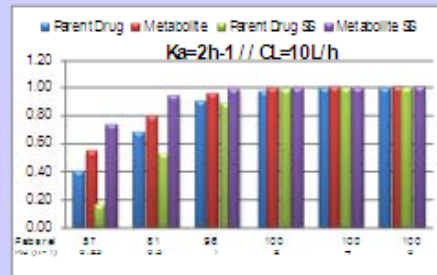
AUC ratio

Cmax ratio

AUC ratio

Cmax ratio

NON-LINEAR



# Class 2 and 4 linear

**HIGH PERMEABILITY**

$K_m = 10000 \text{ mg/L}$

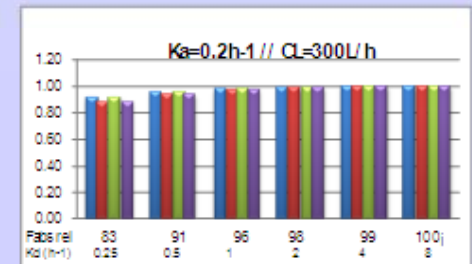
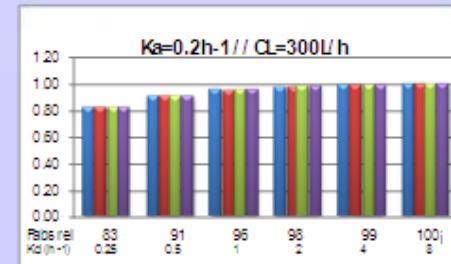
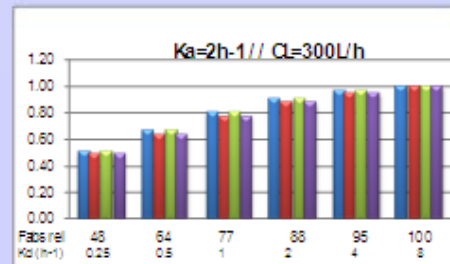
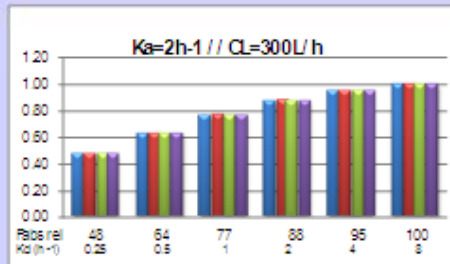
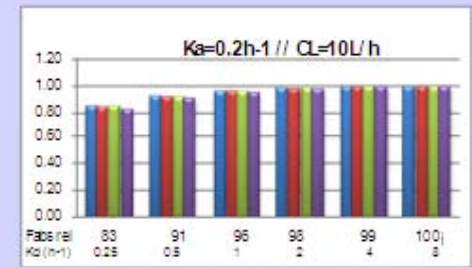
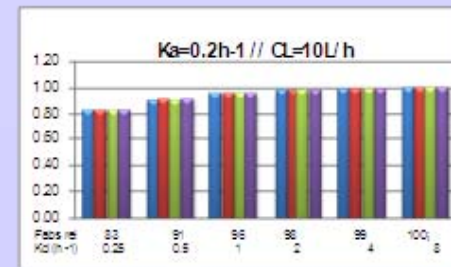
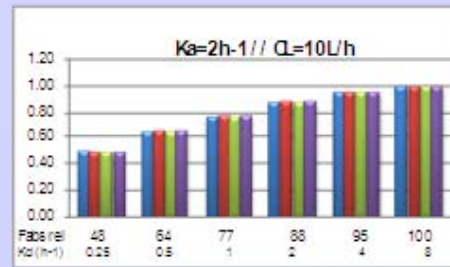
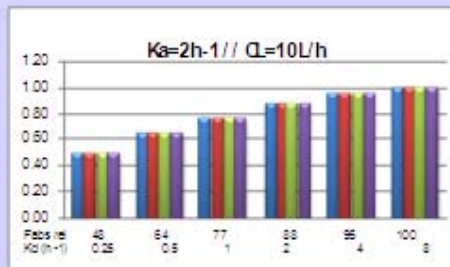
**LOW PERMEABILITY**

**AUC ratio**

**Cmax ratio**

**AUC ratio**

**Cmax ratio**



**LOW SOLUBILITY**

■ Parent Drug   
 ■ Metabolite   
 ■ Parent Drug SS   
 ■ Metabolite SS

# Class 2 and 4 non linear

## LOW SOLUBILITY

■ Parent Drug   
 ■ Metabolite   
 ■ Parent Drug SS   
 ■ Metabolite SS

**HIGH PERMEABILITY**

$K_m = 1 \text{ mg/L}$

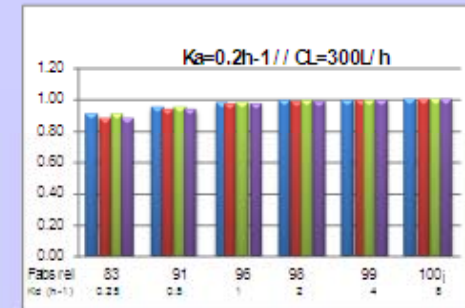
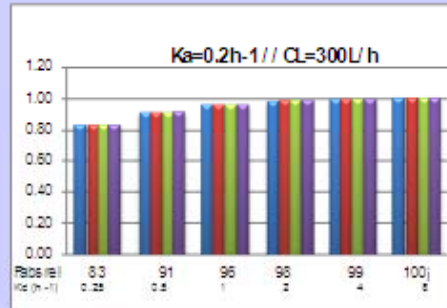
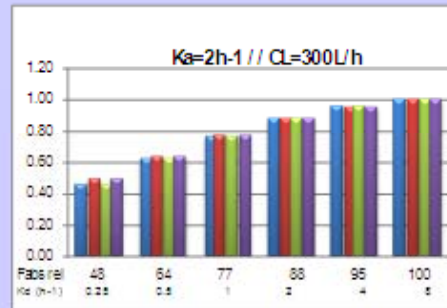
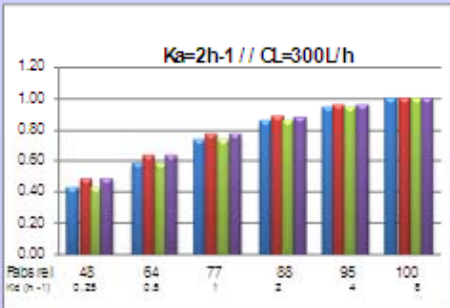
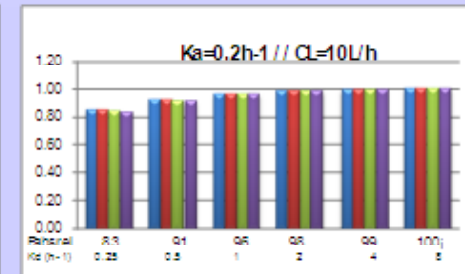
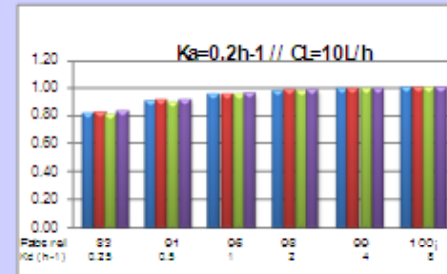
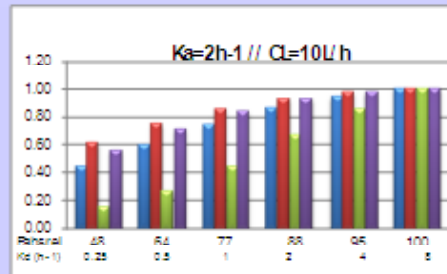
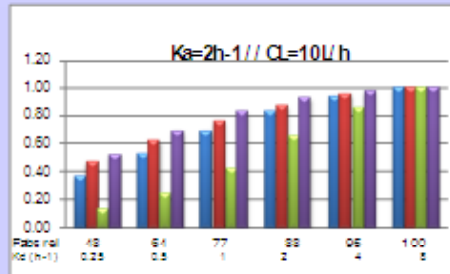
**LOW PERMEABILITY**

AUC ratio

C<sub>max</sub> ratio

AUC ratio

C<sub>max</sub> ratio



- Fernández-Teruel C, Nalda Molina R, González-Alvarez I, Navarro-Fontestad C, García-Arieta A, Casabó VG, Bermejo M.

Computer simulations of bioequivalence trials: Selection of design and analyte in BCS drugs with first-pass hepatic metabolism: **Part I. Linear kinetics. Eur J Pharm Sci. 2009 Jan 31;36(1):137-46.**

- Fernández-Teruel C, Gonzalez-Alvarez I, Navarro-Fontestad C, García-Arieta A, Bermejo M, Casabó VG.

Computer simulations of bioequivalence trials: Selection of design and analyte in BCS drugs with first-pass hepatic metabolism: **Part II. Non-linear kinetics. Eur J Pharm Sci. 2009 Jan 31;36(1):147-56.**

## Evolución de los modelos:

- 1) Monocompartimental dosis única: 1 metabolito
- 2) Bicompartimental dosis única y múltiple: 1 metabolito

## Extensiones del modelo

- 3) Bicompartimental dosis única: 2 metabolitos  
condiciones de no saturación  
condiciones de saturación (1 ó 2 vías metabólicas)
- 4) Bicompart. 2 metabolitos ¿dosis múltiples?

# Conclusions

- **Parent drug in single dose** is the best moiety and design for bioequivalence trials **in almost all the studied scenarios.**
- But ***this general rule has exceptions*** in a few particular cases. (i.e request PD in SS).

The complexity of the PK model could be further increased (protein plasma binding, new compartments) to simulate particular drugs with known PK parameters.

Modelling and Simulation is a powerful tool for the regulatory agencies in order to make science-based recommendations about the analytes in BE scenarios.

## Acknowledgements



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PhD student



Carlos Fernández Ph.D.

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Isabel González-Álvarez  
Ph.D



Alfredo García Arieta  
Ph.D