Unraveling the Pulmonary Fate of Fluticasone and Friends: Meeting the Physiologic and Pharmacokinetic Challenge

Günther Hochhaus

Study teams

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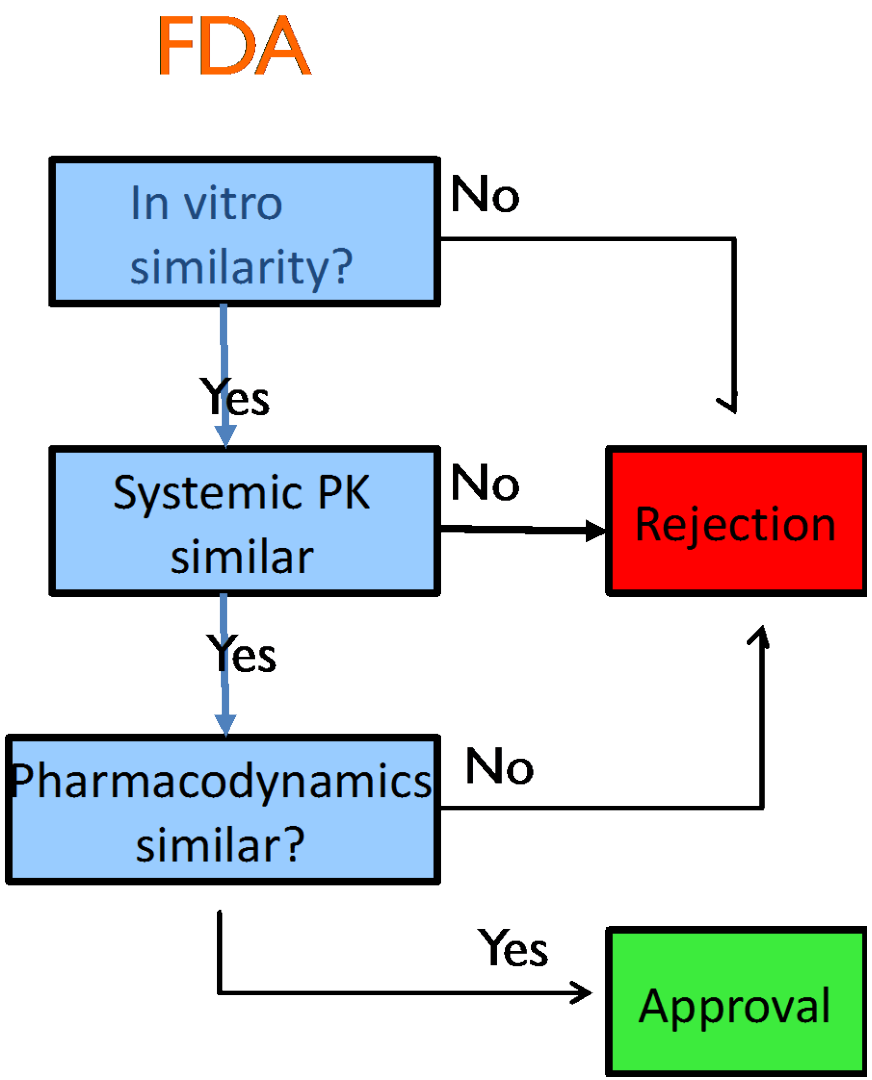
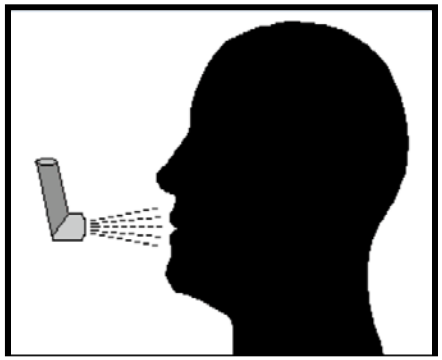
FDA's Weight of Evidence Approach



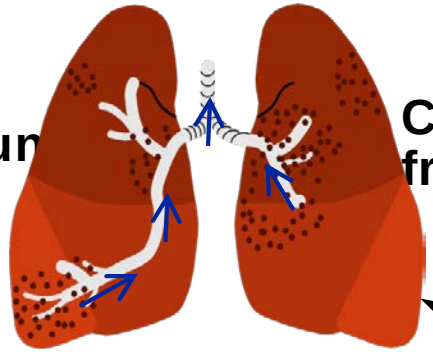
Topics related to Bioequivalence?

dose, regional deposition, time?

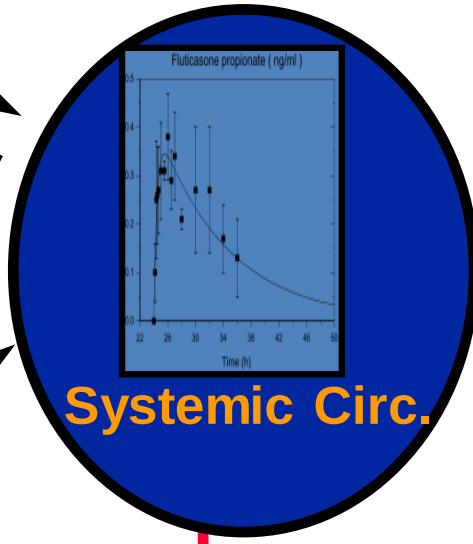


10 - 60 %
Deposited in lun

Cl_{muc}



Complete absorption
from the lung

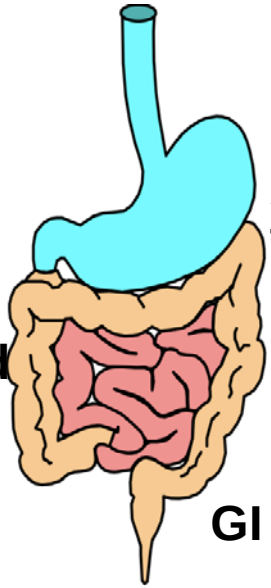


Systemic Circ.

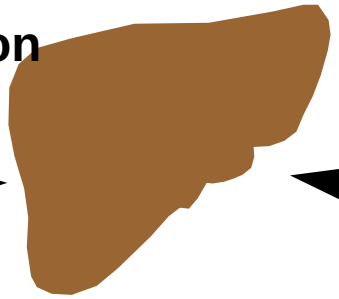
Lung

Mouth and pharynx

Orally bioavailable
fraction



Absorption
from gut



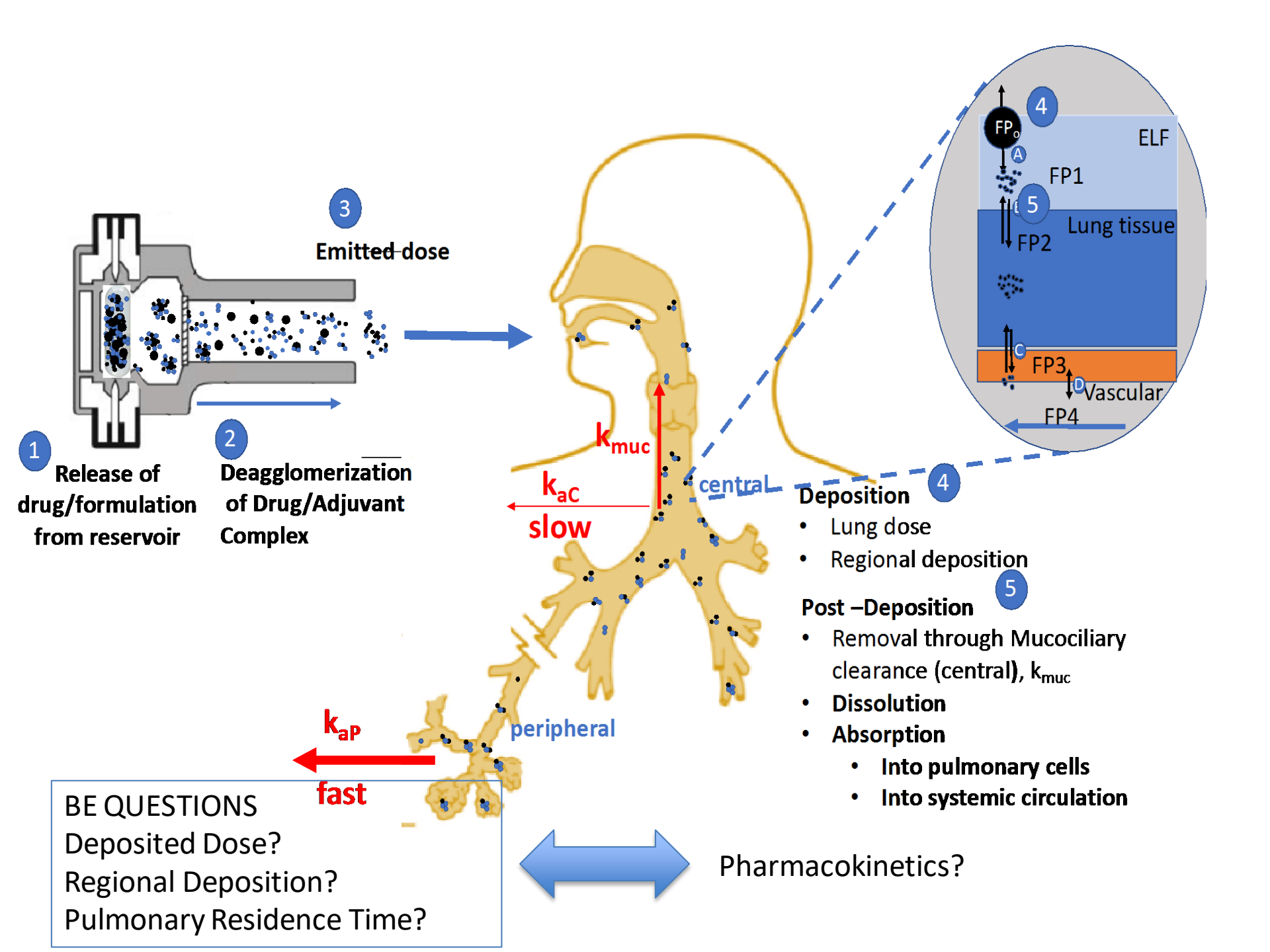
Liver

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

GI tract

First-pass
inactivation

**Systemic
side effects**


3
Emitted dose
1
Release of drug/formulation from reservoir
2
Deagglomerization of Drug/Adjuvant Complex
k_{muc}
k_{aC}
slow
central
k_{aP}
fast
peripheral
4
FP_0
A
FP1
5
B
FP2
Lung tissue
ELF
C
FP3
D
Vascular
FP4
4
Deposition
• Lung dose
• Regional deposition
5
Post –Deposition
• Removal through Mucociliary clearance (central), k_{muc}
• Dissolution
• Absorption
• Into pulmonary cells
• Into systemic circulation
BE QUESTIONS
Deposited Dose?
Regional Deposition?
Pulmonary Residence Time?
Pharmacokinetics?

Alternative Methods for BE Studies?

- **Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIPs)**: PQRI/INFG; Workshop Summary Report. J Aerosol Med Pulm Drug Delivery. 2010; 23: 1–29.
- **Role of pharmacokinetics in establishing bioequivalence for orally inhaled drug products: workshop summary report**. PQRI/RDD. J Aerosol Med Pulm Drug Deliv. 2011; 24:119–35.
- **Current scientific and regulatory approaches for development of orally inhaled and nasal drug products, IPAC-RS/University of Florida Orlando Conference**. AAPS J. 2015;17:1305–11.

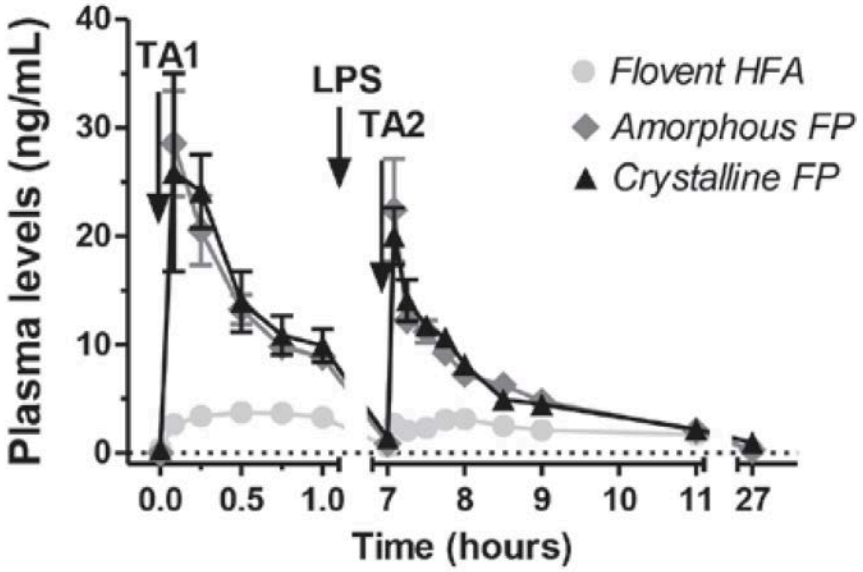
SUGGESTIONS

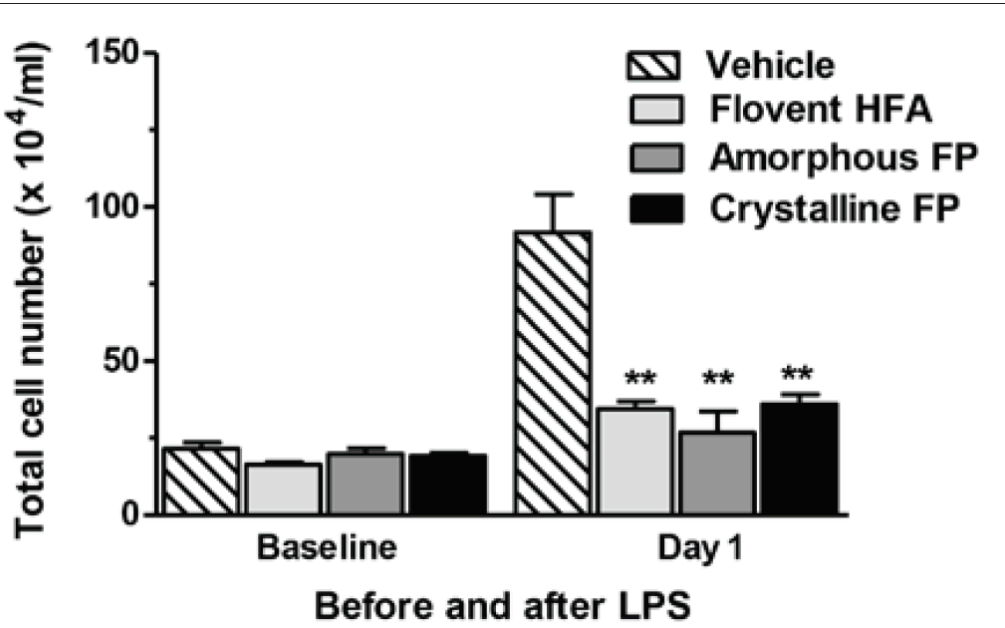
- Use of
  - State of the art in vitro assessments
  - In silico characterization (CFD, PBPK)
  - Pharmacokinetics
- Can replace
  - Clinical/pharmacodynamic studies
- However:

Is Systemic PK Really an Indicator of Pulmonary Deposition? A Fluticasone Propionate Case Study

Philip J. Kuehl,[1] Edward G. Barrett,[1] Michael Burke,[2] Ramesh Chand,[1] Devon DuBose,[2] Benjamin Moeller,[1] Karin Rudolph,[1] Ryan Sheeler,[1] and David Vodak[2]

Is PK unable to provide information relevant to the fate in the lung?





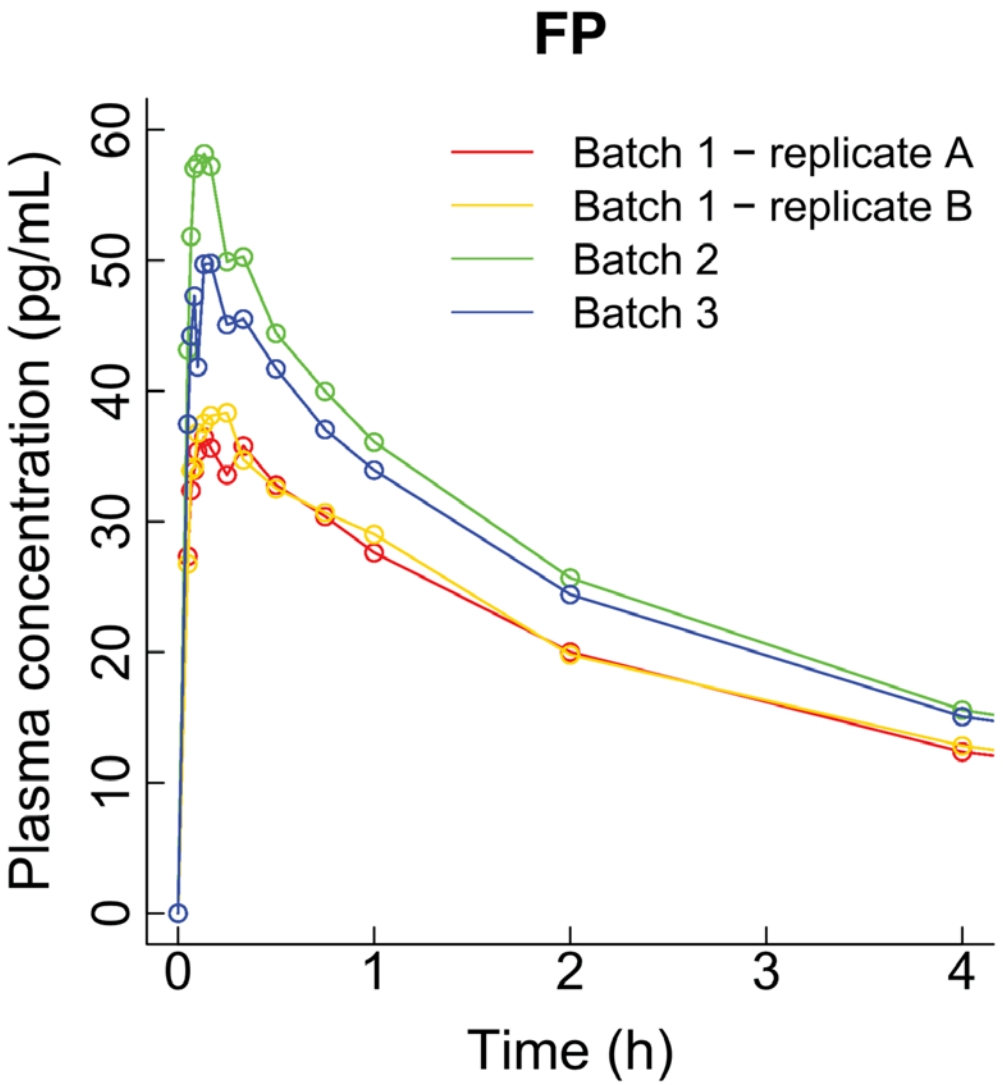
Kuehl et al. RDD 2016

PK not always accurately predict pulmonary dose and correlate to local efficacy.

Pharmacokinetic Behavior of Fluticasone Propionate and Salmeterol from Advair Diskus: The Consequences of Batch Variability

Elise Burmeister Getz,[1] Kevin J. Carroll,[2] Johanna Mielke,[3] Byron Jones,[3] and Leslie Z. Benet[4]

PK too sensitive???



Differences between in vitro, PK and clinical studies

	In Vitro	PK	PD
Advair vs Wixela (7) (8)	equivalent	equivalent	equivalent
Diskus vs RPID (5)	good match	not equivalent	equivalent
Diskus vs Diskhaler (5)	small differences	not equivalent in healthy similar in asthmatics	equivalent
FP HFA vs FP CFC (5)	good match	not equivalent	equivalent
HFA vs CFC FP and Sal (12)	FP: similar Sal: similar	FP: similar Sal: different	equivalent equivalent
FP DPIs (6)		different	equivalent

5 Daley-Yates, Parkins et al. Expert Opinion Drug Deliv, 2011
7 Haughie et al. J Aerosol Med Pulm Drug Deliv. 2019; 32:1–9.
8 Ng et al, J Aerosol Med Pulm Drug Deliv. 2019; 33: 1547
12 Clearie et al. . Br J Clin Pharmacol. 2011 Apr;7: 504–13.
6 Kuehl et al. RDD 2016
RPID: Reservoir powder inhalation device

Questions?

- Is PK too sensitive? IS PK relevant?
- Are in vitro tests too insensitive or don't we use the right in vitro tests?
- Do we lack a sound understanding of processes involved?

- Hypothesis:
  - PK is relevant
  - A better understanding of pulmonary events might link in vitro, PK and consequently PD.
  - Work might provide arguments for streamlined BE approval strategies.

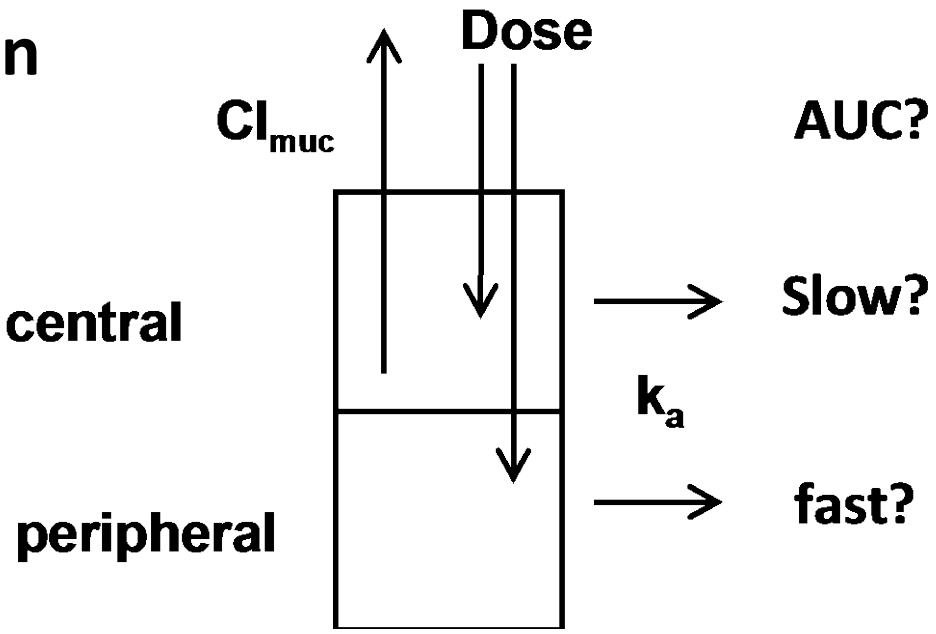
Actual Question of this research Project

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

extract Information on :

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

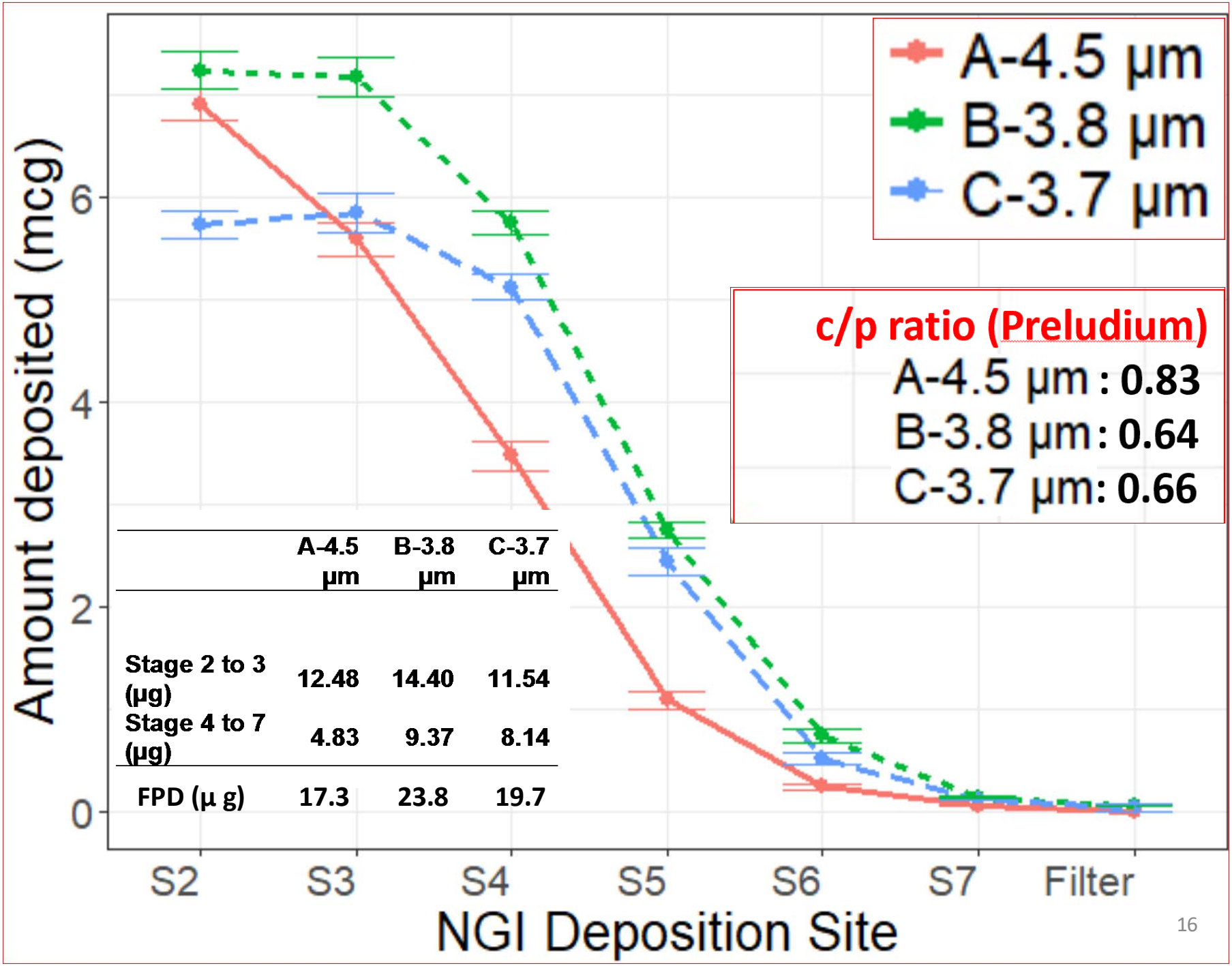
Hypothesis:
After dose-normalization:
AUC and/or Cmax will be be able to
Detect differences in regional deposition



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)



	A-4.5 µm	B-3.8 µm	C-3.7 µm
Stage 2 to 3 (µg)	12.48	14.40	11.54
Stage 4 to 7 (µg)	4.83	9.37	8.14
FPD (µ g)	17.3	23.8	19.7

Cascade Impactor Data

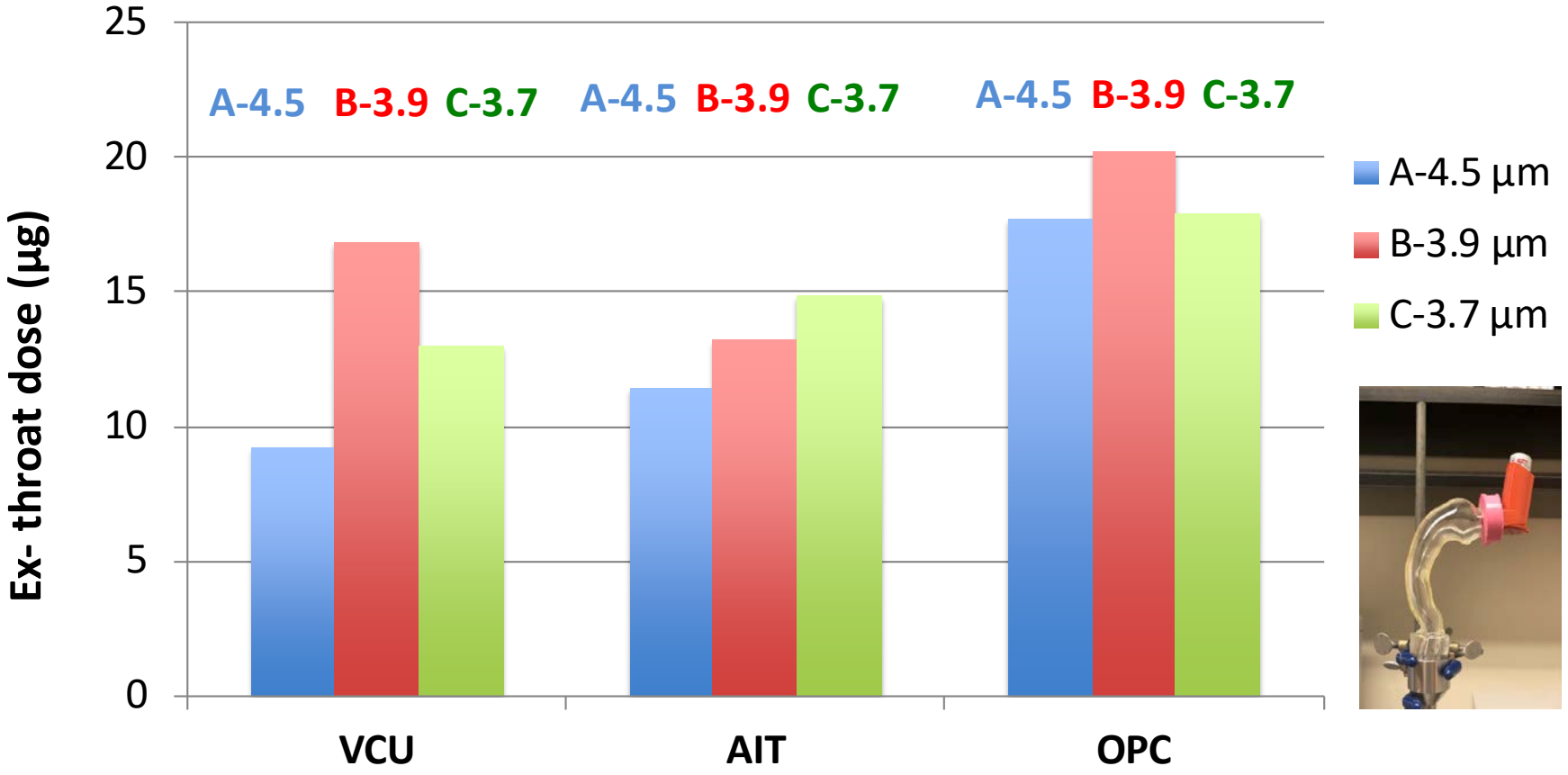
Mass deposition	Particle size (µm)	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
Mass Median Aerodynamic Diameter		**4.50**	**3. 8**	**3.7**
Larger Particles	2.8 - 8.1 µm	**12.5**	**14.4**	**11.5**
Smaller Particles[P] (µg)	< 2.8 µm	**4.8**	**9.4**	**8.1**
Relative Ex Throat Dose (Anatomical Throat)		**1**	**1.3**	**1.2**

[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 the same lung dose?

Ex-throat dose: anatomical throats, typical inhalation profile

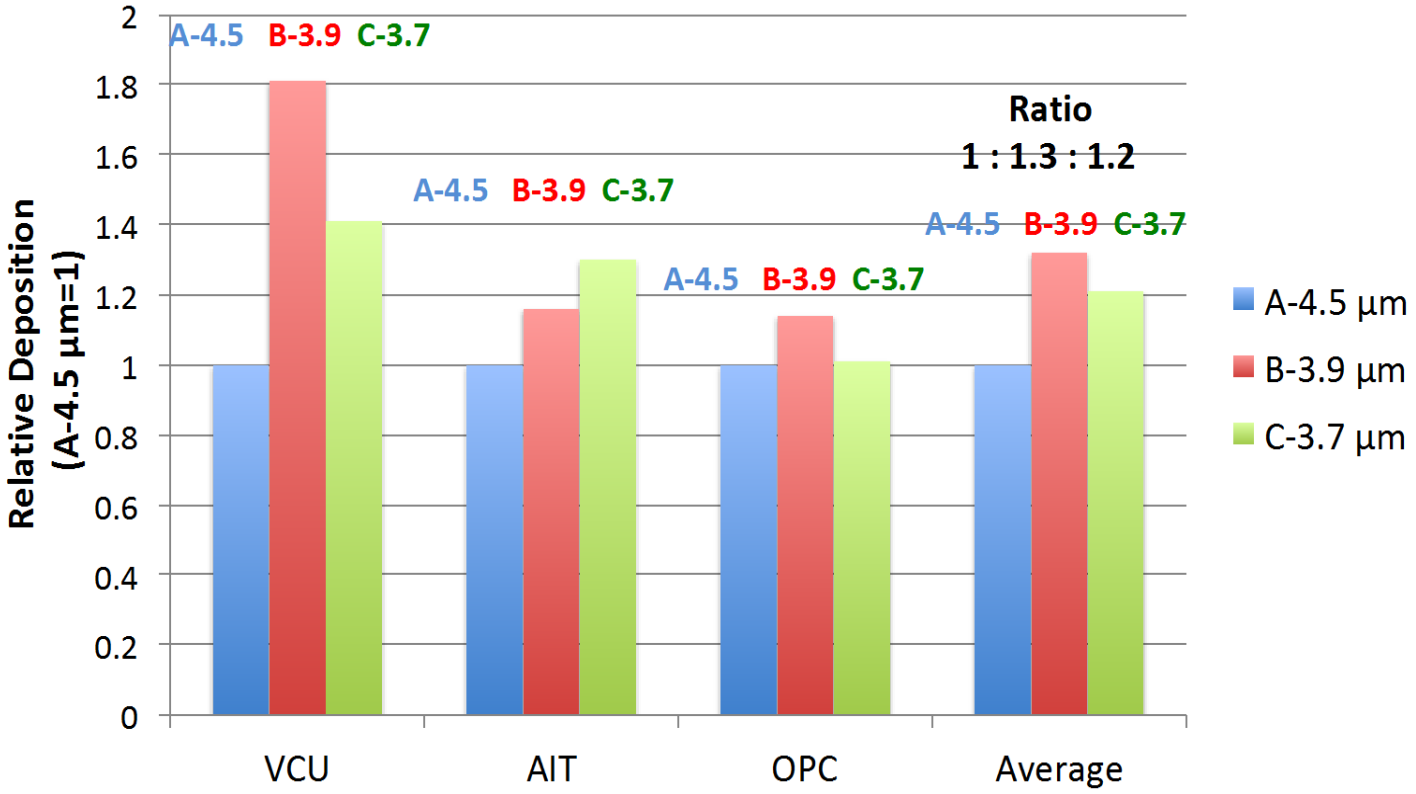


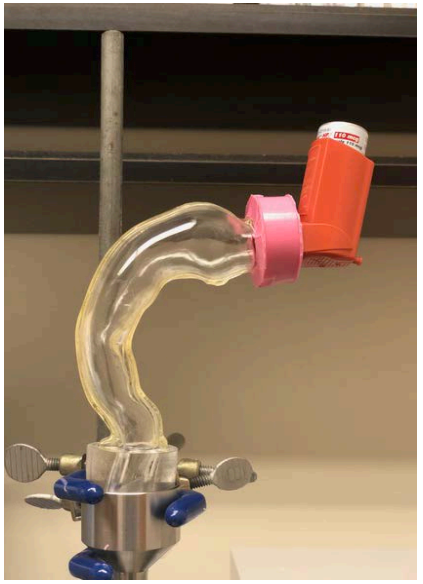
- **Throats differ in deposited amounts**
- **Projected Lung Doses will differ**
- **By which factor?**

Dr. Mike Hindle , VCU

Relative Ex-throat dose

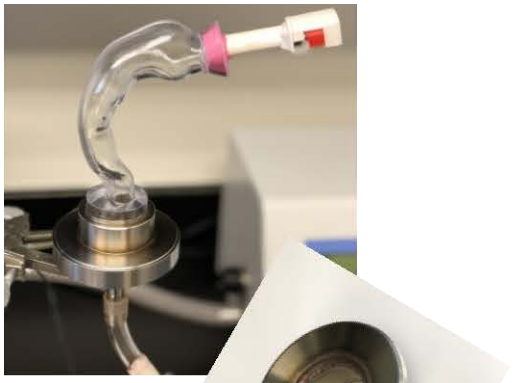
(anatomical throats, typical inhalation profile)

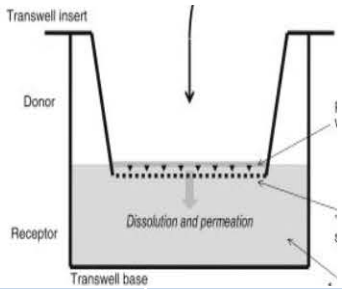


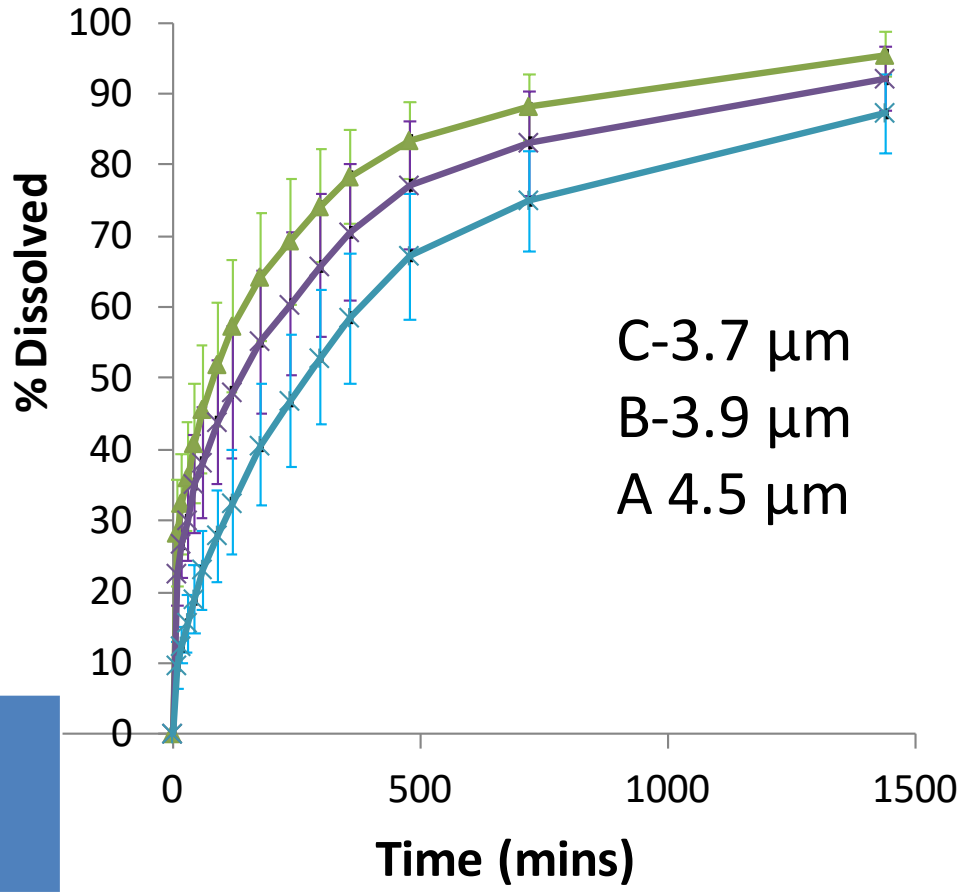


- Throats differ in rank-order and ratio
- Mean ratio for A4.5µm :B3.9µm: C3.7µm: 1: 1.3 : 1.2

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





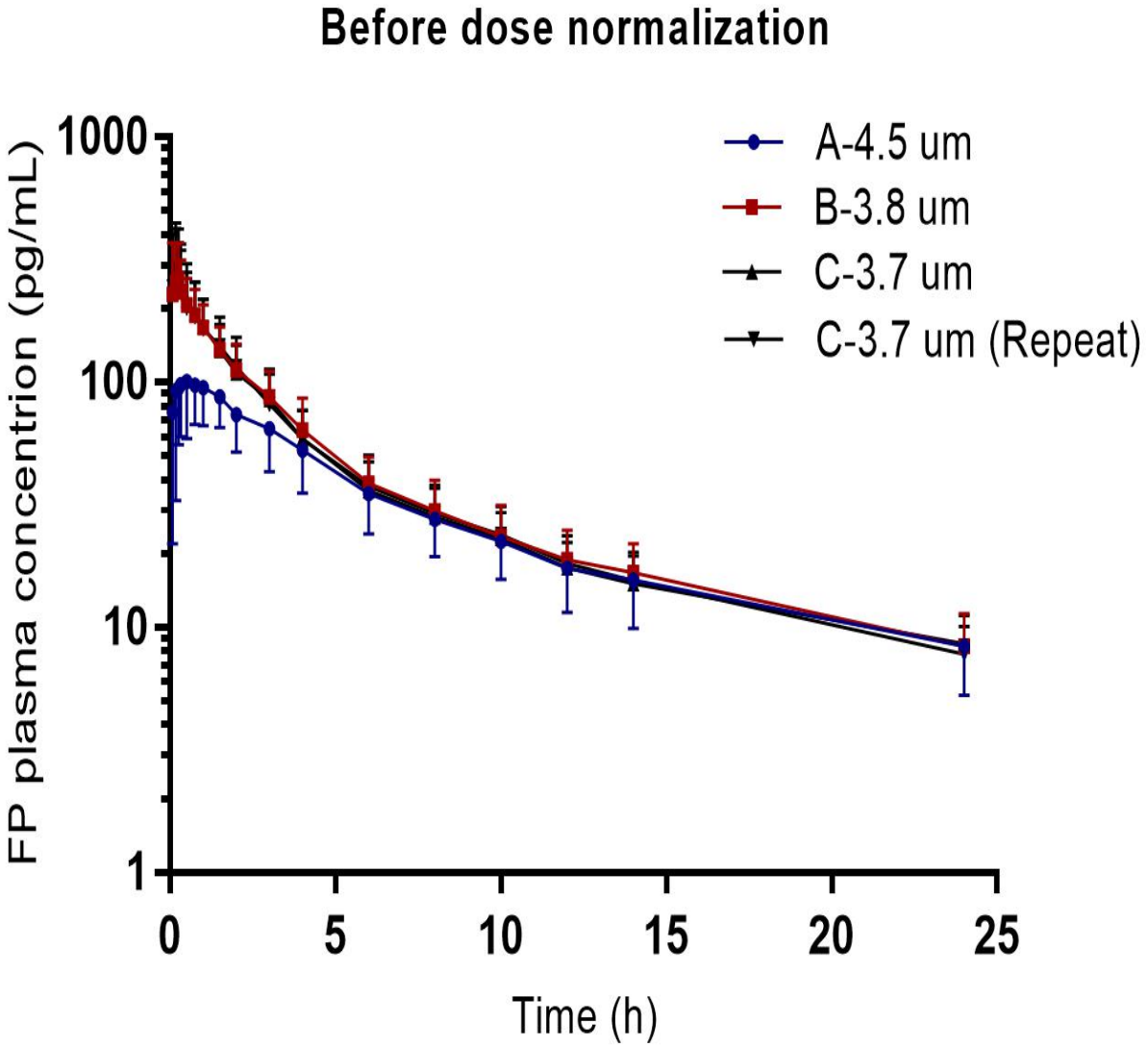


Formulation	MDT (h)	Relative surface area
A-4.5 µm	15.4	0.5
B-3.9 µm	13.3	0.7
C-3.7 µm	10.3	1

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

PART 1: NCA ANALYSIS



Conclusion I: NCA/BE

Overall:

Before dose Normalization

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

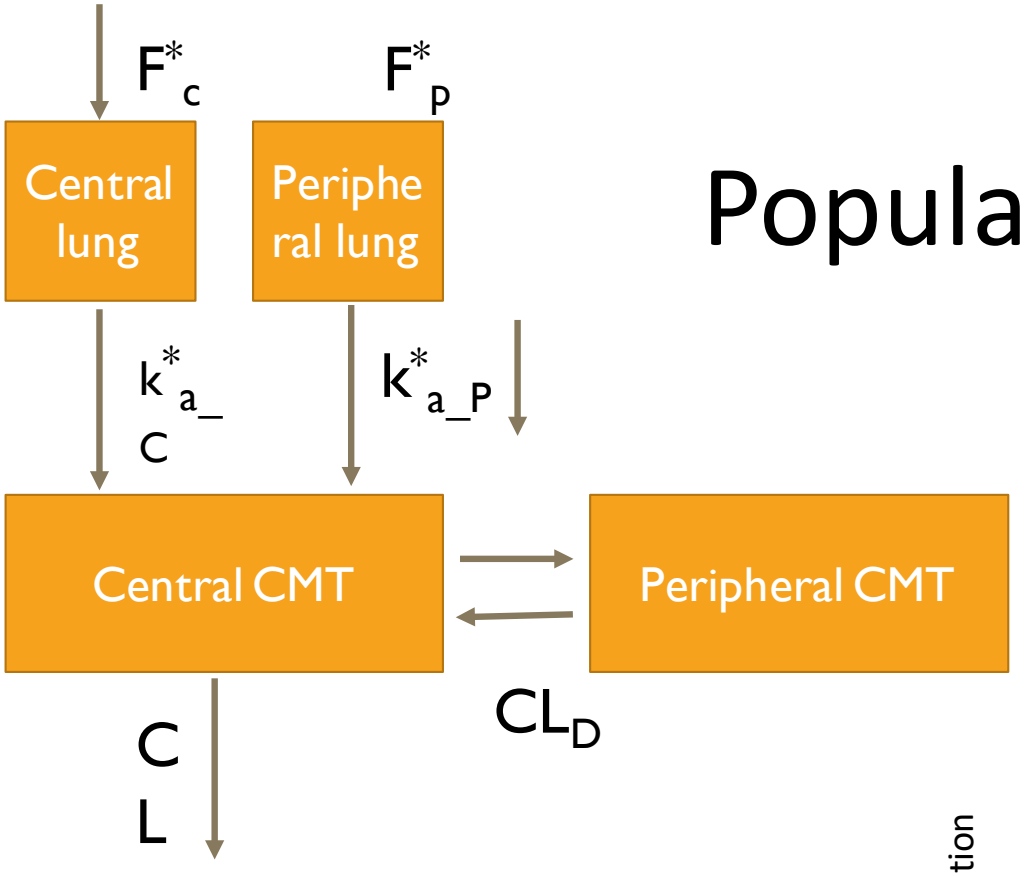
After Dose Normalization

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

AUC: c/p Differences could not be shown

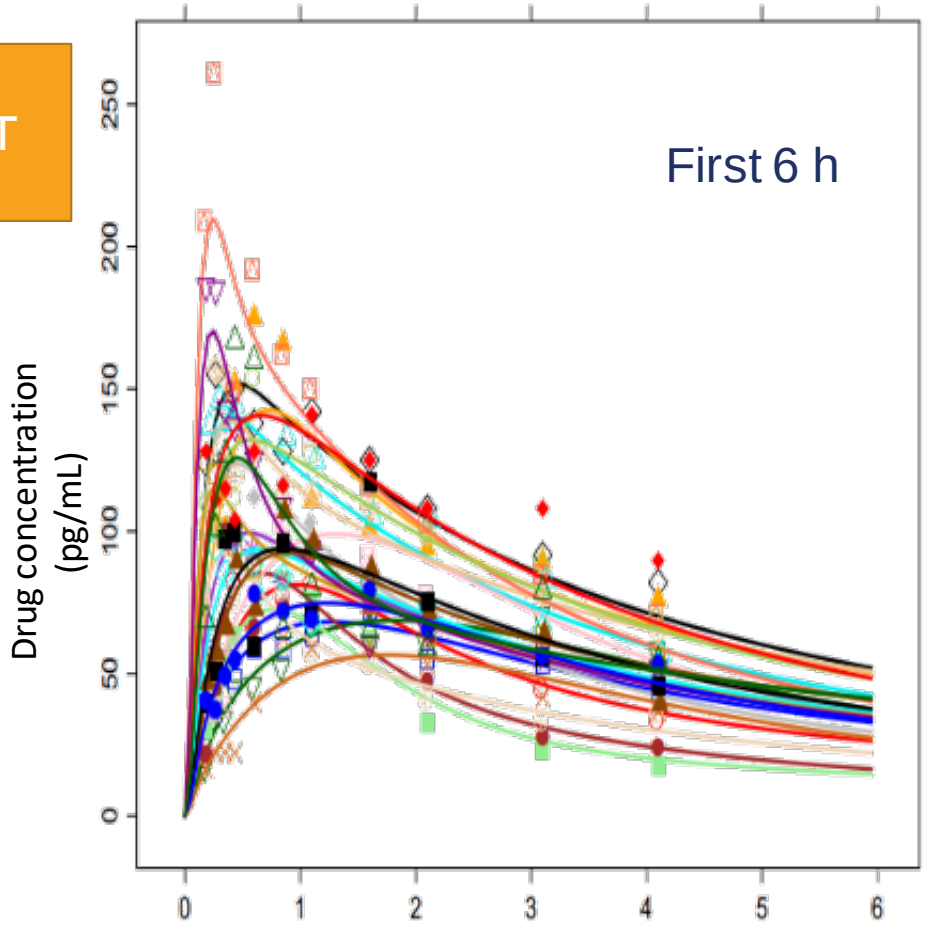
C_{max}: c/p Differences ????

PART 2: Population PK analysis.



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

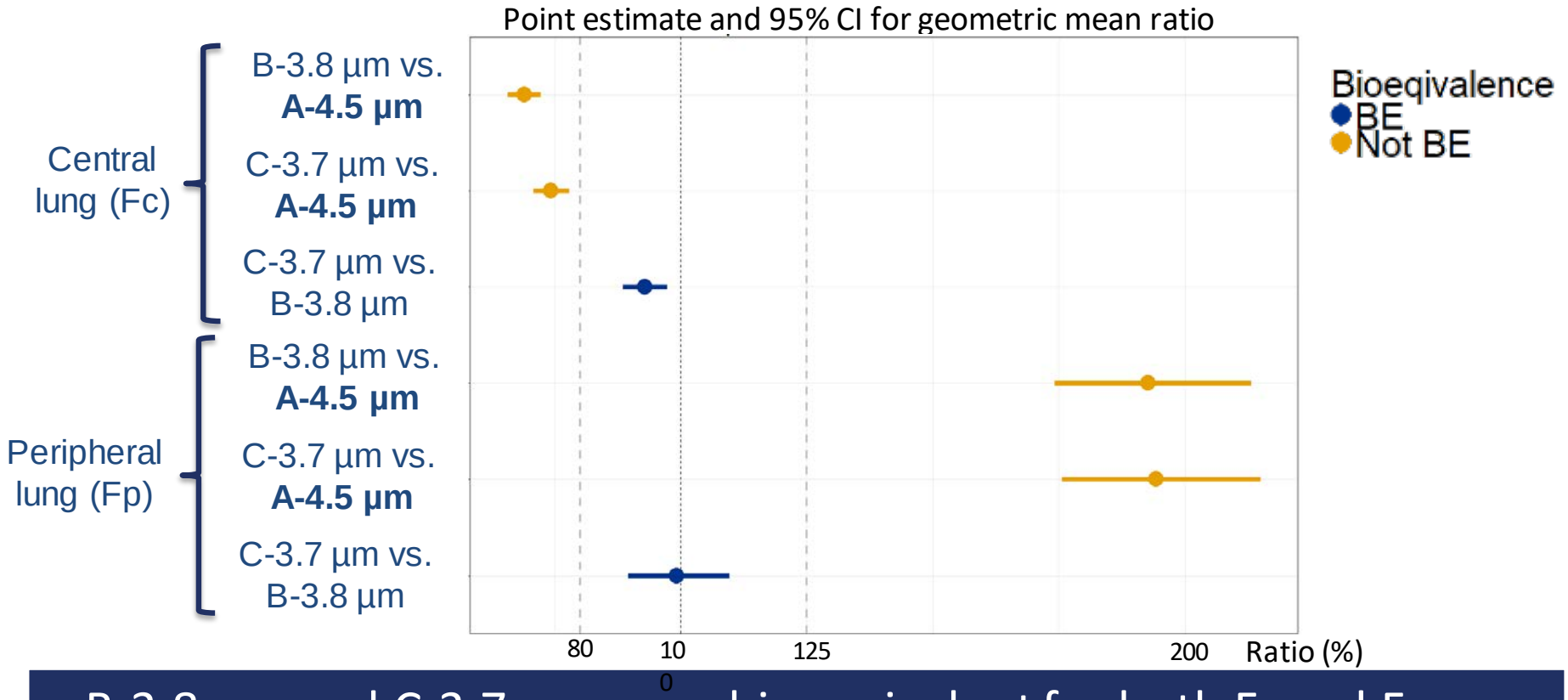
Fp: absorbed dose fraction from the central region of the lungs



Lung related population mean PK parameter estimates

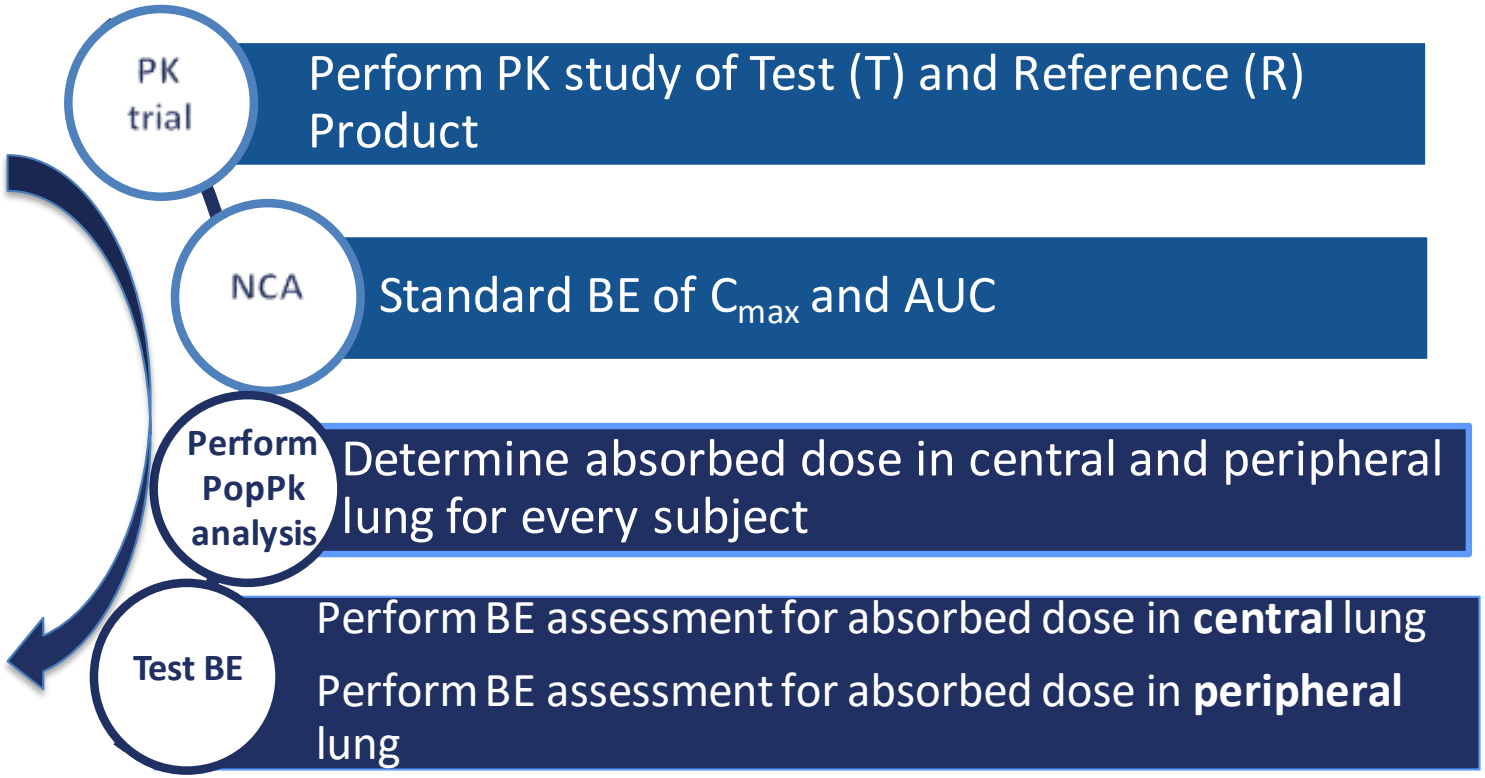
Parameters	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
	Mean (SE%)	Mean (SE%)	Mean (SE%)
Absorption $t_{1/2}$ for central lung (h)	3. 9	3.2	3.6
Absorption $t_1$peripheral lung (h)	**0.28**	0.12	0.13
c/p ratio	**2.32**	**0.6**	**0.51**

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

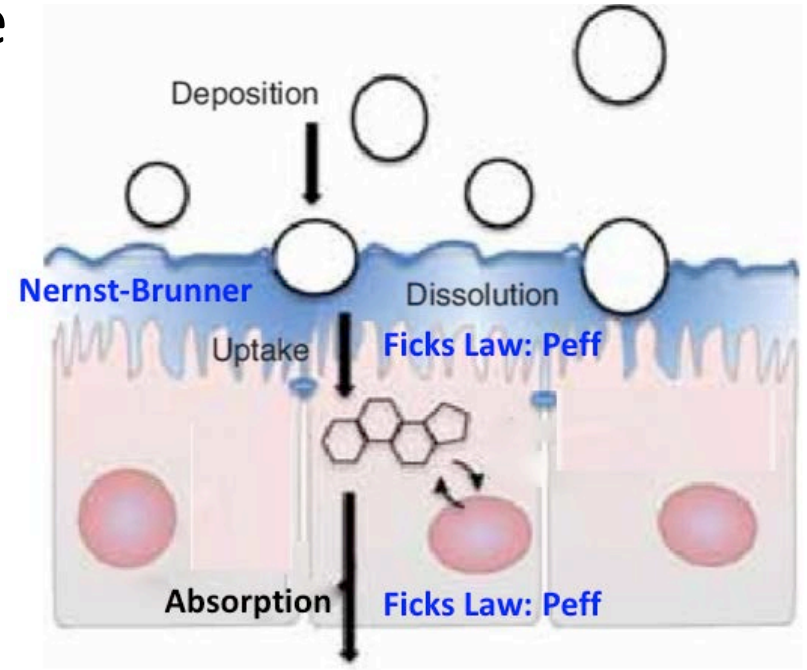


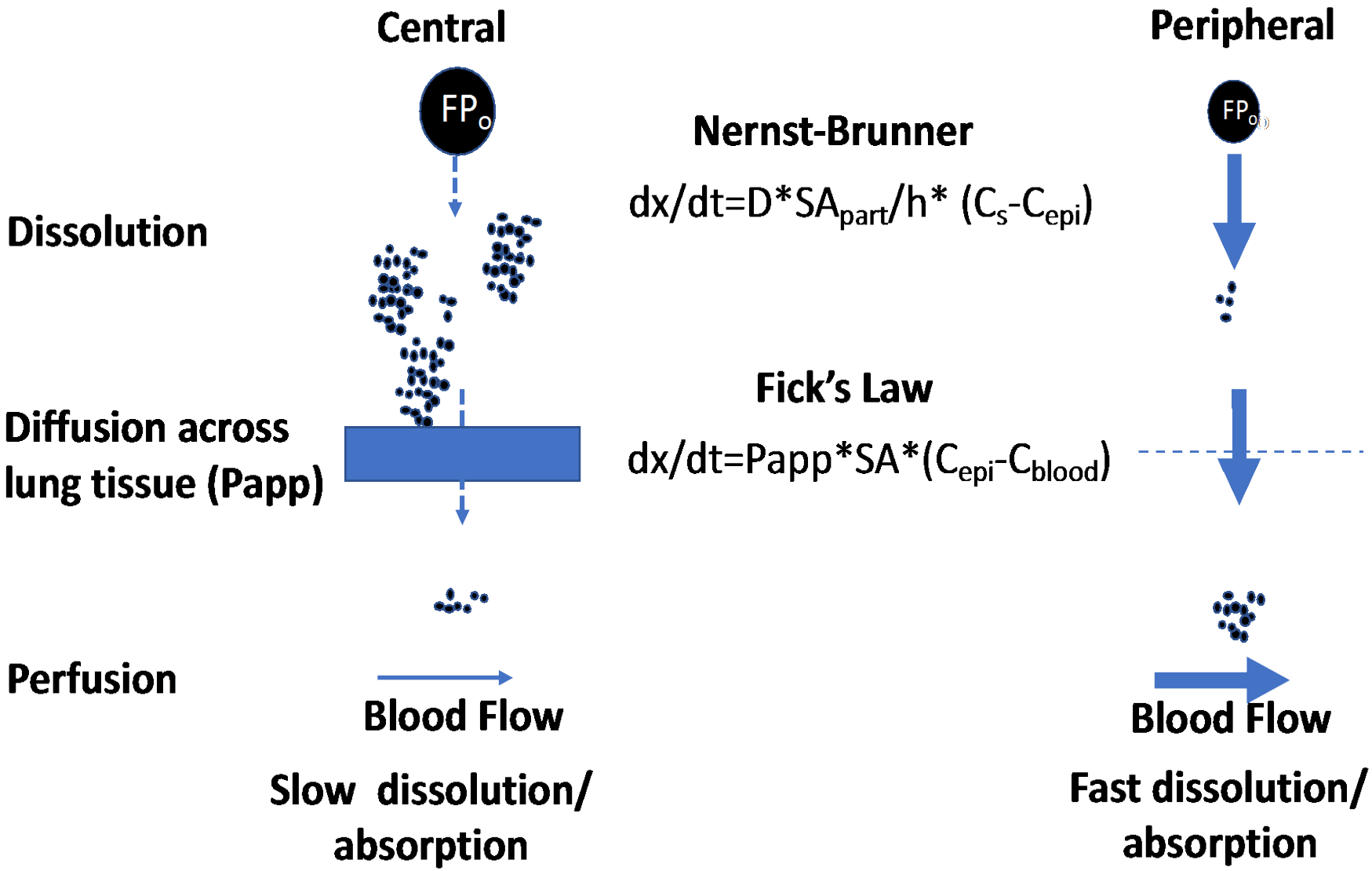
PART 3:
Can we explain PopPK results by PBPK? Can PBPB lead to a less complex method?

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

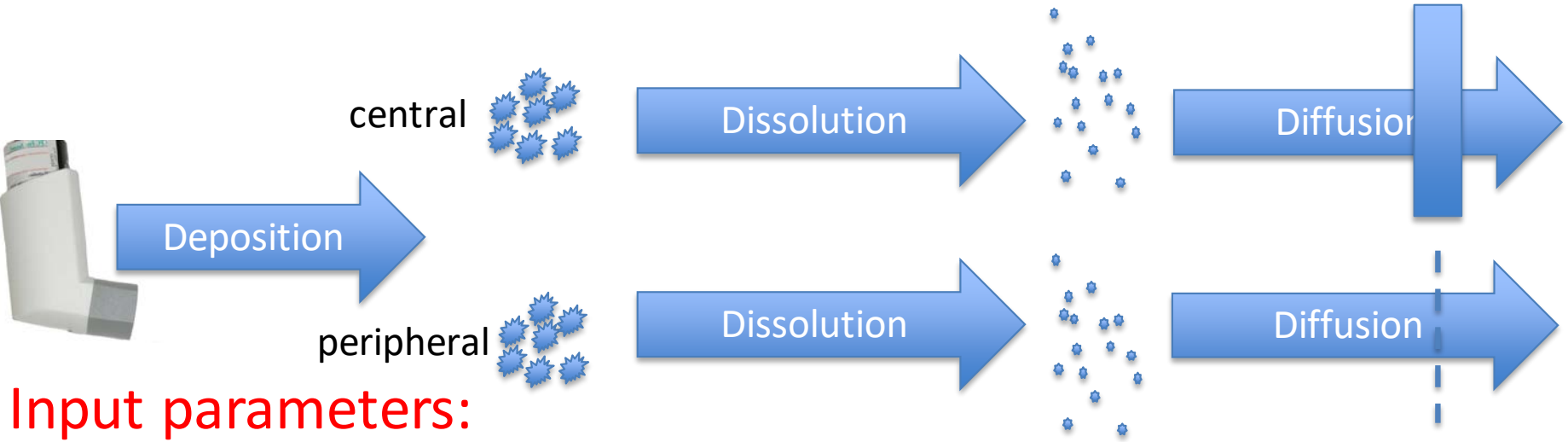
- PBPK Parameters
  - Deposited dose (in vitro)
  - c/p ratio (MMAD)
  - Dissolution (MMAD, GSD)
  - Permeability
    - caco-2-cells

(isolated perfused lung




Central
Peripheral
FP$_o$
FP$_o$
Nernst-Brunner
dx/dt=D*SA$_{part}$/h* (C$_s$-C$_{epi}$)
Dissolution
Fick's Law
dx/dt=Papp*SA*(C$_{epi}$-C$_{blood}$)
Diffusion across lung tissue (Papp)
Perfusion
Blood Flow
Blood Flow
Slow dissolution/ absorption
Fast dissolution/ absorption

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)

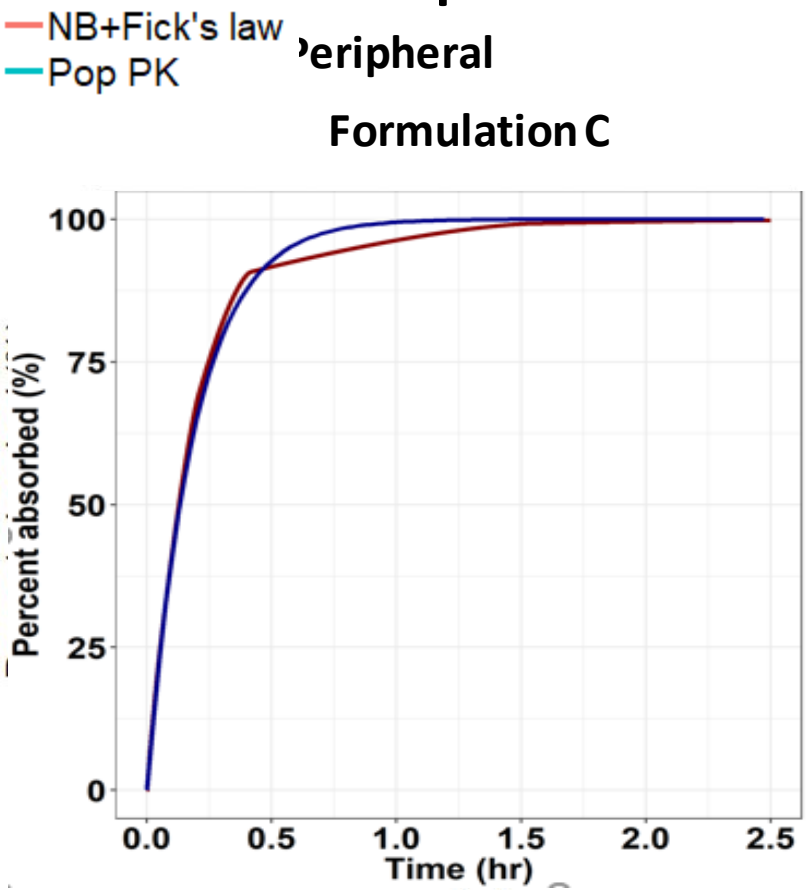
In-silico

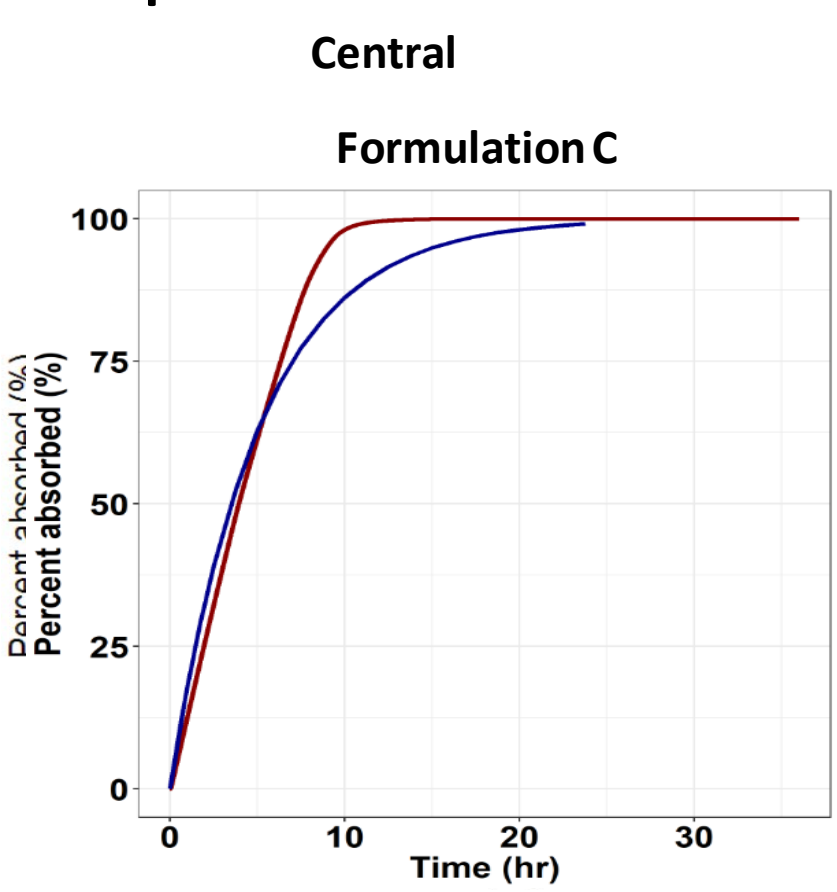
- Ficks-law (scaling)

Output

- **Absorption rate**

Absorption Profile: PopPK vs PBPK



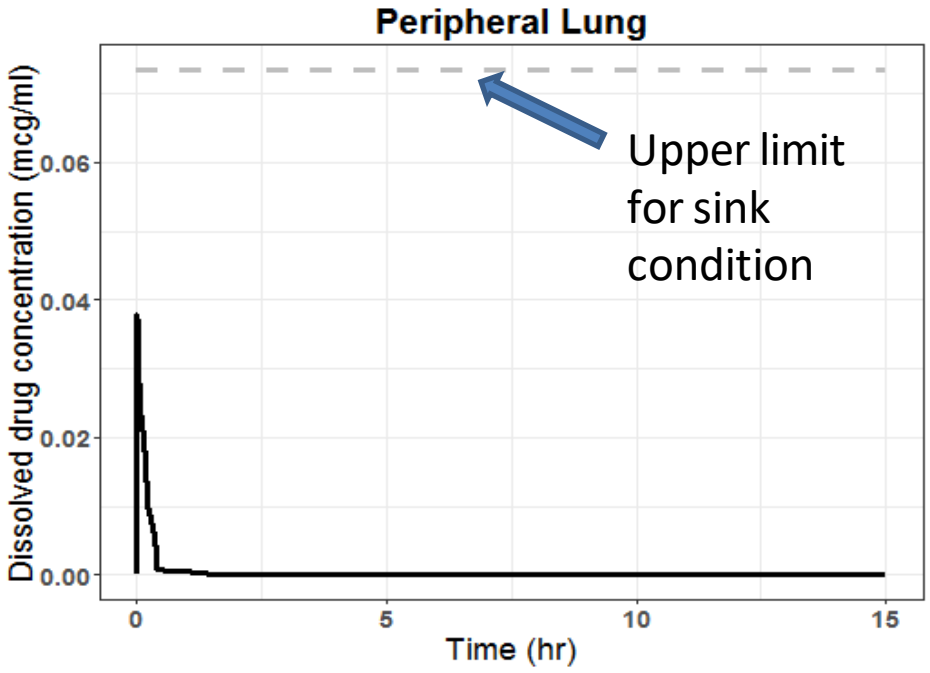


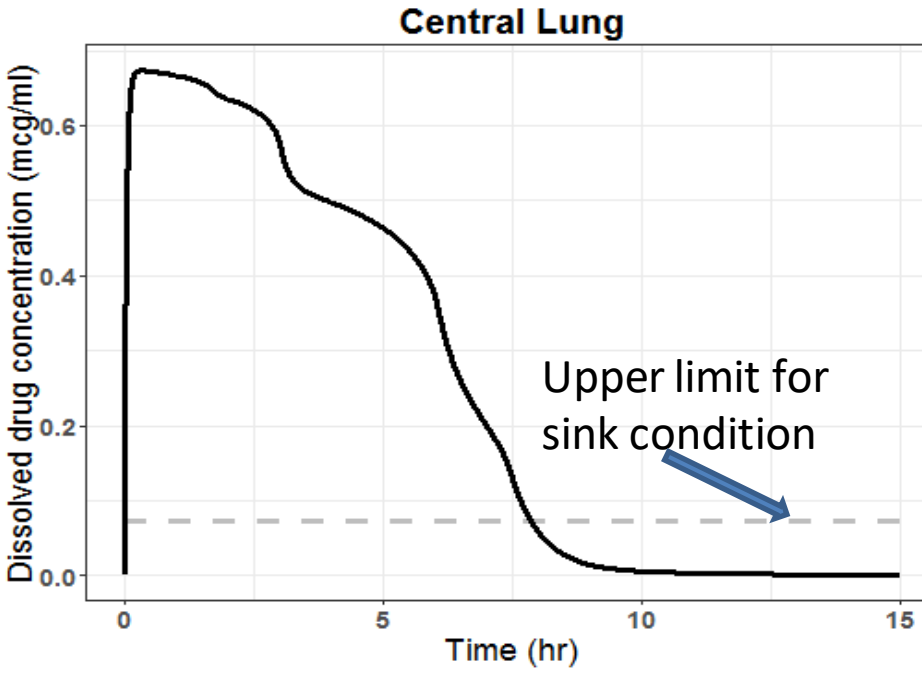
MMAD= 3.8 µm, GSD=2.0

Dose: 54 mcg, **Preludium**
Surface area: 60.2 *10^4 cm^2
Permeability Peff: 13.8*10^-3 cm/h (Eriksson)
Fitted Parameter:
Solubility: 0.70 µg/ml (Literature =0.4-1.4 µg/ml)

Dose 25 mcg, **Preludium**
Surface area: 1.00E+04 cm^2
Solubility: 0.70 µg/ml
Peff: 0.06*10^-3(BB)- 1.5*10^-3 (bb)
Fitted Parameter:
Permeability: 0.72*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?

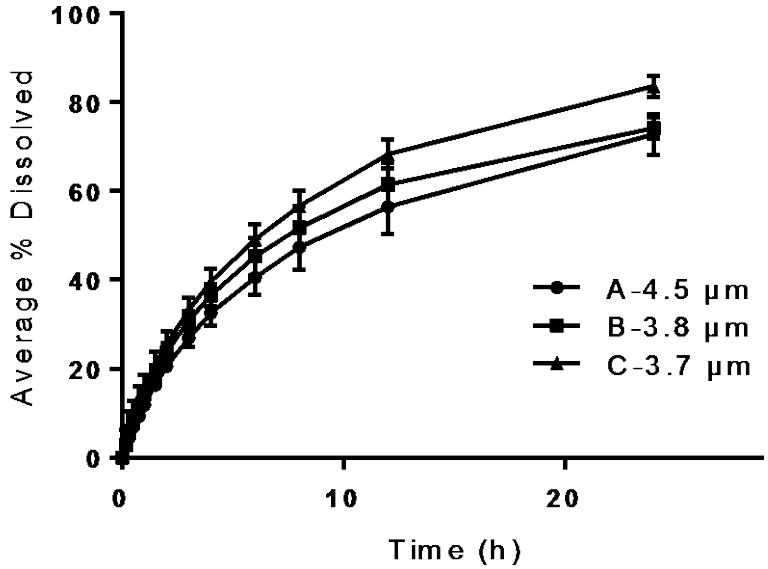
Differences in Dissolution Rate

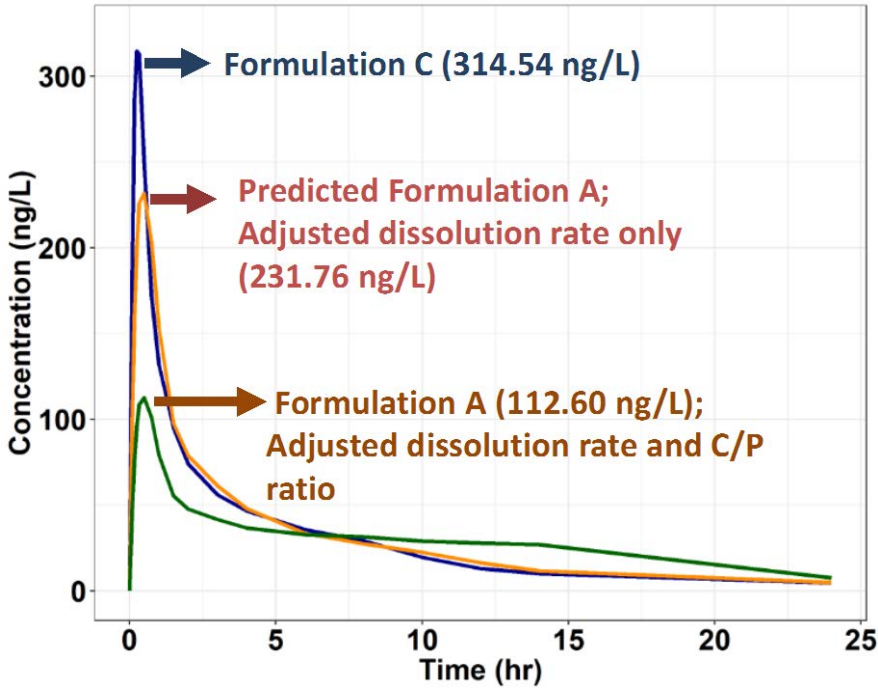
	MDT (h)	Relative surface area
A-4.5 µm	19.2	0.5
C-3.7 µm	13.4	1

Integrate in PBPK Model Nernst-Brunner Ficks Law

C_{max}, if only dissolution differs

C_{max} ratio	Predicted	Measured
C/A	1.35	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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