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

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

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- **Views expressed in this presentation do not necessarily reflect the official policies of the U.S. Food and Drug Administration**,
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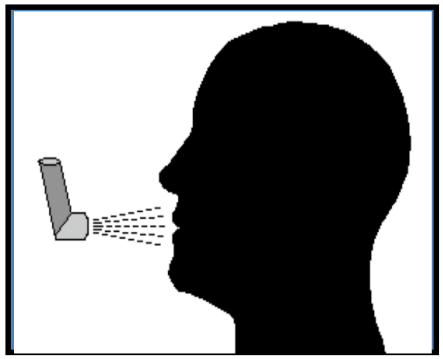
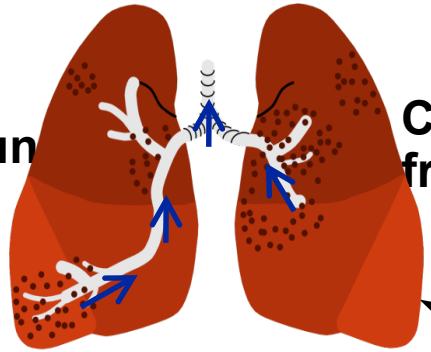
Topics related to Bioequivalence?

dose, regional deposition, time?

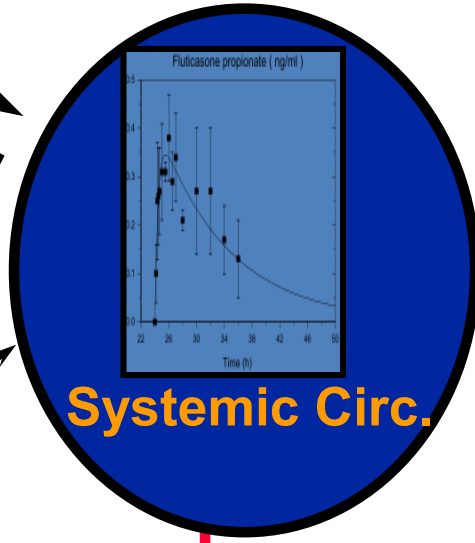


10 - 60 %
Deposited in lun

Cl_{muc}



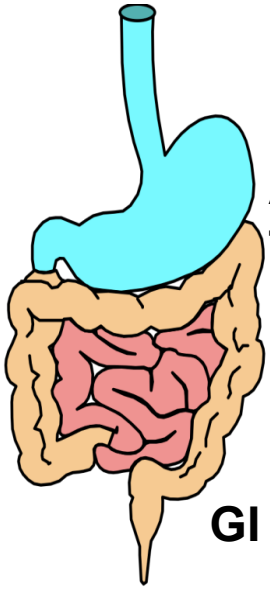
Complete absorption
from the lung



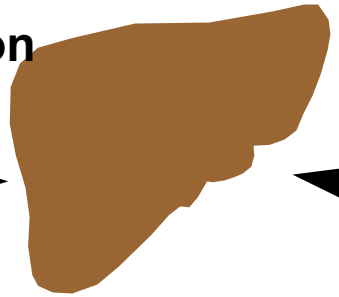
Lung

Mouth and pharynx

Orally bioavailable
fraction



Absorption
from gut



Liver

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

GI tract

First-pass
inactivation

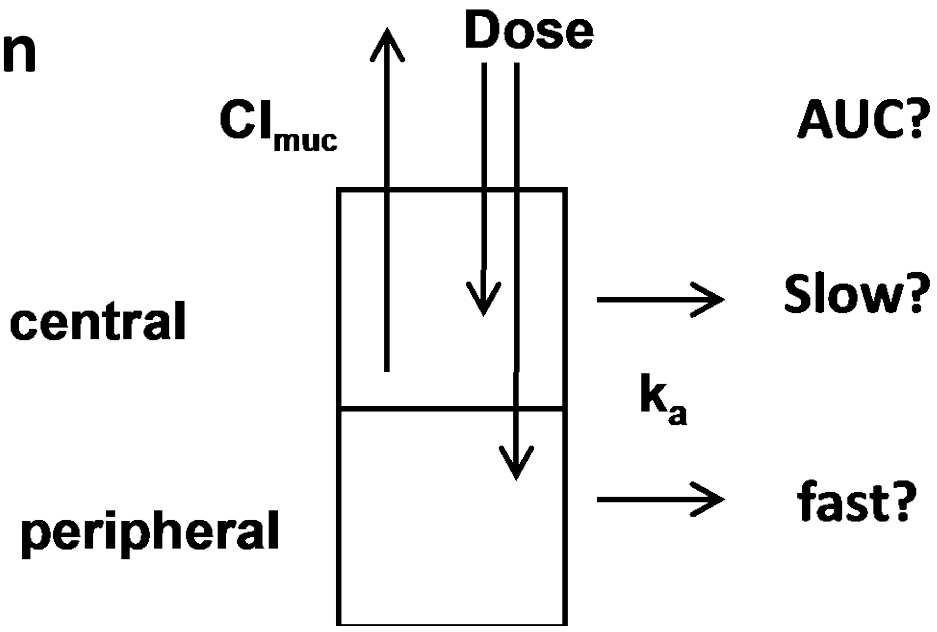
**Systemic
side effects**

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)

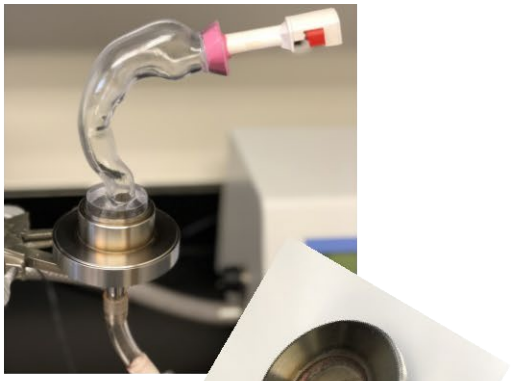
Cascade Impactor Data

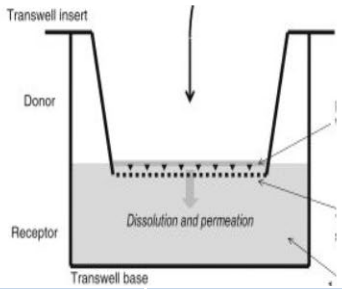
Mass deposition	Particle size (µm)	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
Mass Median Aerodynamic Diameter		**4.50**	**3. 8**	**3.7**
Larger Particles	2.8 - 8.1 µm	**12.5**	**14.4**	**11.5**
Smaller Particles[P] (µg)	< 2.8 µm	**4.8**	**9.4**	**8.1**
Relative Ex Throat Dose (Anatomical Throat)		**1**	**1.3**	**1.2**

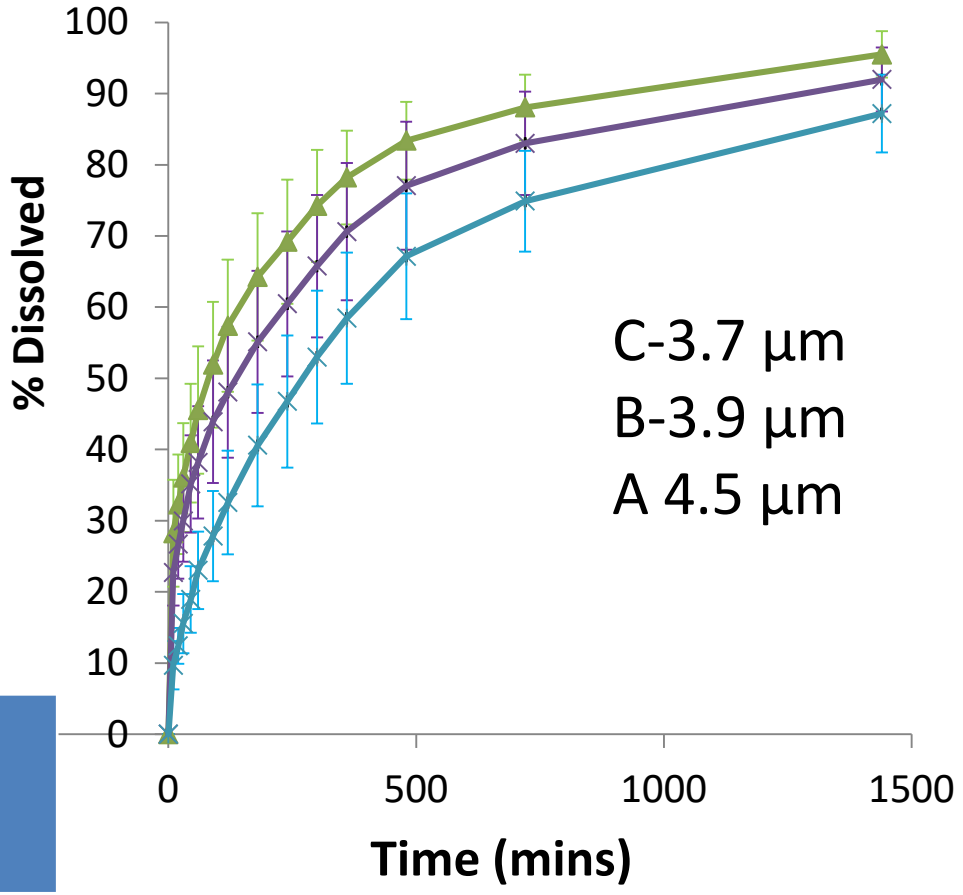
[C] and [P] presumable representing central and peripheral lung deposition, respectively

- 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





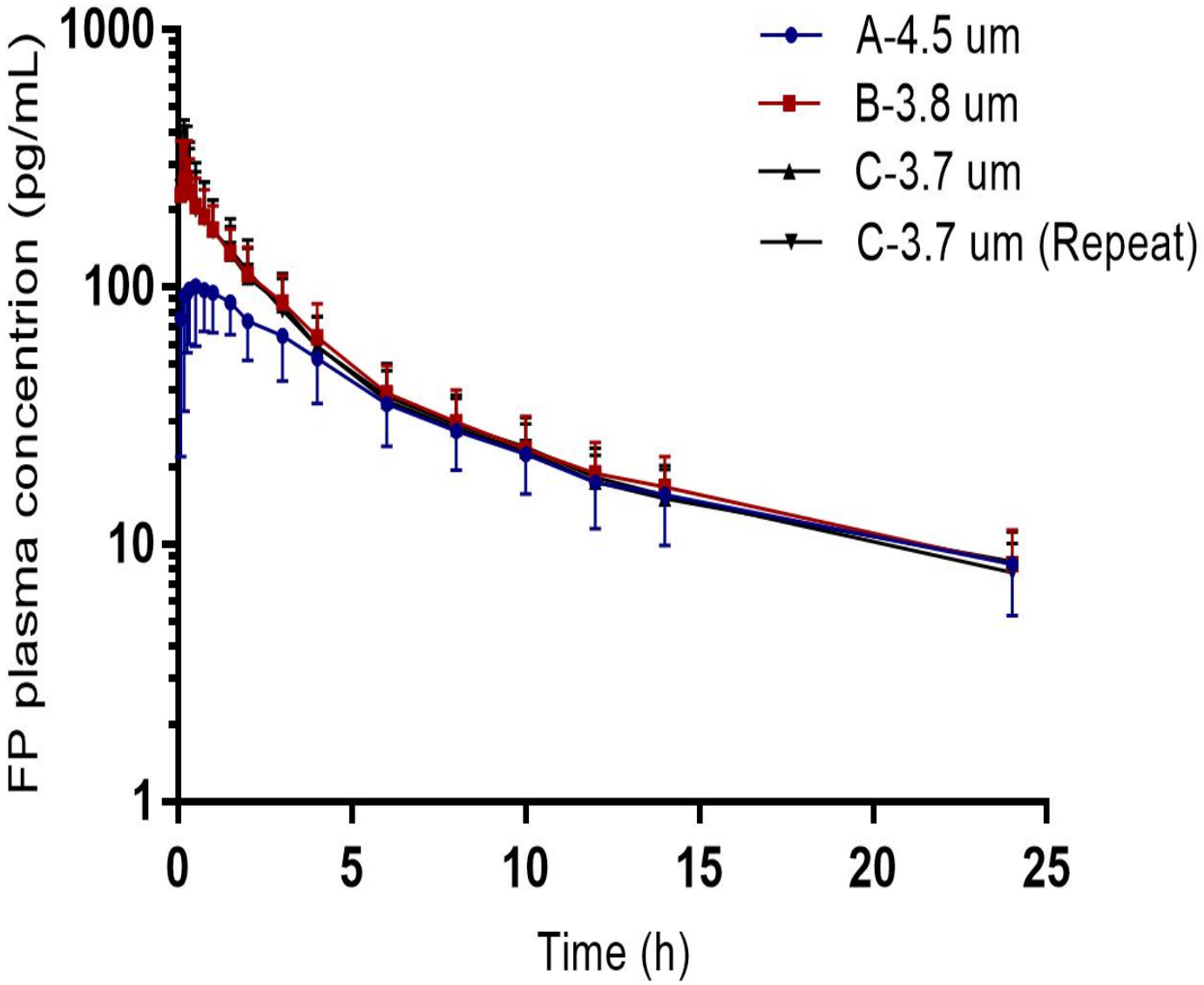


Formulation	MDT (h)	Relative surface area
A-4.5 µm	15.4	0.5
B-3.9 µm	13.3	0.7
C-3.7 µm	10.3	1

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

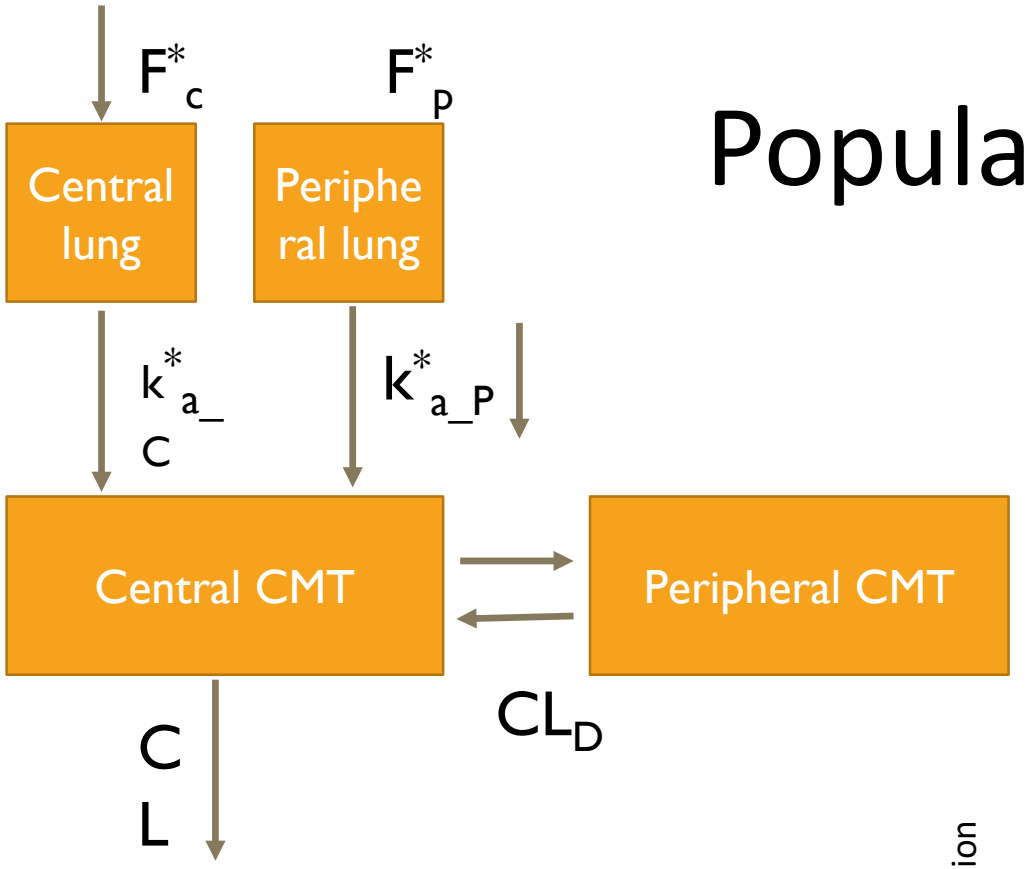
After Dose Normalization

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

AUC: c/p Differences could not be shown

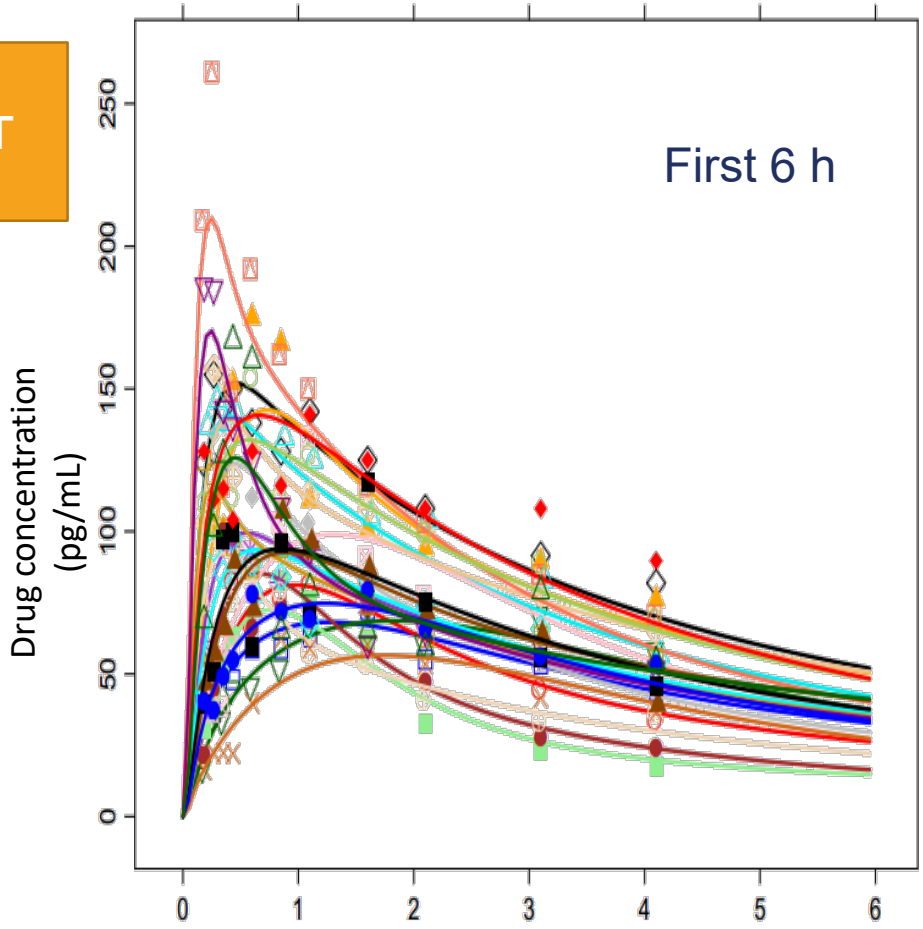
C_{max}: c/p Differences ????

Population PK analysis.



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

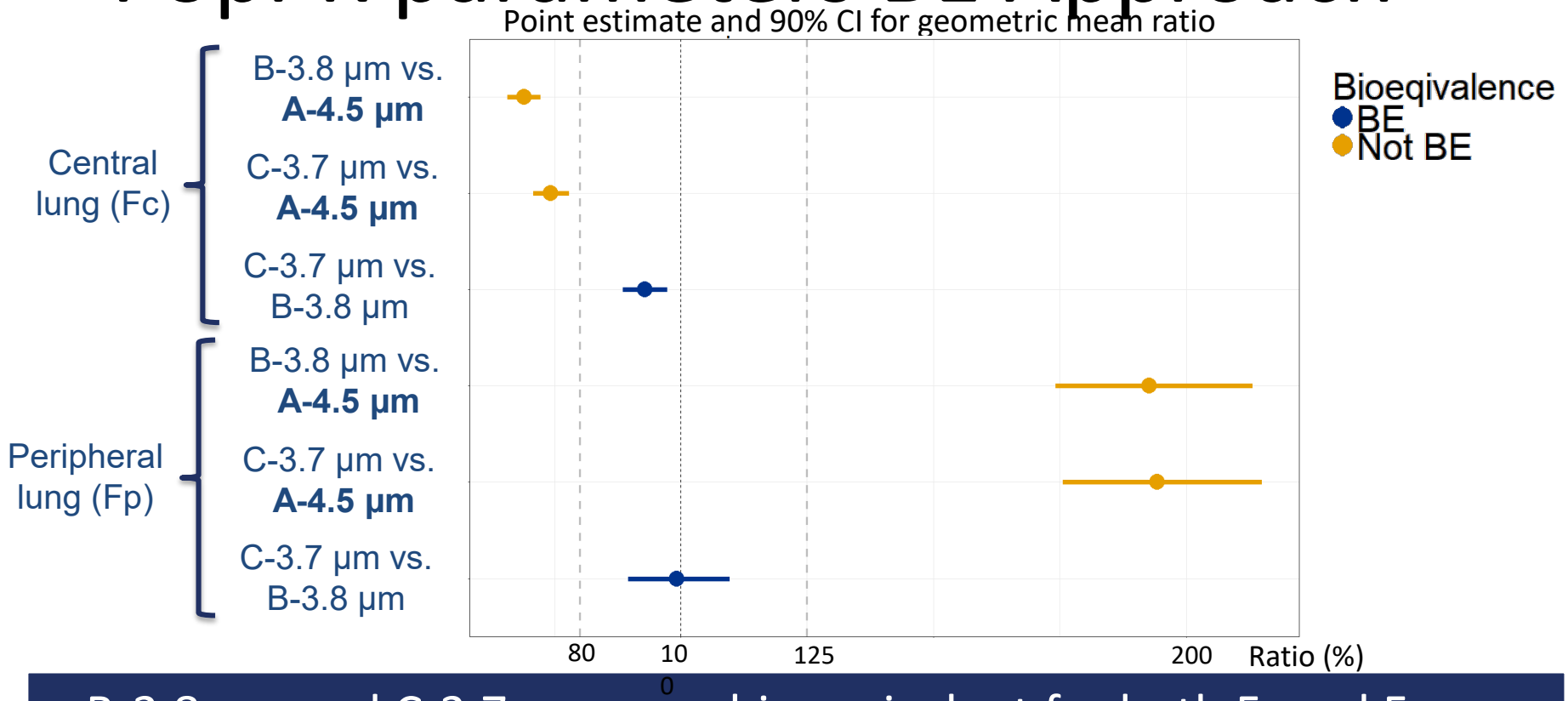
Fp: absorbed dose fraction from the central region of the lungs



Lung related population mean PK parameter estimates

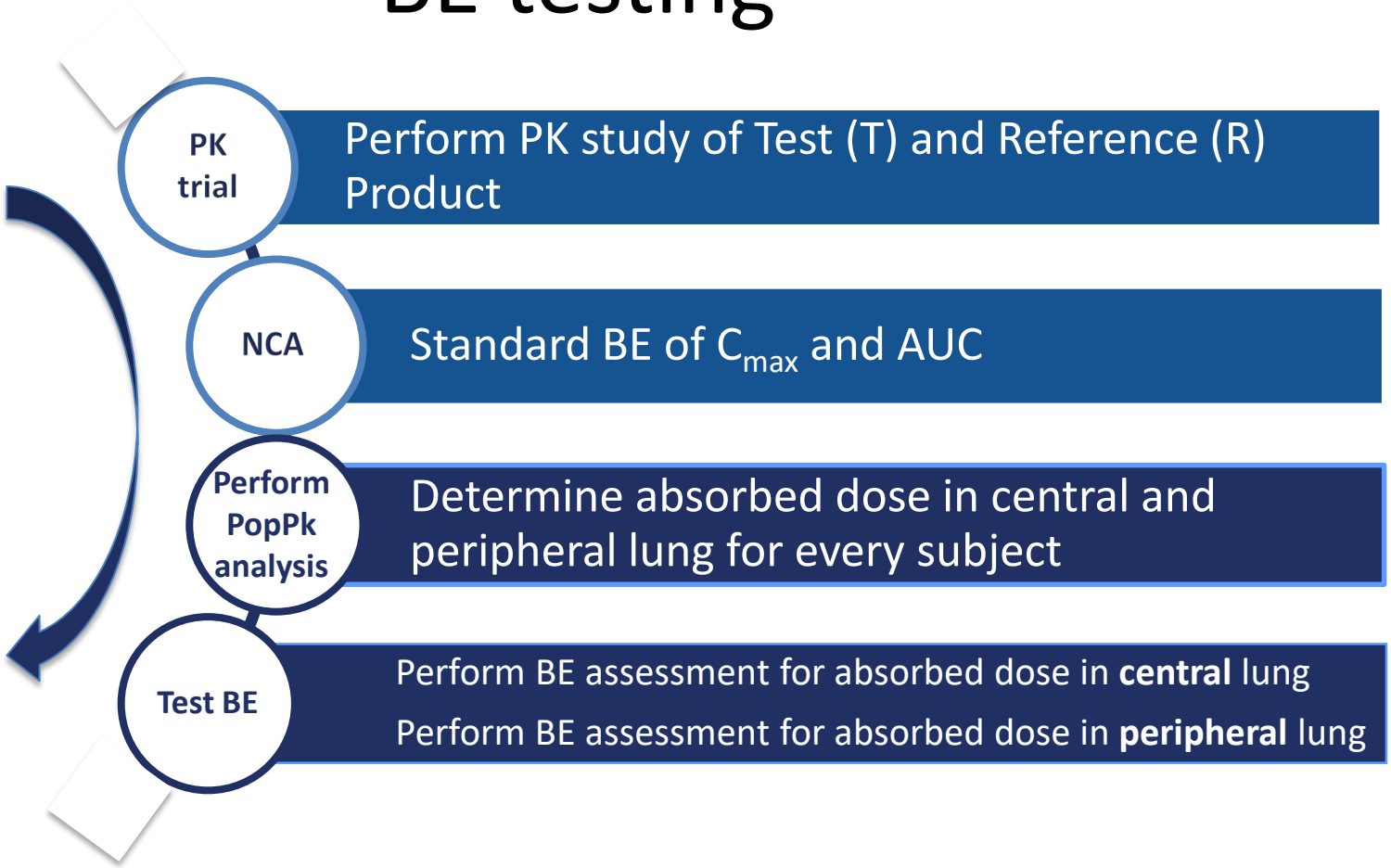
Parameters	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
	Mean (SE%)	Mean (SE%)	Mean (SE%)
Absorption $t_{1/2}$ for central lung (h)	6.2	7.9	9.1
Absorption $t_1$peripheral lung (h)	**0.241**	0.114	0.096
Absorbed dose - central lung (%)	**6.4 (18.2%)**	**4.4 (19.9%)**	**4.8 (15.1%)**
Absorbed dose-peripheral lung (%)	**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

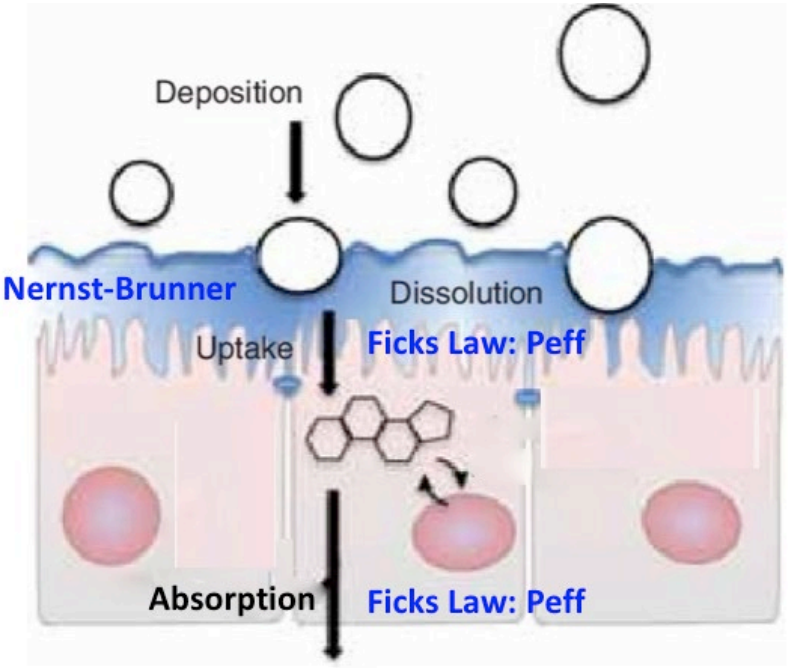


Can we explain PopPK results by PBPK?

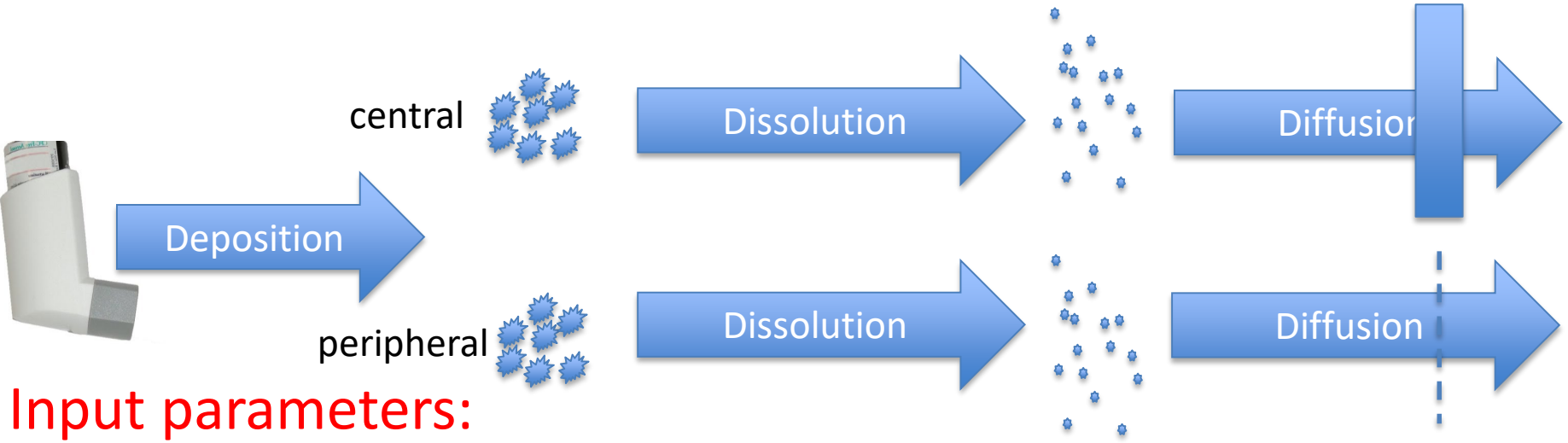
- We Know from PopPK
  - peripheral and central dose
  - central and peripheral ka

- 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)

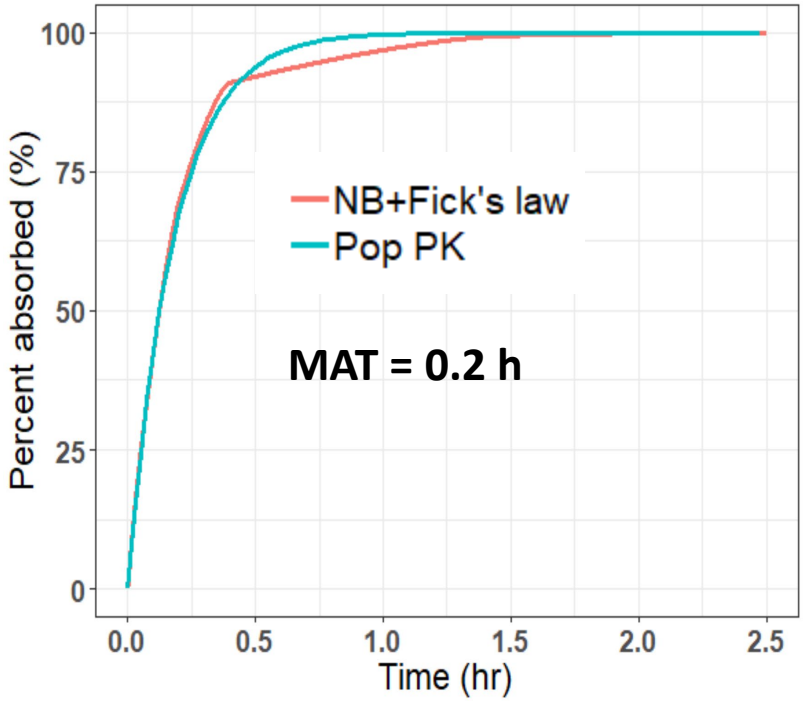
Output

- **Absorption rate**

Absorption Profile: PopPK vs PBPK

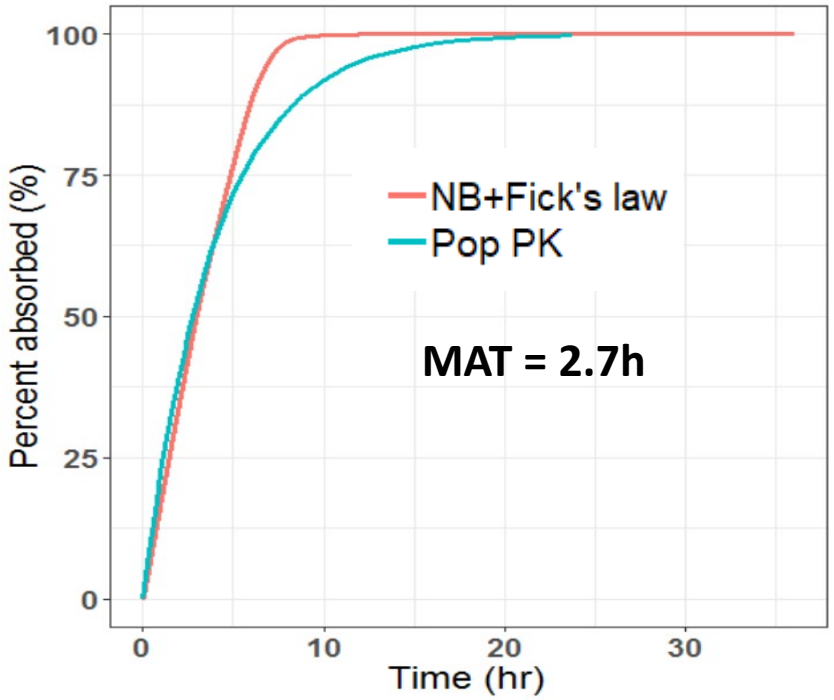
Peripheral

Formulation C



Central

Formulation C

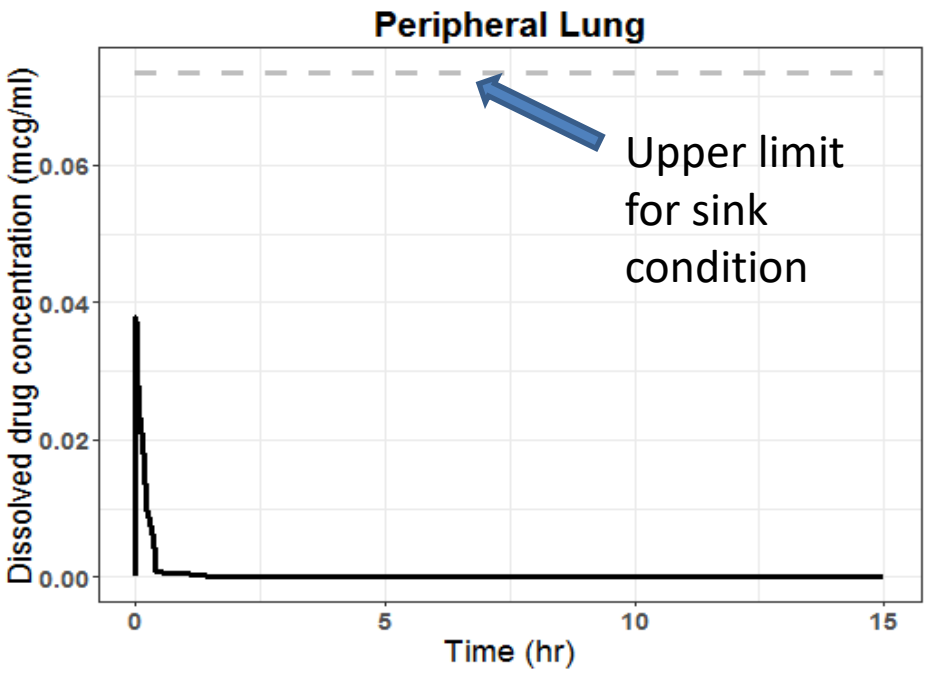


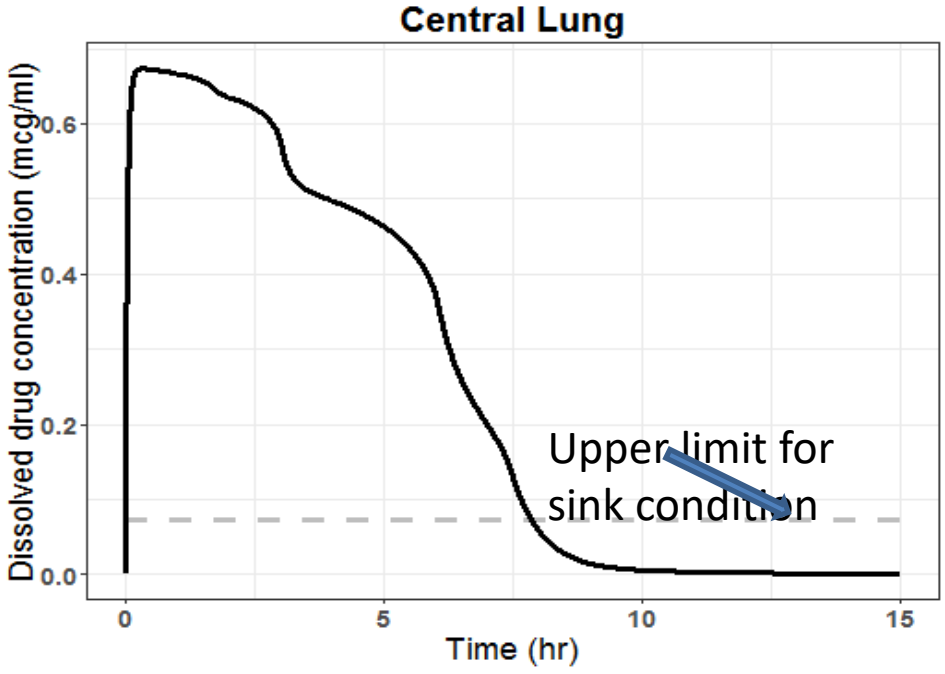
MMAD= 3.8 µm, GSD=2.0

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?

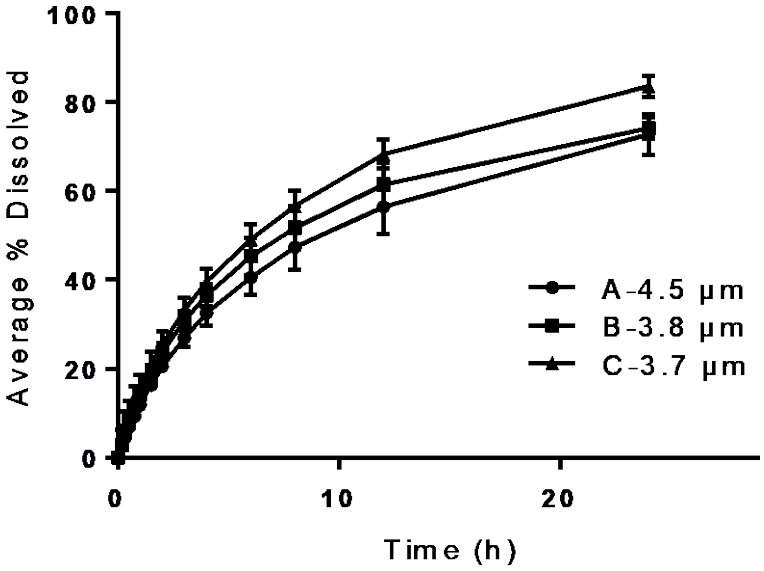
Differences in Dissolution Rate

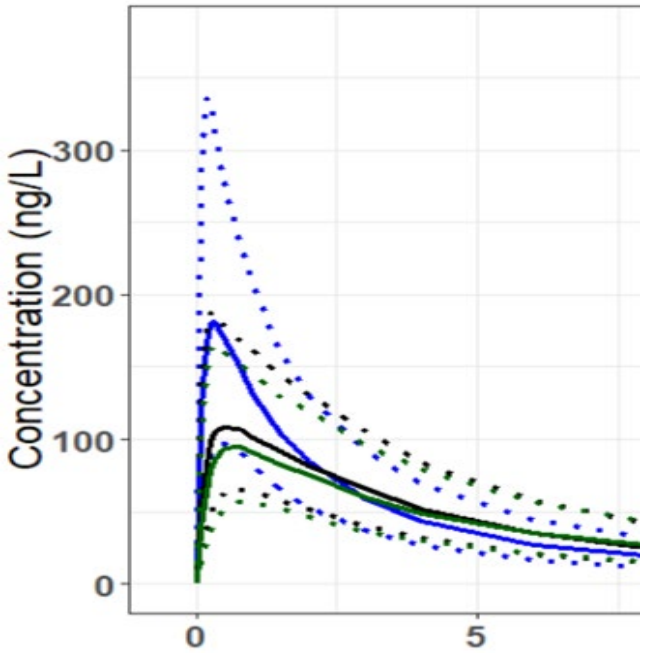
	MDT (h)	Relative surface area
A-4.5 µm	19.2	0.5
C-3.7 µm	13.4	1

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

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