Using PBPK to link systemic PK to local delivery in the lung

Günther Hochhaus and Jürgen Bulitta

In collaboration with
Rob Price, Jag Shur (Univ. of Bath)
Mike Hindle (VCU)

PBPK MODELING FOR THE DEVELOPMENT AND APPROVAL OF LOCALLY ACTING DRUG PRODUCTS
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Disclaimer

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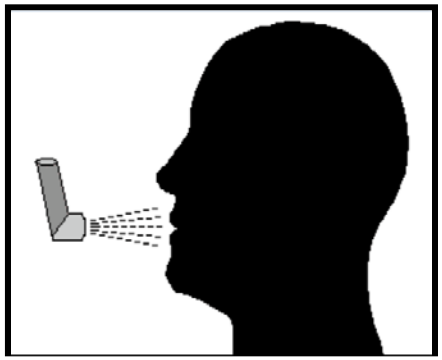
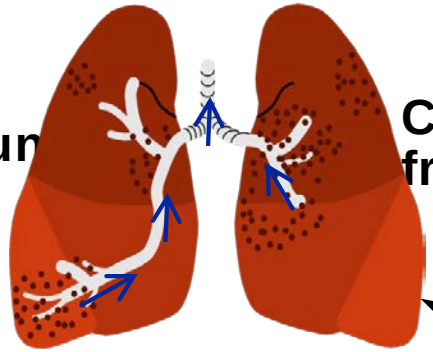
Topics related to Bioequivalence?

dose, regional deposition, time?

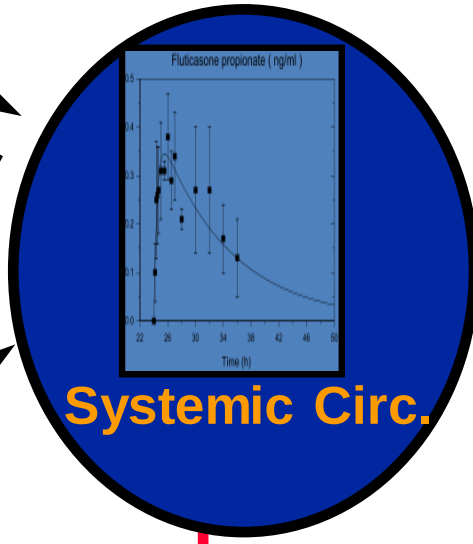


10 - 60 %
Deposited in lun

Cl_{muc}



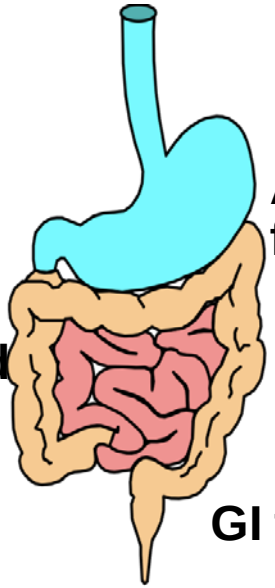
Complete absorption
from the lung



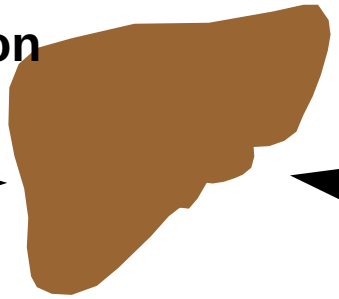
Lung

Mouth and pharynx

Orally bioavailable
fraction



Absorption
from gut



Liver

40 - 90 % Swallowed
(reduced by spacer
or mouth rinsing)

GI tract

First-pass
inactivation

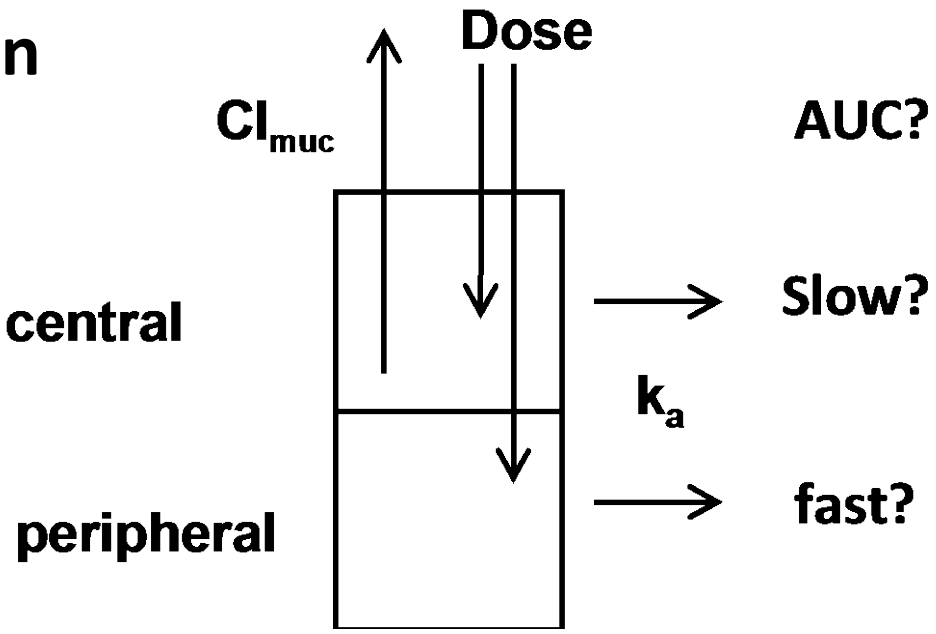
**Systemic
side effects**

Actual Question of this research Project

Can PK (NCA, PBPK/semi-mechanistic models)

extract Information on :

- Dose
- Dissolution/Absorption
- **Regional Deposition**



A-4.5 µm	Lactohale LH201 (20% %)
B-3.8 µm	Lactohale LH230 (10%)
C-3.7µm	Lactohale LH 3oo (2.5%)
All Formulations: Respitose SV003 + 0.8% FP	

Study Outline

- **Develop three DPI-FP formulations (R. Price/Jag Shur)**
  - Same dose
  - Same dissolution rate
  - Difference in central to peripheral lung deposition.
- **Characterize through in vitro experiments**
  - Ex throat dose (Mike Hindle)
  - Cascade impactor profile
  - Dissolution rate
- **Perform PK (4 way cross-over, repeat one formulation)**
  - Inhalation profiles measured for each inhalation
  - Intra-subject variability
  - NCA, compartmental population PK modeling (PBPK)

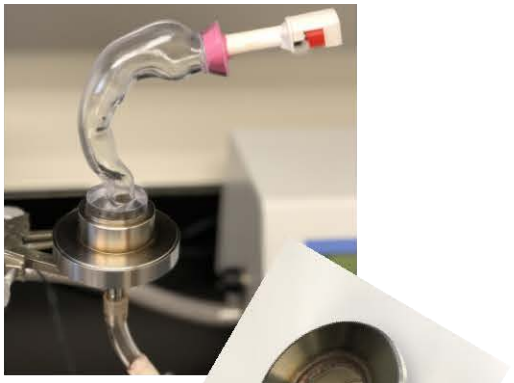
Cascade Impactor Data

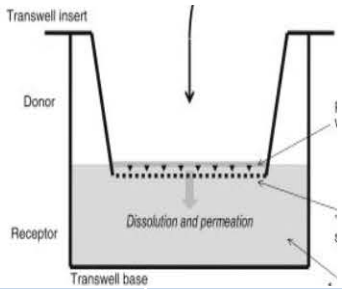
Mass deposition	Particle size (µm)	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
Mass Median Aerodynamic Diameter		**4.50**	**3. 8**	**3.7**
Larger Particles	2.8 - 8.1 µm	**12.5**	**14.4**	**11.5**
Smaller Particles[P] (µg)	< 2.8 µm	**4.8**	**9.4**	**8.1**
Relative Ex Throat Dose (Anatomical Throat)		**1**	**1.3**	**1.2**

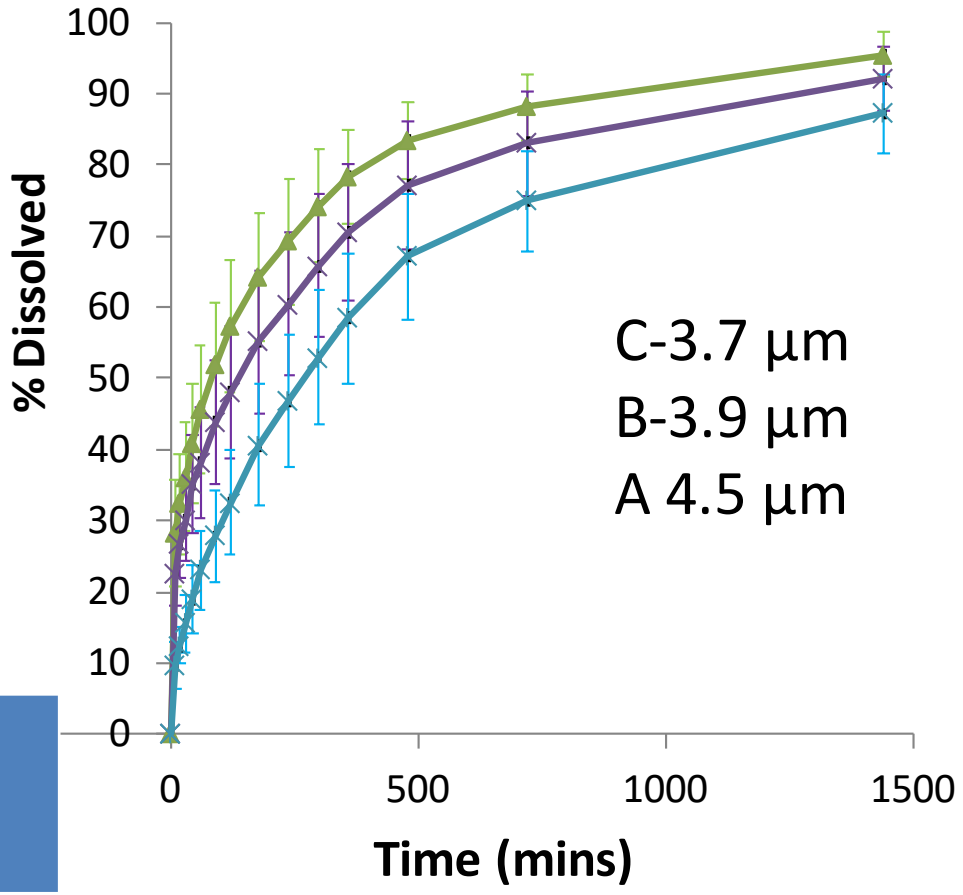
[C] and [P] presumable representing central and peripheral lung deposition, respectively

- Similar mass deposition on larger stages
- Mass deposition on smaller stages was substantially smaller for A-4.5µm

Do formulations provide same absorption rate? In vitro dissolution and permeation





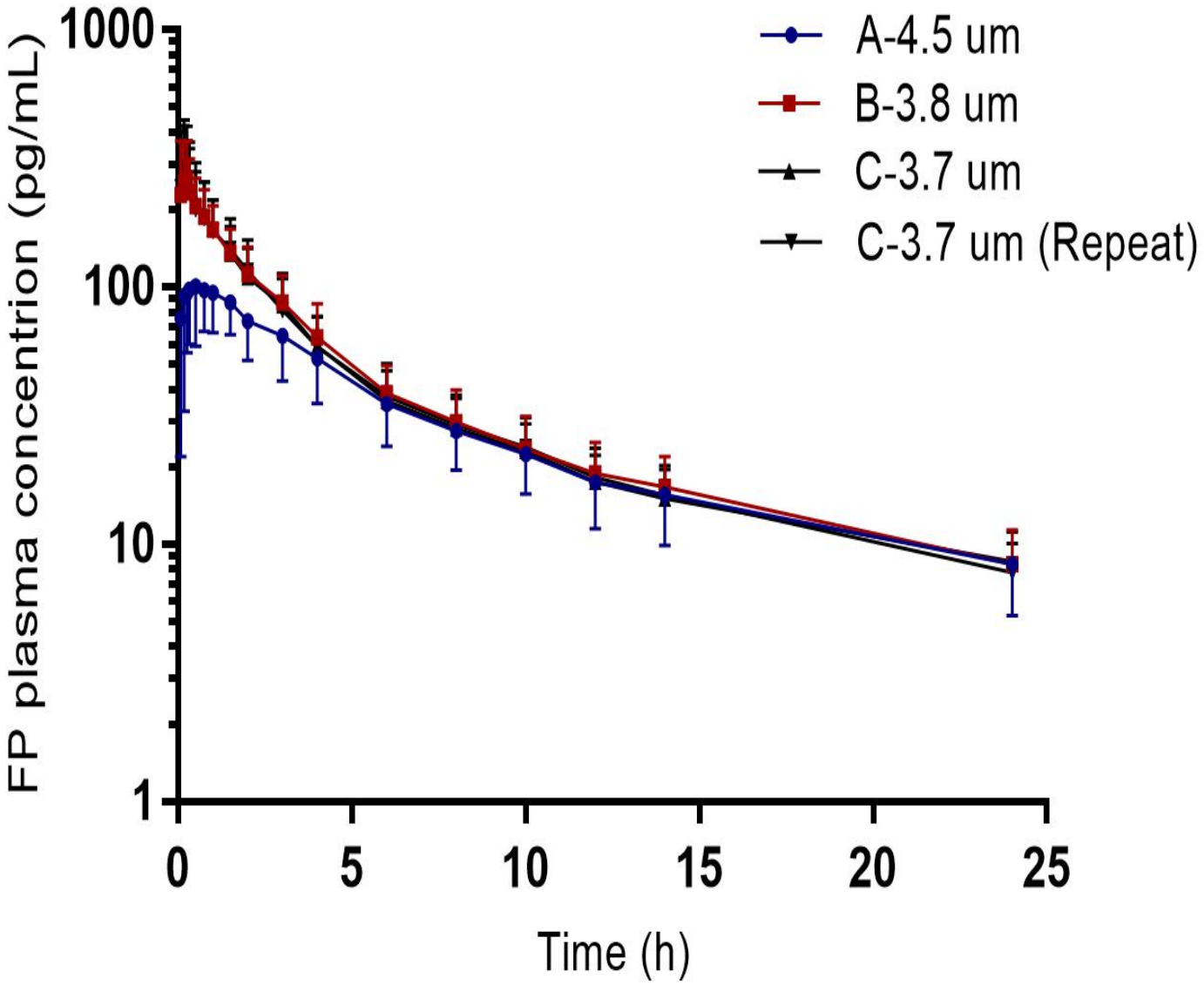


Formulation	MDT (h)	Relative surface area
A-4.5 µm	15.4	0.5
B-3.9 µm	13.3	0.7
C-3.7 µm	10.3	1

PK Study Design

- 4-way, cross-over, double blind
- 24 healthy volunteers
- Dose: 5 * 100 µg
- Record individual inhalation profiles
- Non-compartmental Analysis + Compartmental Analysis (population-PK)
- PBPK based evaluation of popPK results

Before dose normalization



Conclusion I: NCA/BE

Overall:

Before dose Normalization

- AUC and C_{max}: A # B = C

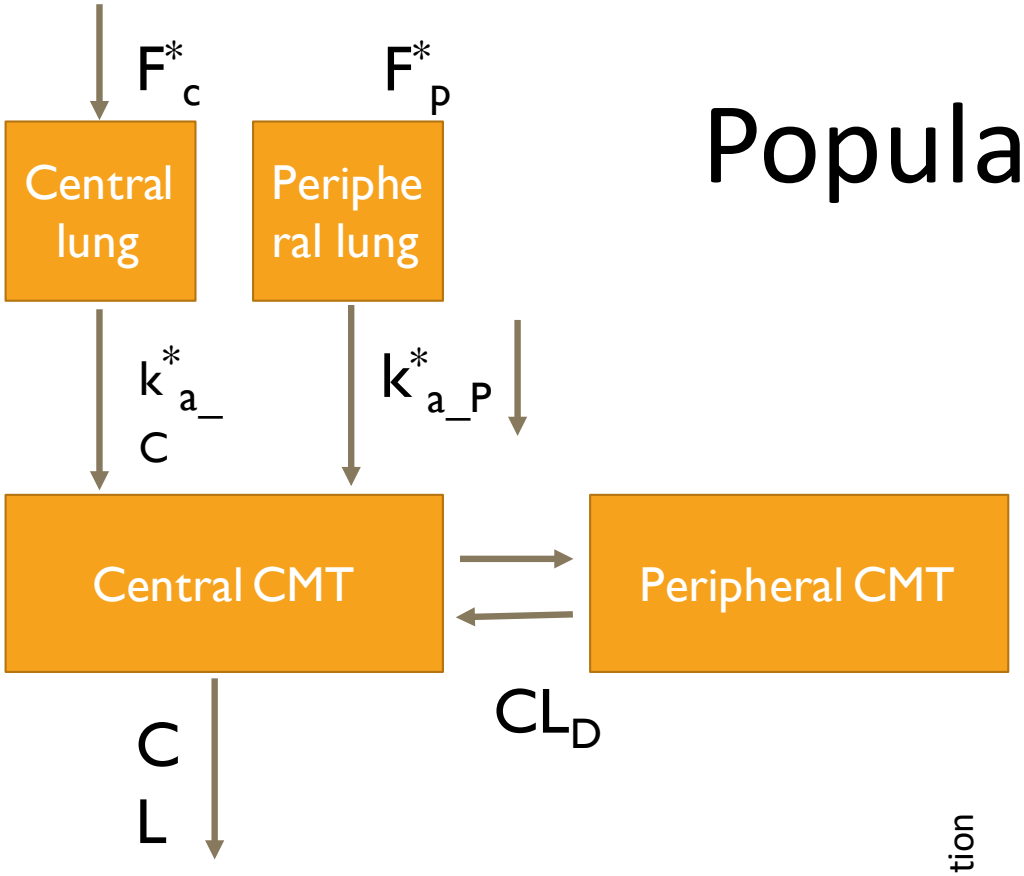
After Dose Normalization

- AUC: A=B=C
- C_{max}/Dose: A # B=C

AUC: c/p Differences could not be shown

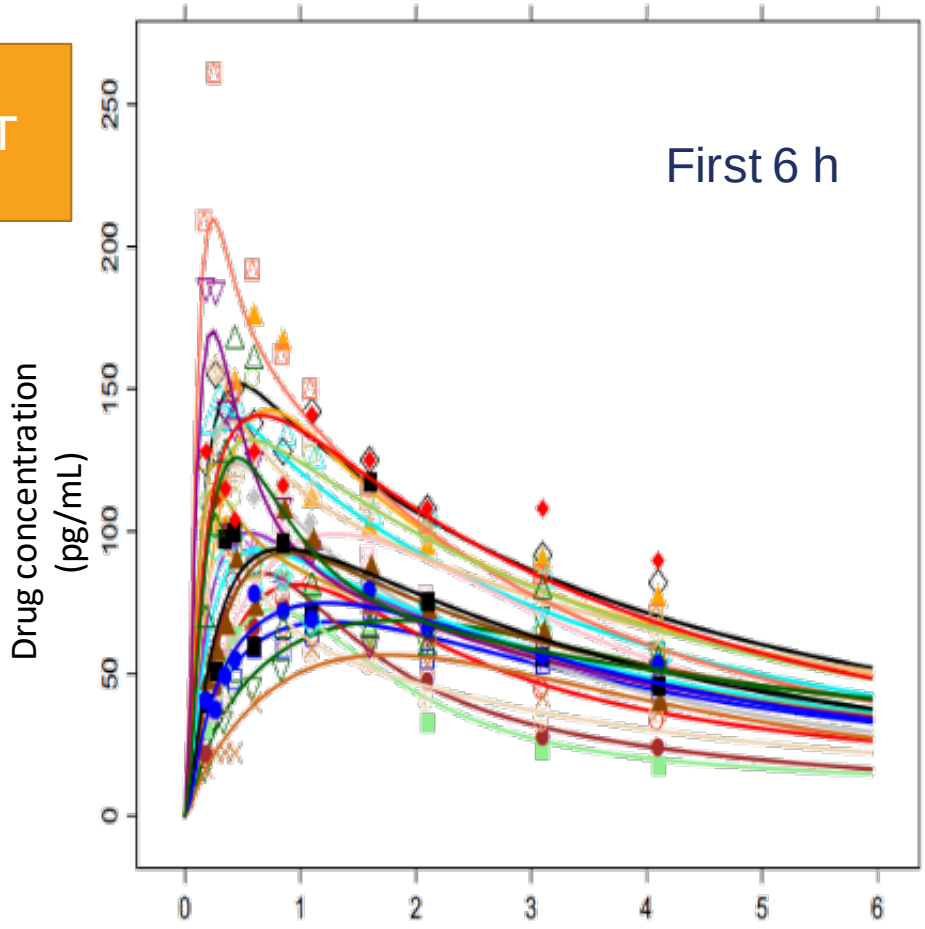
C_{max}: c/p Differences ????

Population PK analysis.



Fc: absorbed dose fraction from the central region of the lungs

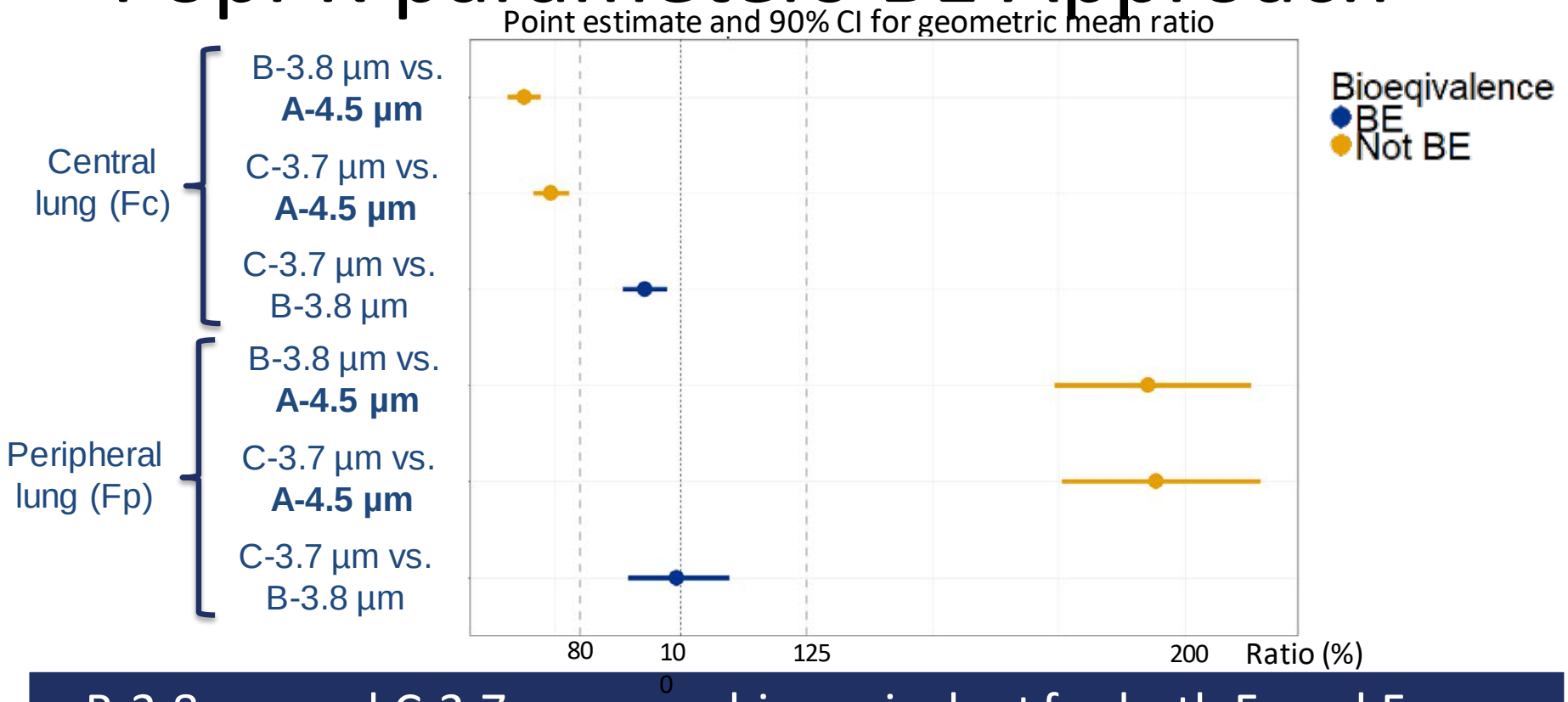
Fp: absorbed dose fraction from the central region of the lungs



Lung related population mean PK parameter estimates

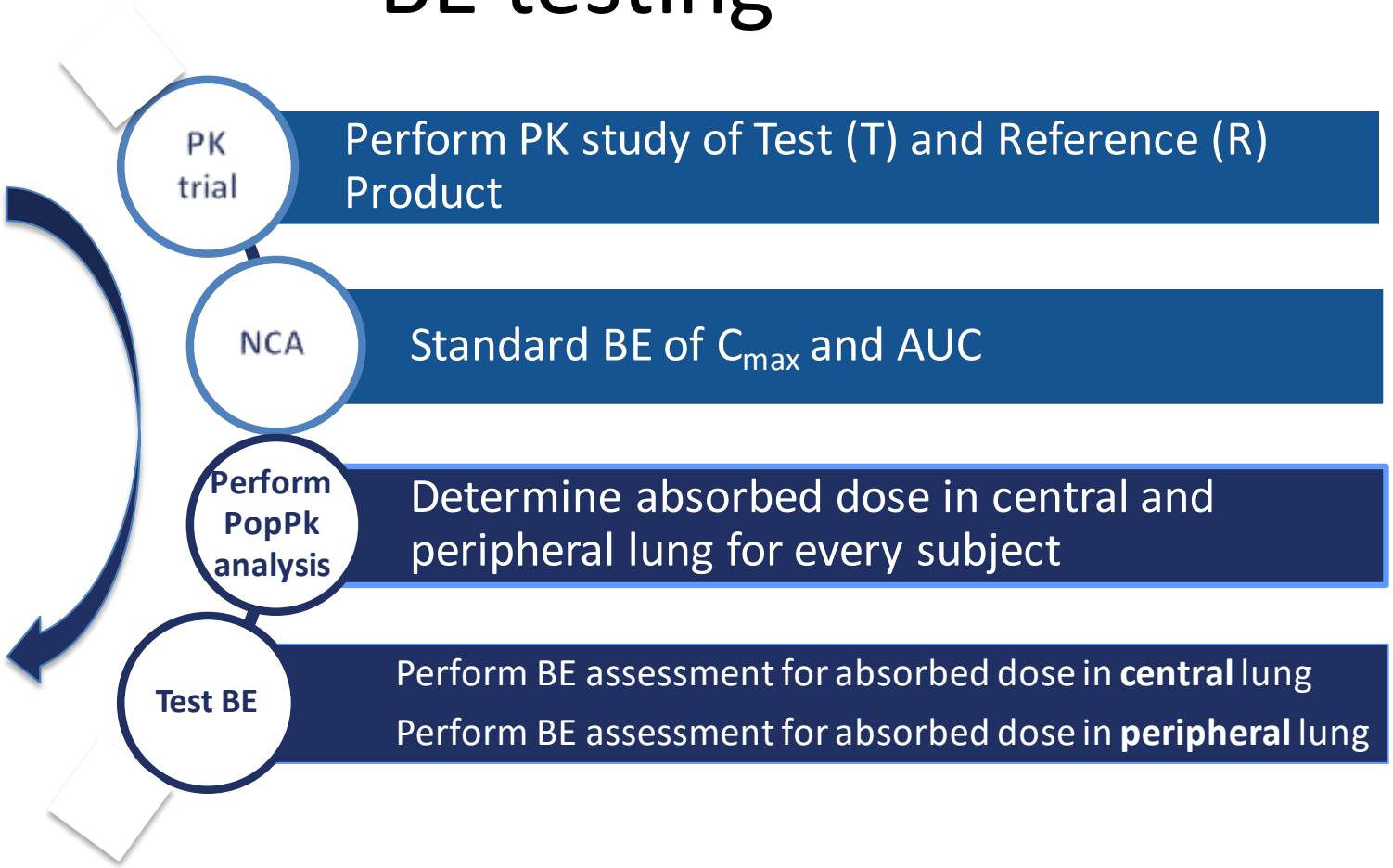
Parameters	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
	Mean (SE%)	Mean (SE%)	Mean (SE%)
Absorption $t_{1/2}$ for central lung (h)	6.2	7.9	9.1
Absorption $t_1$peripheral lung (h)	**0.241**	0.114	0.096
Absorbed dose - central lung (%)	**6.4 (18.2%)**	**4.4 (19.9%)**	**4.8 (15.1%)**
Absorbed dose-peripheral lung (%)	**5.1 (13%)**	**9.9 (17%)**	**9.9 (11%)**
c/p ratio	**1.25**	**0.44**	**0.48**

PopPK parameters BE Approach



- B-3.8 µm and C-3.7 µm were bioequivalent for both F_c and F_p
- A-4.5 µm vs B-3.8 µm and A-4.5 µm vs. C-3.7 µm were not bioequivalent

Conclusion 2:
Proposed New Methodology for PopPK BE testing

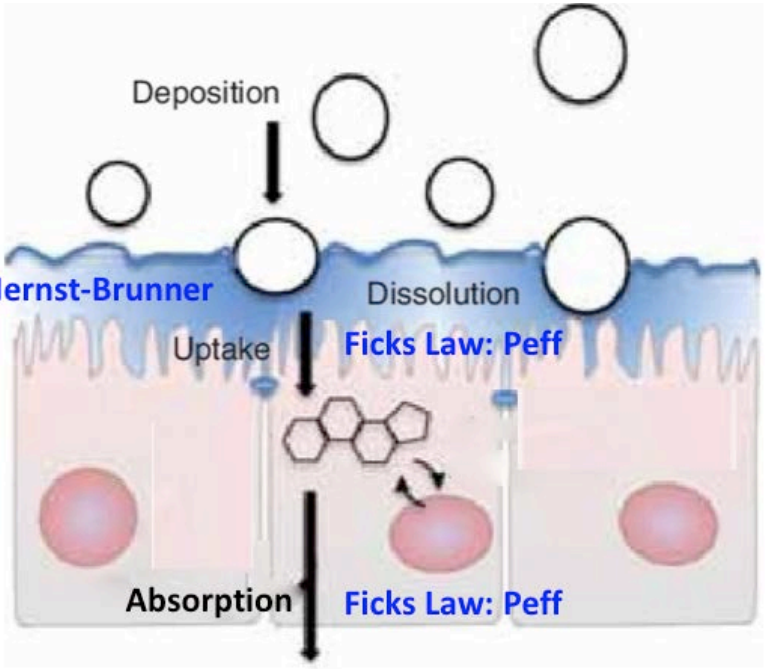


Can we explain PopPK results by PBPK?

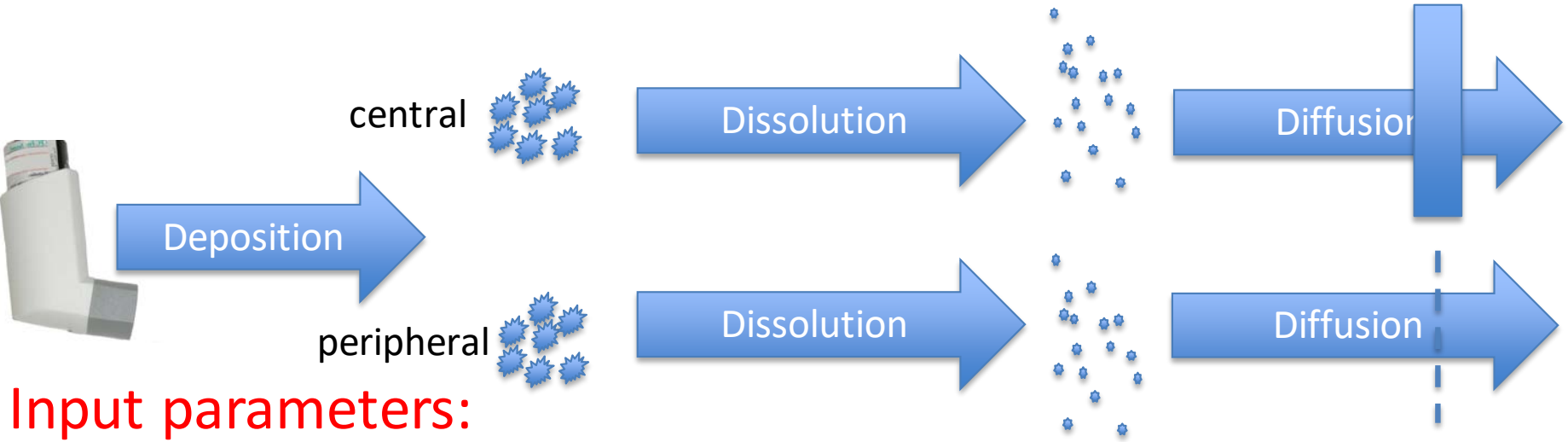
- We Know from PopPK
  - peripheral and central dose
  - central and peripheral ka

- PBPK Parameters
  - Deposited dose (in vitro)
  - c/p ratio (MMAD)
  - Dissolution (MMAD, GSD)
  - Permeability
    - caco-2-cells

(isolated perfused lung



PBPK Approach



Input parameters:

Deposition:

Subject related

Inhalation profile

In vitro:

- Ex-throat dose
- Cascade impactor

In silico Assessment: Deposition Modeling

Output

- c/p ratio
- Regional doses

Dissolution:

Subject related:

Healthy/Patient

In vitro:

- Solubility
- Particle Size
- Dissolution rates

In-silico

- Agglomeration factor
- Noyes-Brunner

Output

- **Dissolution rate**

Diffusion:

Subject related:

Surface Areas, Thickness

In vitro:

- Peff (caco-2)

In-silico

- Ficks-law (scaling)

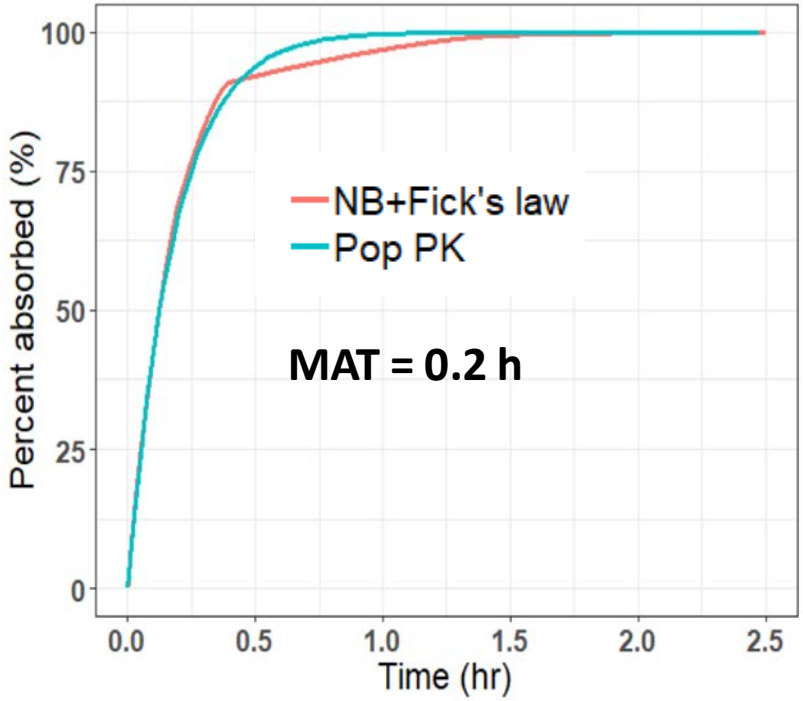
Output

- **Absorption rate**

Absorption Profile: PopPK vs PBPK

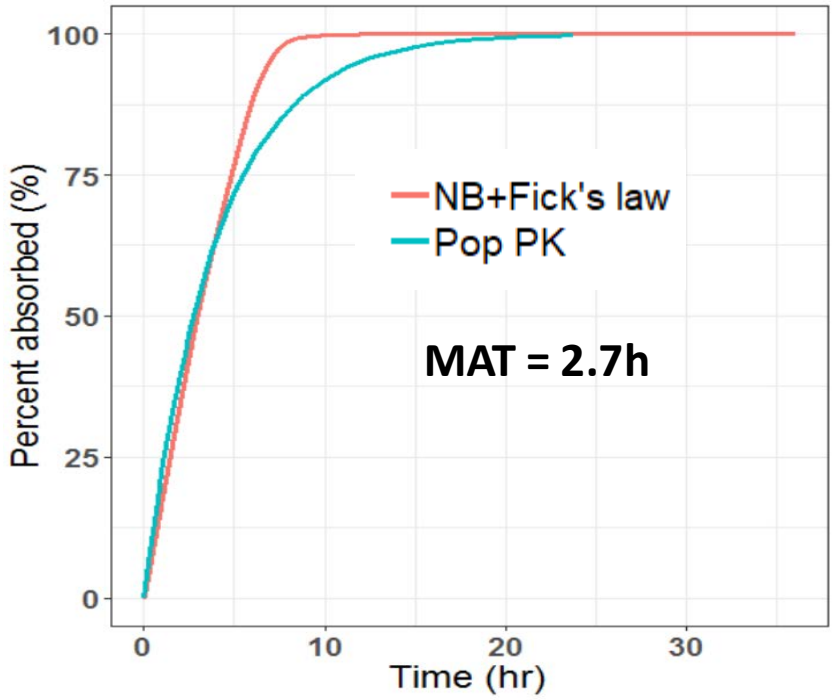
Peripheral

Formulation C



Central

Formulation C

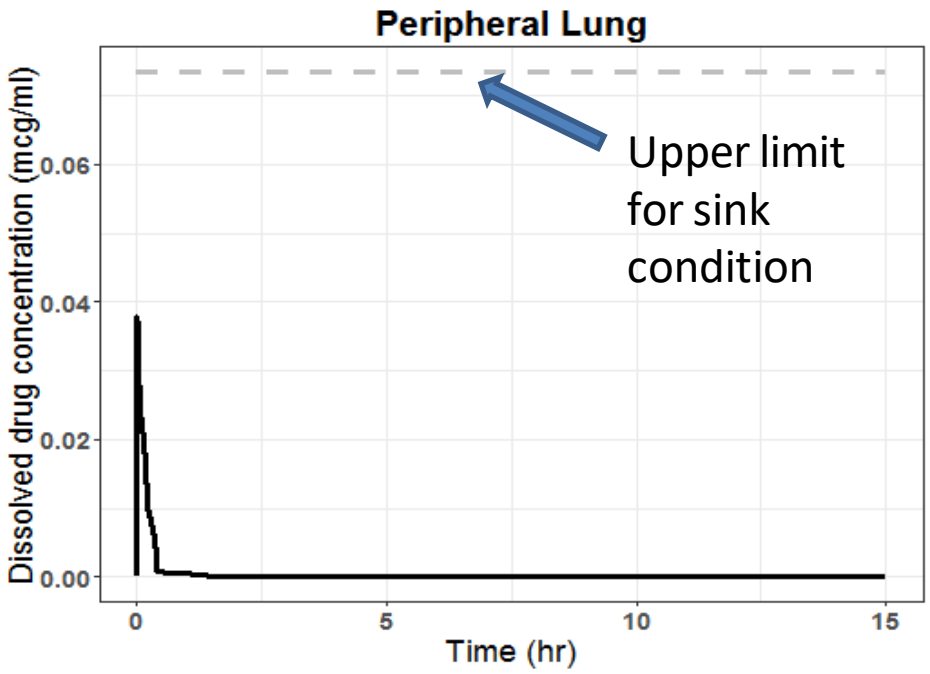


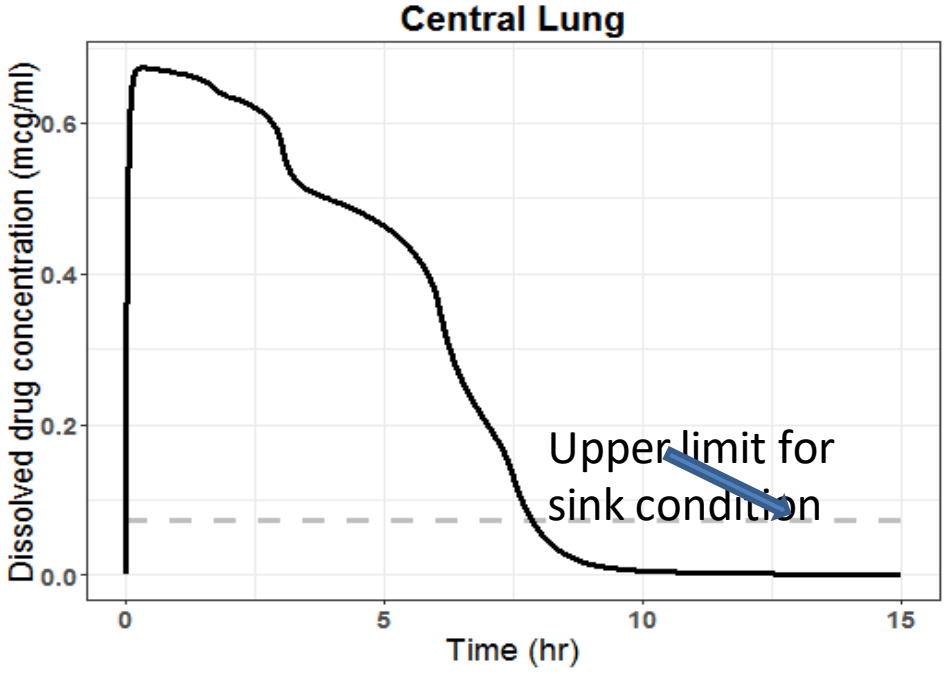
MMAD= 3.8 µm, GSD=2.0

Dose: 54 mcg, **Preludium**
Surface area: 60.2 *10^4 cm^2
Permeability Peff: 13.8*10^-3 cm/h (Eriksson)
Fitted Parameter:
Solubility: 0.73 µg/ml (Literature =0.5-1.4 µg/ml)

Dose 25 mcg, **Preludium**
Surface area: 1.00E+04 cm^2
Solubility: 0.73 µg/ml
Fitted Parameter:
Permeability: 0.7*10^-3 cm/h

Drug Concentration in Lining Fluid





Conclusion (Part 3)

- PBPK model appears to be able to describe central and peripheral absorption by considering dissolution and permeation.
- Slow **central** absorption due to **lack of sink conditions** and combined effects of dissolution and permeation.
- PBPK approach should be able to predict PK of formulations differing in regional deposition, dose and dissolution

- Can PBPK support NCA approach?

Is C_{max} sensitive to c/p ratio?

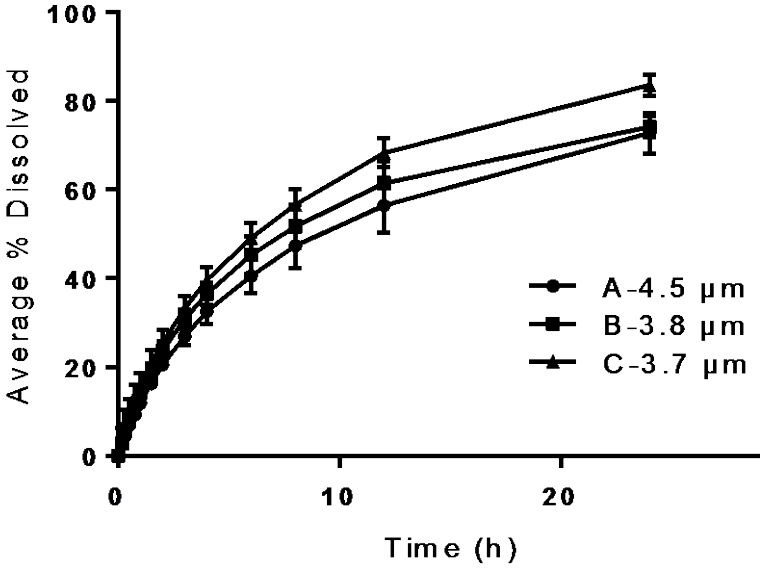
Differences in Dissolution Rate

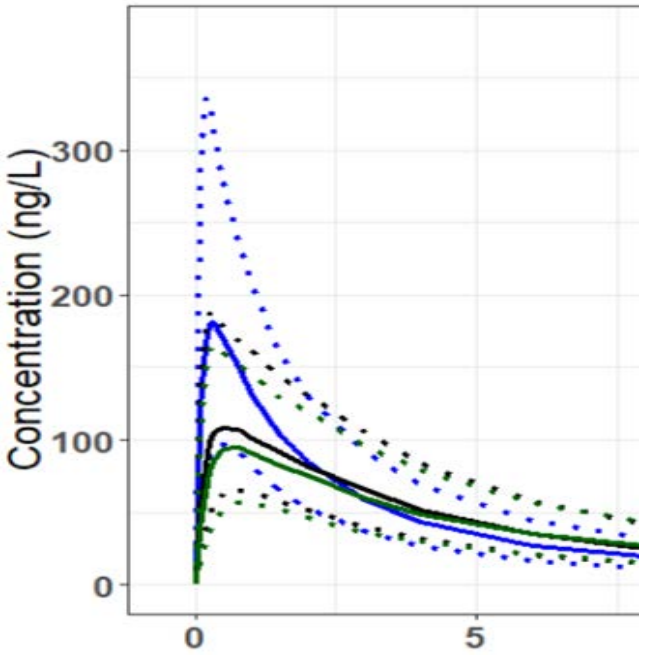
	MDT (h)	Relative surface area
A-4.5 µm	19.2	0.5
C-3.7 µm	13.4	1

Integrate in PBPK Model Nernst-Brunner Ficks Law

C_{max}, if only dissolution differs

C_{max} ratio	Predicted	Measured
C/A	1.15	1.8





Conclusions

- NCA Analysis are able to answer relevant questions related to BE assessment of Inhalation drugs (at least for lipophilic corticosteroids)
  - Dose
  - Residence time
  - Regional deposition
- Clinical studies might not be necessary
- Work underlines that PK may be able to provide supportive information important for pulmonary bioequivalence assessment

Study teams

UF Team.
Jürgen Bulitta, Ph.D.
Mong-Jen Chen, Ph.D.
Yuanyuan Jiao, Ph.D.
Uta Schilling, Ph.D.
Sharvari Bhagwat, Ph.D.
Abhinav Kurumaddali

UF Team
Sandra Baumstein, Pharm.D
Brandon Seay, MD
Mutasim N Abu Hasan, MD
Jie Shao
Elham Amini, Pharm. D.
Ann Ross, MHA

FDA Team
Denise Conti, Ph.D.
Renish Delvadia, Ph.D.
Minori Kinjo, Ph.D.
Bavna Saluja, Ph.D.
Murewa Oguntimein, M.H.S.

- HHSF223201110117A, HHSF223201610099C, HHSF223201300479A
- 1U01FD004950

UB
Jag Shur, Ph.D.
Robert Price, Ph.D.

VCU
Mike Hindle, Ph.D.
Xiangyin Wei, Ph.D.