A Semi-physiological Approach for Evaluating the Sensitivity of Pharmacokinetics to Detect Differences in Regional Lung Deposition of Orally-inhaled Drug Products (OIDPs)

Abhinav Kurumaddali, MS, PhD

Department of Pharmaceutics

University of Florida

(Advisor: Prof. Günther Hochhaus)

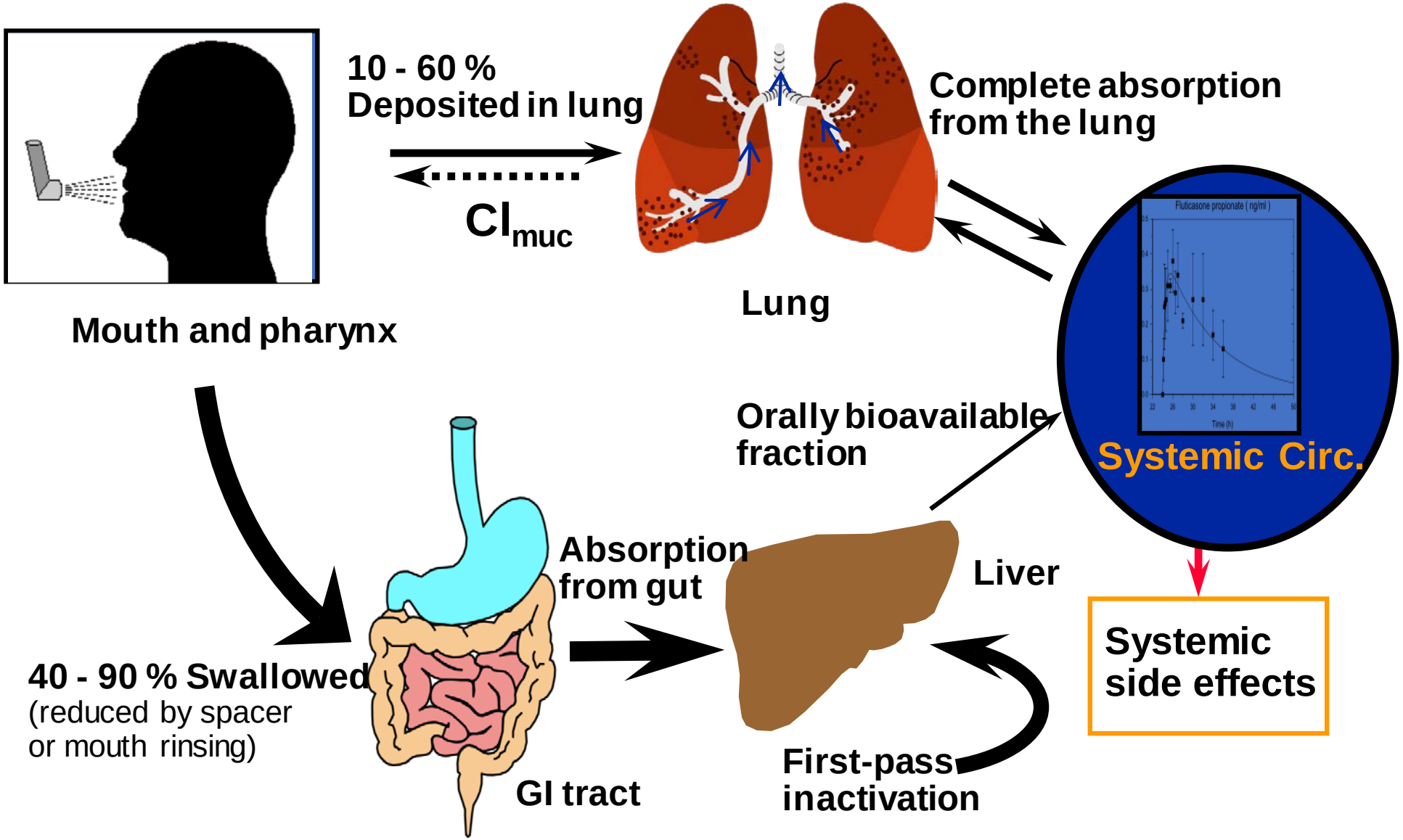
Disclaimer

- Funding for the PK clinical trial and in vitro work was supported by:
  - U.S. Food and Drug Administration through contracts HHSF223201610099C, HHSF223201300479A, HHSF223201110117A, and HHSF223201000090C;
  - U.S. Food and Drug Administration through grants 1U01FD004950 and 1U01FD005231;
  - National Center for Advancing Translational Sciences of the National Institute of Health through award UL1TR001427.

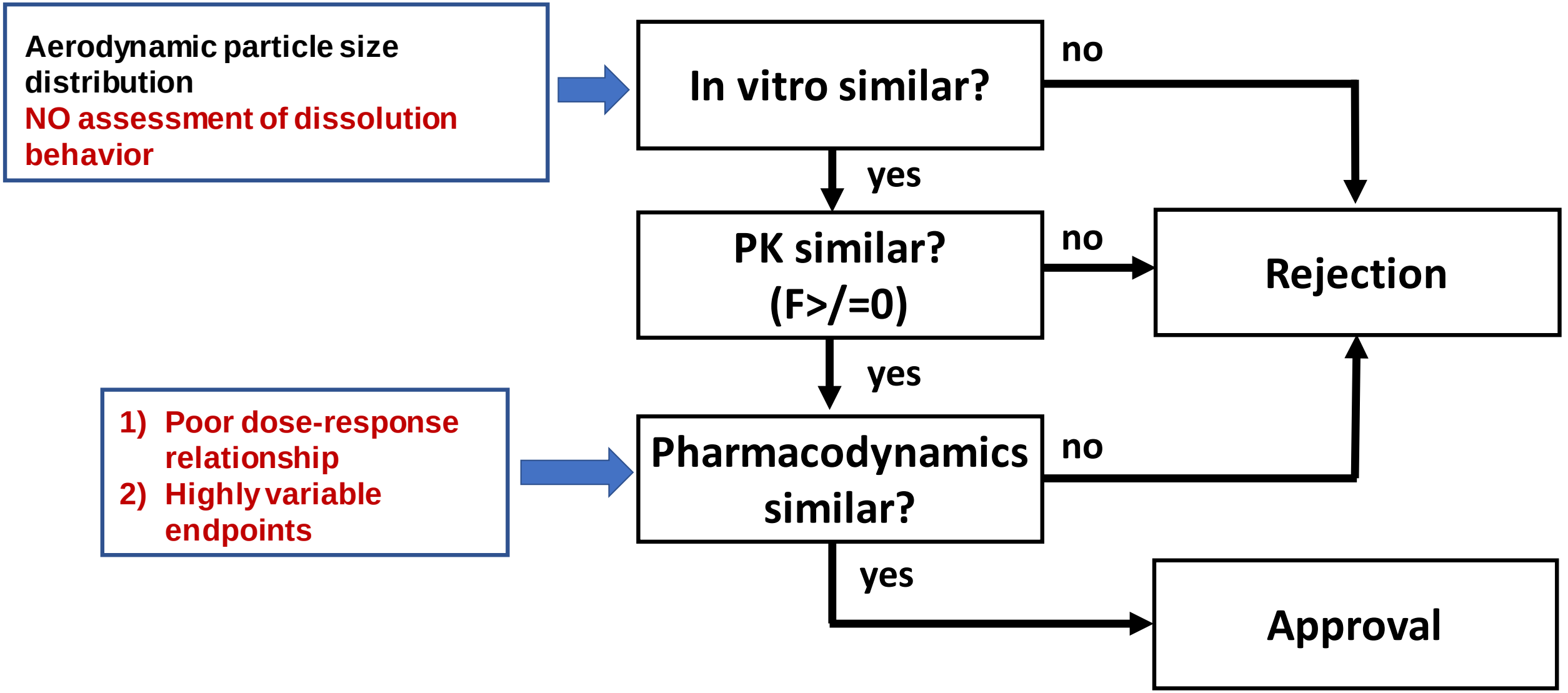
- Views expressed in this presentation are from the authors and do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Topics related to Bioequivalence

dose, time, regional deposition?



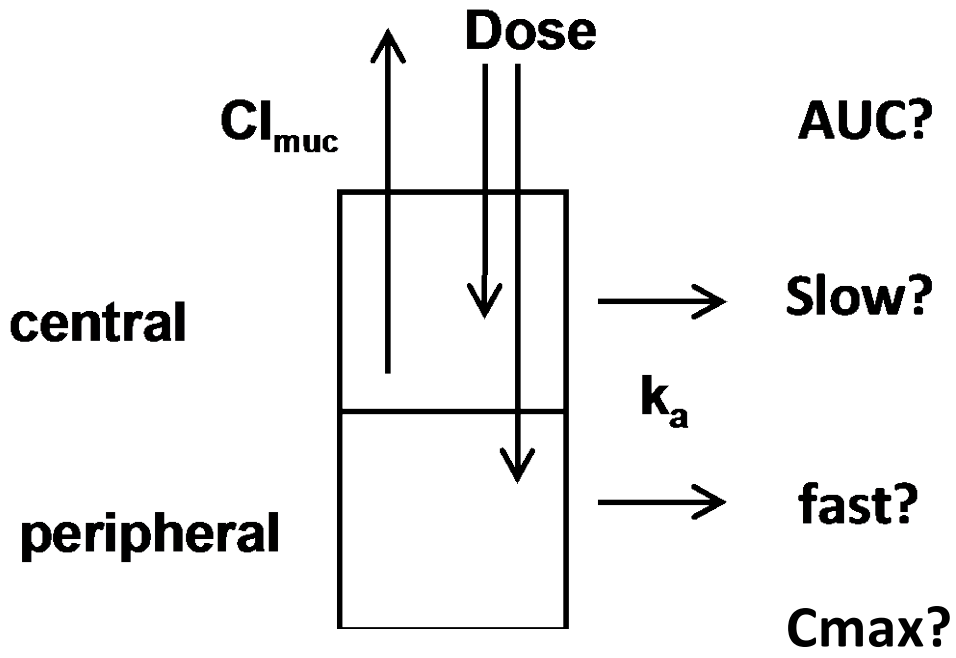
FDA's weight of evidence approach



Actual Question of this Research Project

Can PK (NCA, PBPK/semi-mechanistic models) along with *in vitro* tests extract information on:

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



Study Outline

1) Develop three DPI-Fluticasone Propionate formulations (R. Price/Jag Shur)

Same dose
Same dissolution rate
Difference in central to peripheral lung 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	

2) Characterize through *in vitro* experiments

- Ex throat dose (Mike Hindle, VCU)
- Cascade impactor profile
- Dissolution rate

3) Perform PK (4 way cross-over, repeat one formulation)

- Non-Compartmental Analysis (NCA)
- Population PK analysis
- Mechanistic PK modeling/simulations

In vitro Studies

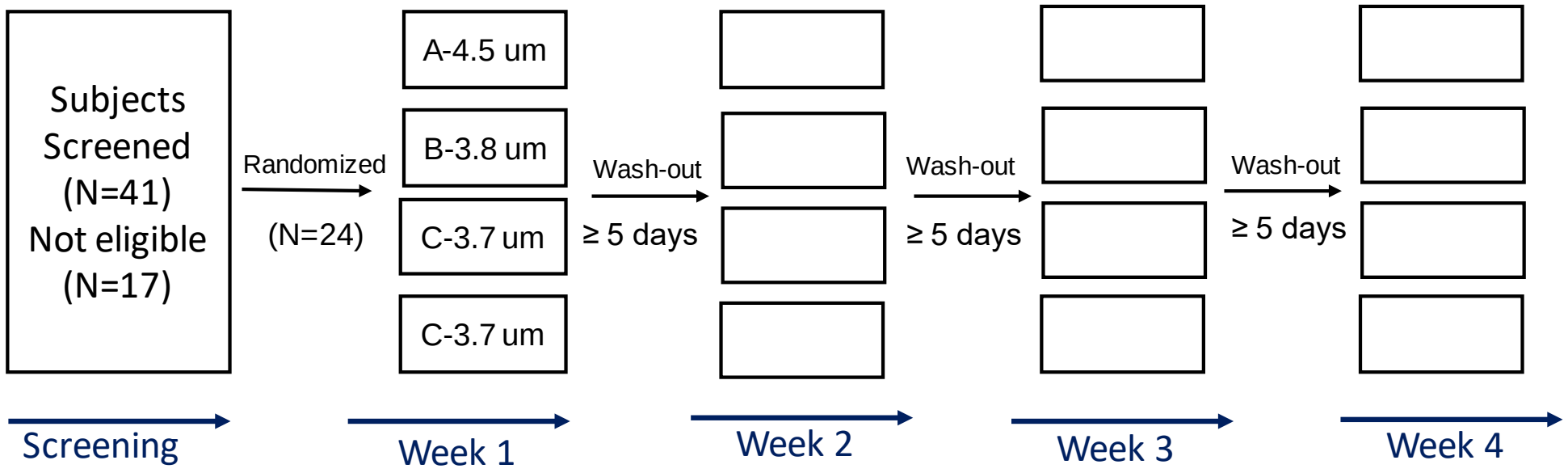
Formulation	MMAD (GSD)*, µm	Mean dissolution time (MDT, h)	Relative ex-throat dose
A-4.5 µm	4.5 (1.9)	15.4	1.00
B-3.8 µm	3.8 (2.0)	13.3	1.32
C-3.7 µm	3.7 (2.1)	10.3	1.21

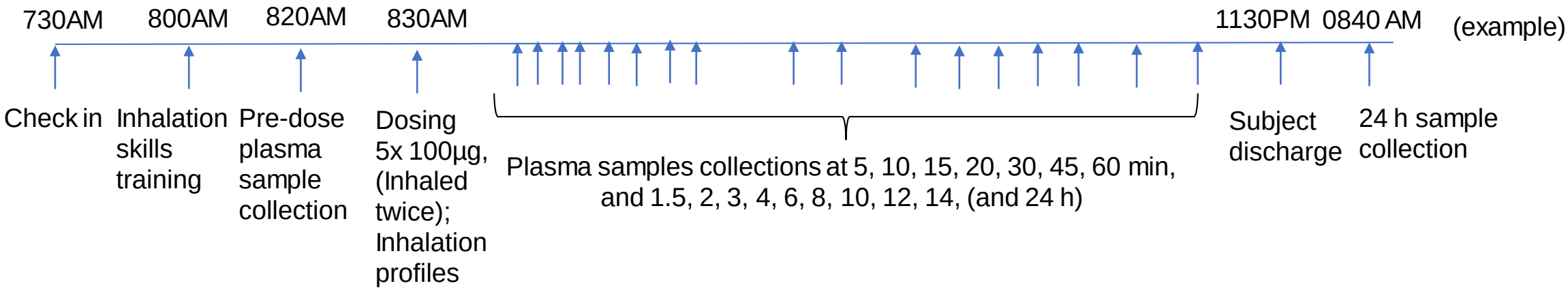
*MMAD (GSD): Median mass aerodynamic diameter (Geometric Standard Deviation)

- MMAD of A-4.5 µm larger than those of B-3.8 µm and C-3.7 µm
- Dissolution rates differed
- Ex-throat dose (surrogate for lung dose) differed

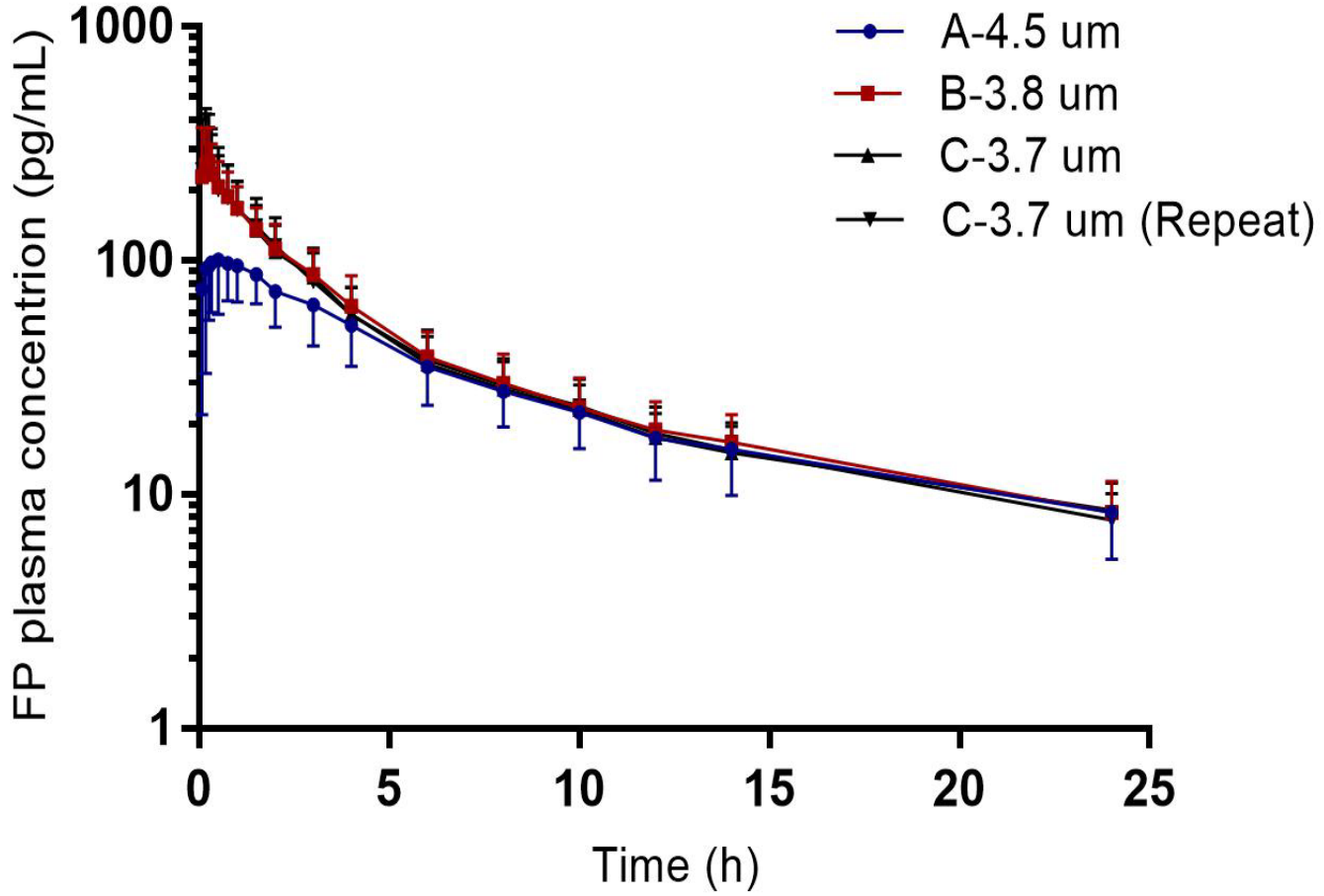
PK Clinical Study Design

Double-blinded, single center, 4 way-crossover, single dose, randomized trial



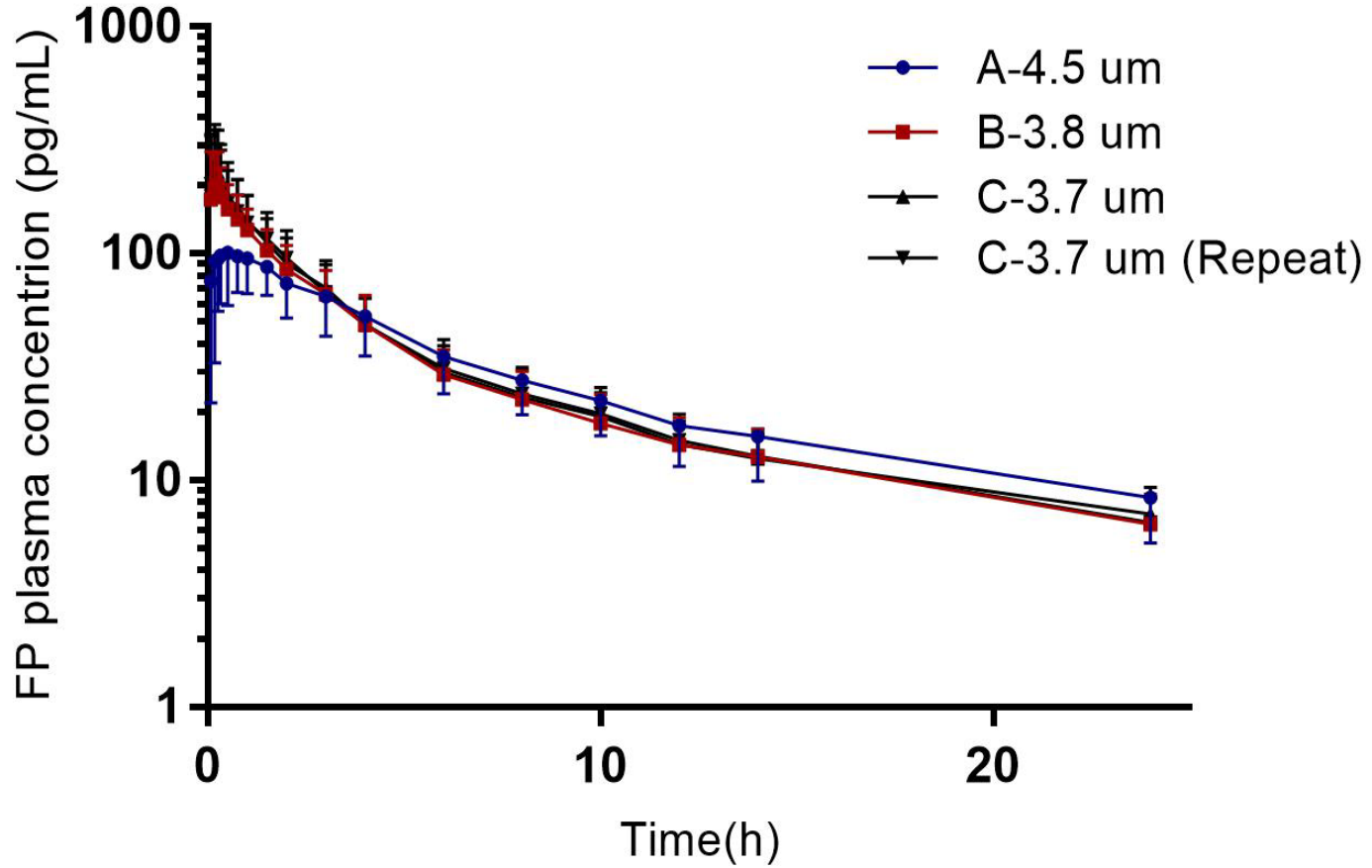


Plasma PK Profiles of FP DPI Formulations (before lung dose normalization)



- PK profiles of B-3.8 µm and C-3.7 µm were similar
- C_{max} and AUC of A-4.5 µm was smaller

Plasma PK Profiles of FP DPI Formulations (after lung dose normalization)



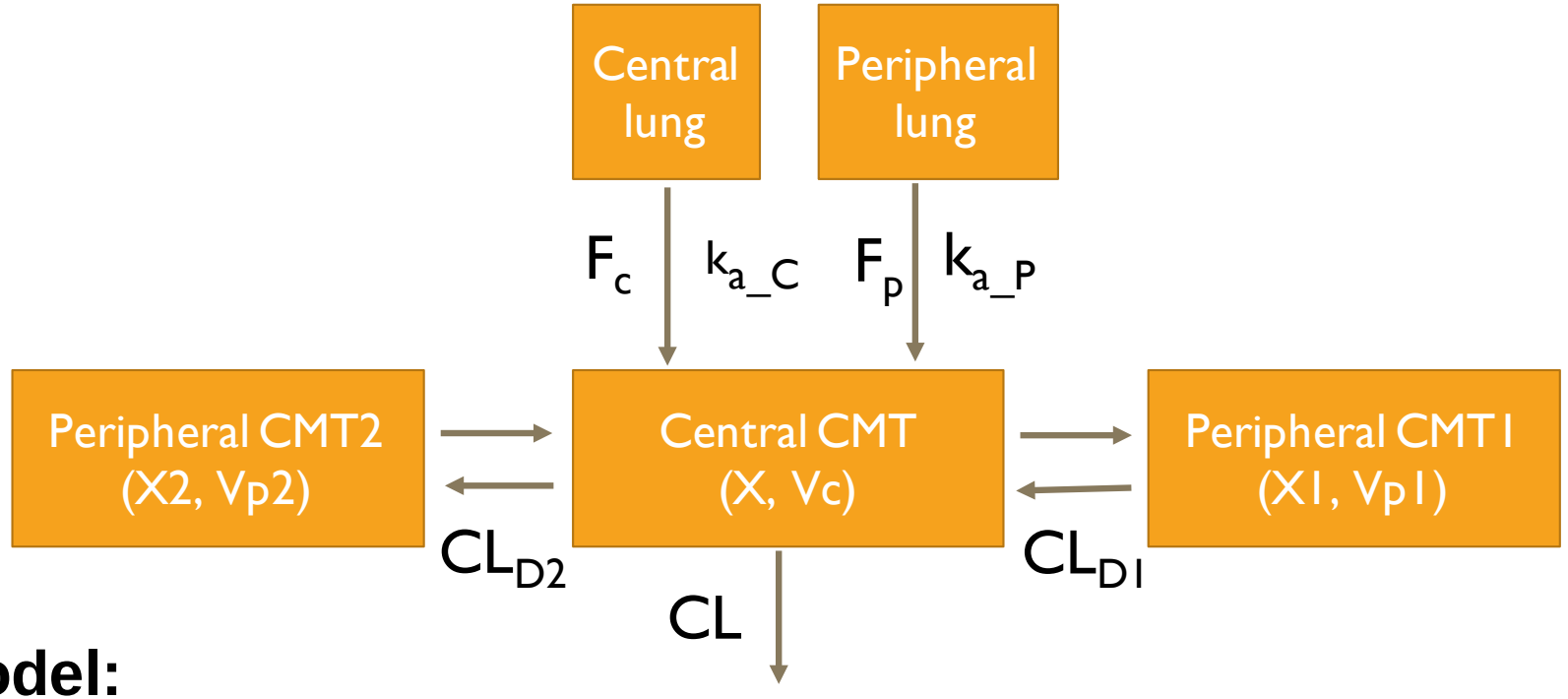
Dose normalized C_{max} of A-4.5 µm was smaller than those of B-3.8 µm and C-3.7 µm

- **Dissolution Properties ?**
- **Regional Deposition ???**

Population PK analysis

To develop a model for assessing the regional deposition differences between formulations

Structural model:



Statistical model:

Inter-individual variability (IIV): Exponential error model

Inter-occasion variability (IOV): Exponential error model

Residual variability (RV): Combined additive proportional error model

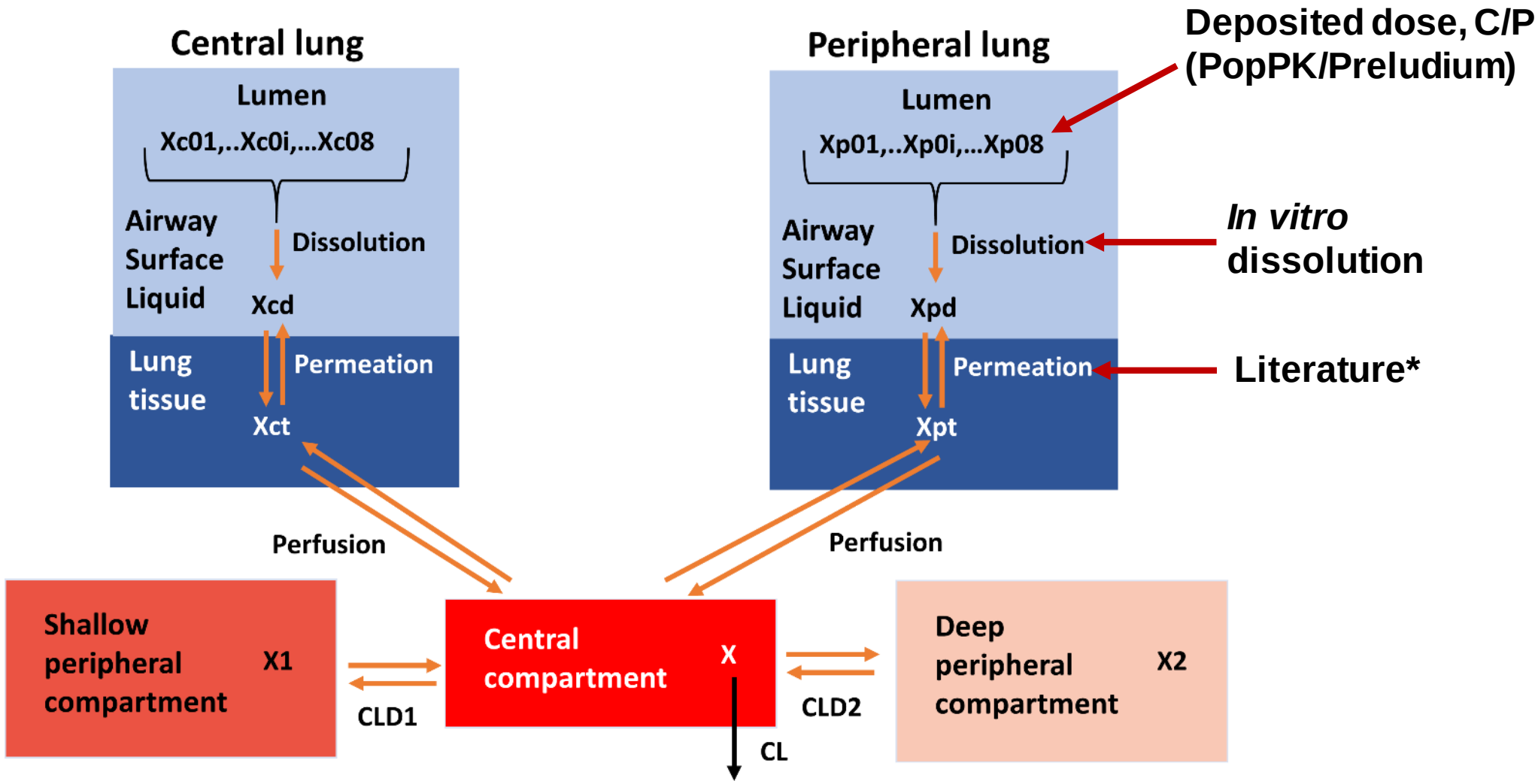
Lung related population mean PK parameter estimates

Parameter	A-4.5 µm Mean (% RSE)	B-3.8 µm Mean (% RSE)	C-3.7 µm Mean (% RSE)
1) Ka – central lung (hr^{-1})	0.195 (9.82)	0.270 (30)	0.252 (28)
2) Ka – peripheral lung (hr^{-1})	2.65 (16)	5.66 (23.7)	5.55 (21)
3) Absorbed dose – central lung (%)	6.42 (8.26)	5.86 (28.9)	5.07 (21.1)
4) Absorbed dose – peripheral lung (%)	3.85 (7.78)	10.45 (8.77)	10.80 (9.34)
5) C/P ratio	**1.67**	**0.56**	**0.47**

Semi-Physiological Model and Simulations

- **Can we link the Pop PK estimates to lung anatomy and physiology?**
- **Can we link differences in dose-adjusted Cmax to regional deposition differences using semi-physiological model?**

Semi-physiological model structure

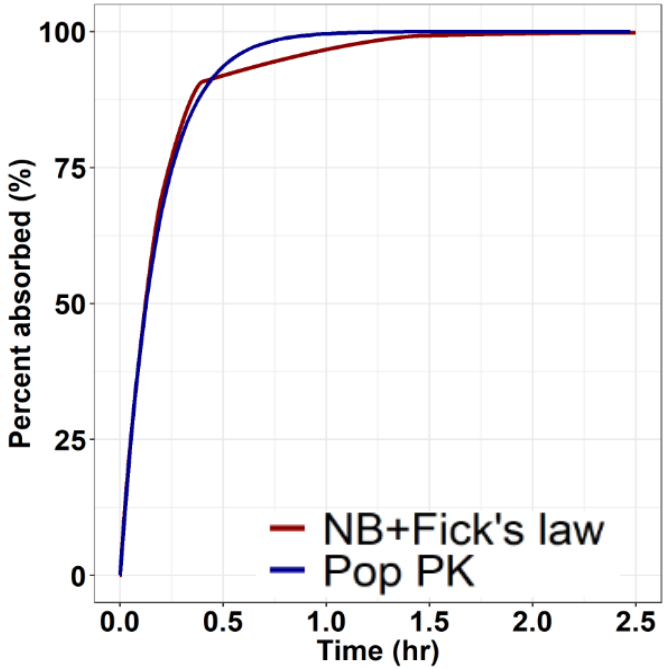


*Eriksson J, Thorn H, Sjogren E, Holmsten L, Rubin K, Lennernas H. *Mol Pharm. 2018; 16(7): 3053-3064*

Absorption Profile: Semi-physiological vs Pop PK model

Formulation C

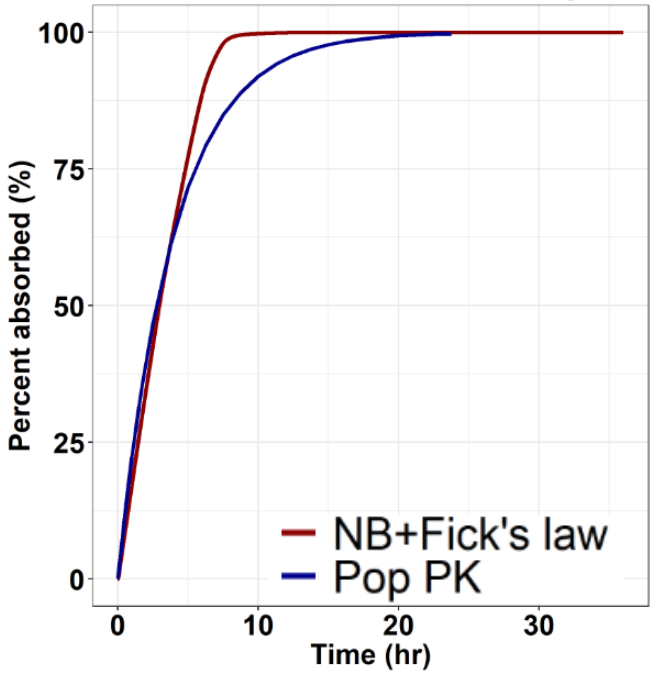
Peripheral Lung



Dose: 54 mcg, Pop PK
Surface area: 60200 cm^2 (Preludium)
PSD/MMAD (GSD): 3.7 (2.0) µm
Permeability: 13.68e-3 cm/h (Eriksson et al., 2018)

Fitted Parameter:
Solubility: 0.74 µg/ml
(Literature =0.41 to 0.51 µg/ml)

Central Lung

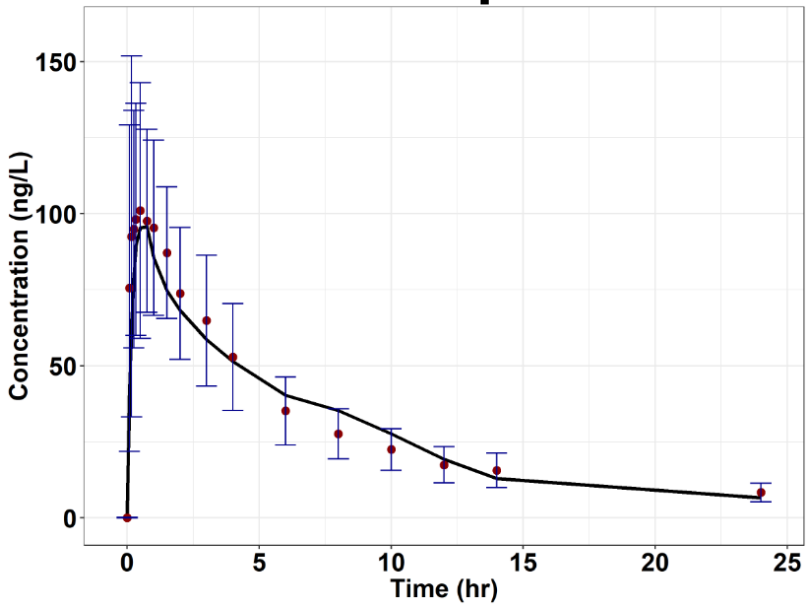


Dose: 25 mcg, Pop PK
Surface area: 4830 cm^2 (Preludium)
PSD/MMAD (GSD): 3.7 (2.0) µm
Solubility: 0.74 µg/ml

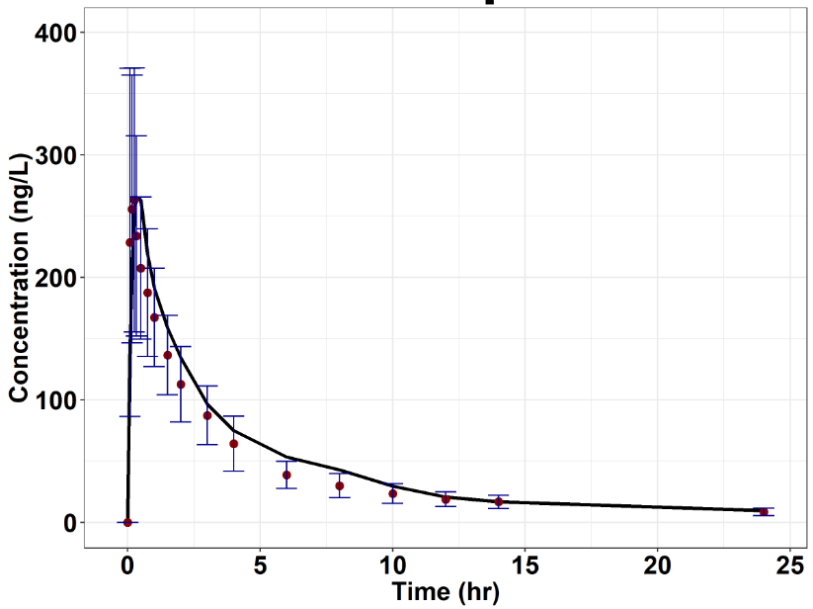
Fitted Parameter:
Permeability: 1.364e-3 cm/h (10 times thicker!)
(Scaled by thickness: 0.0063e-3 to 1.5e-3 cm/h)

Semi-physiological PK model prediction and validation

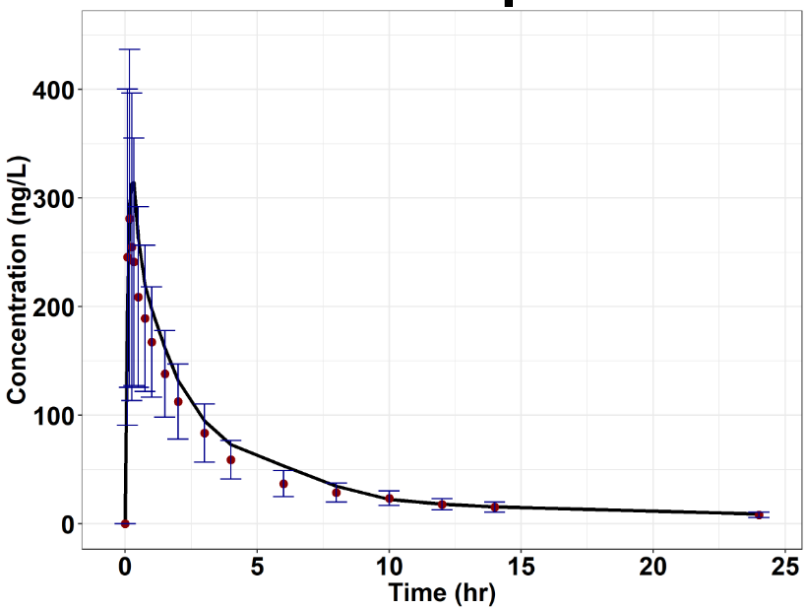
A-4.5 µm



B-3.8 µm

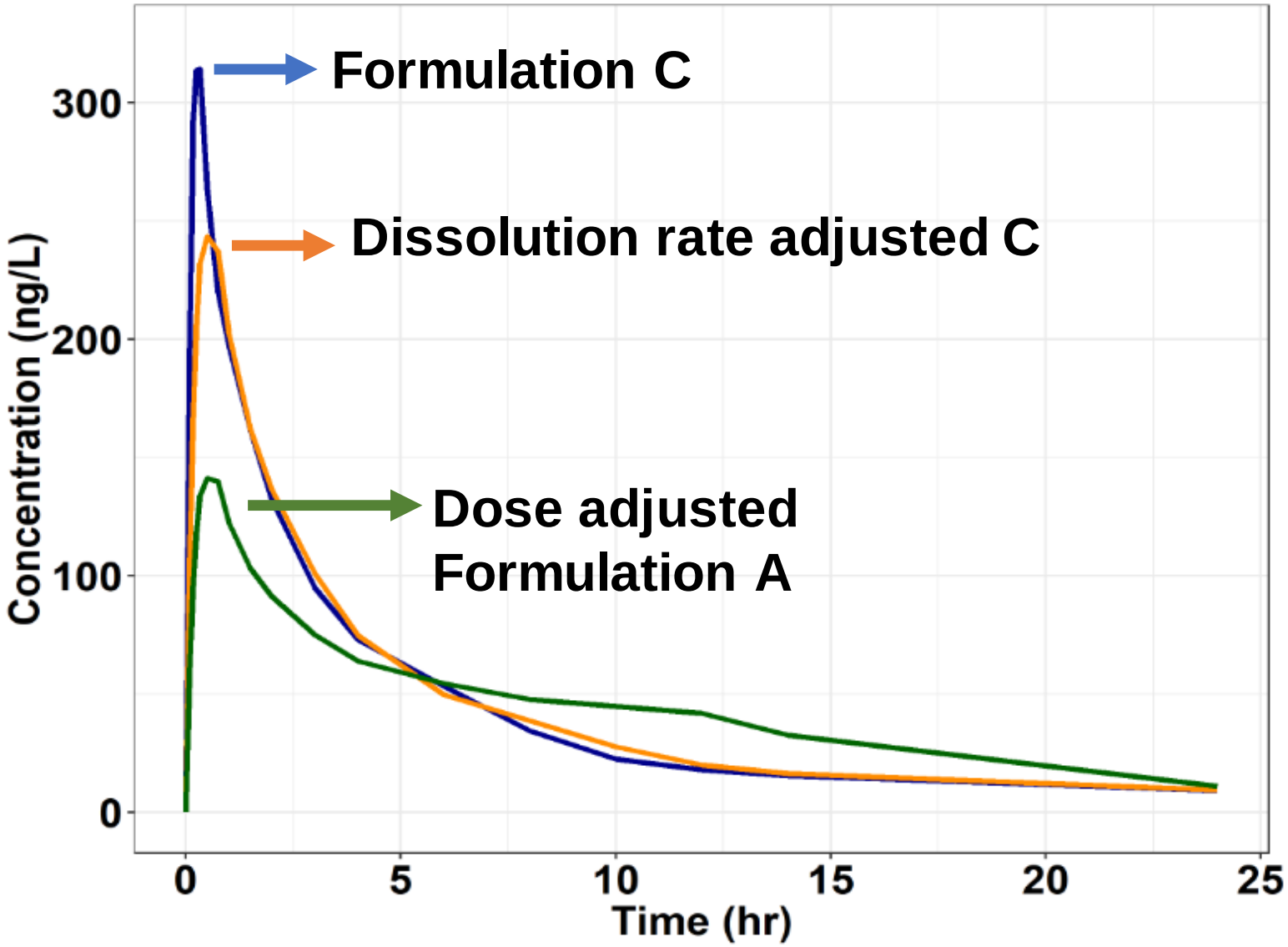


C-3.7 µm

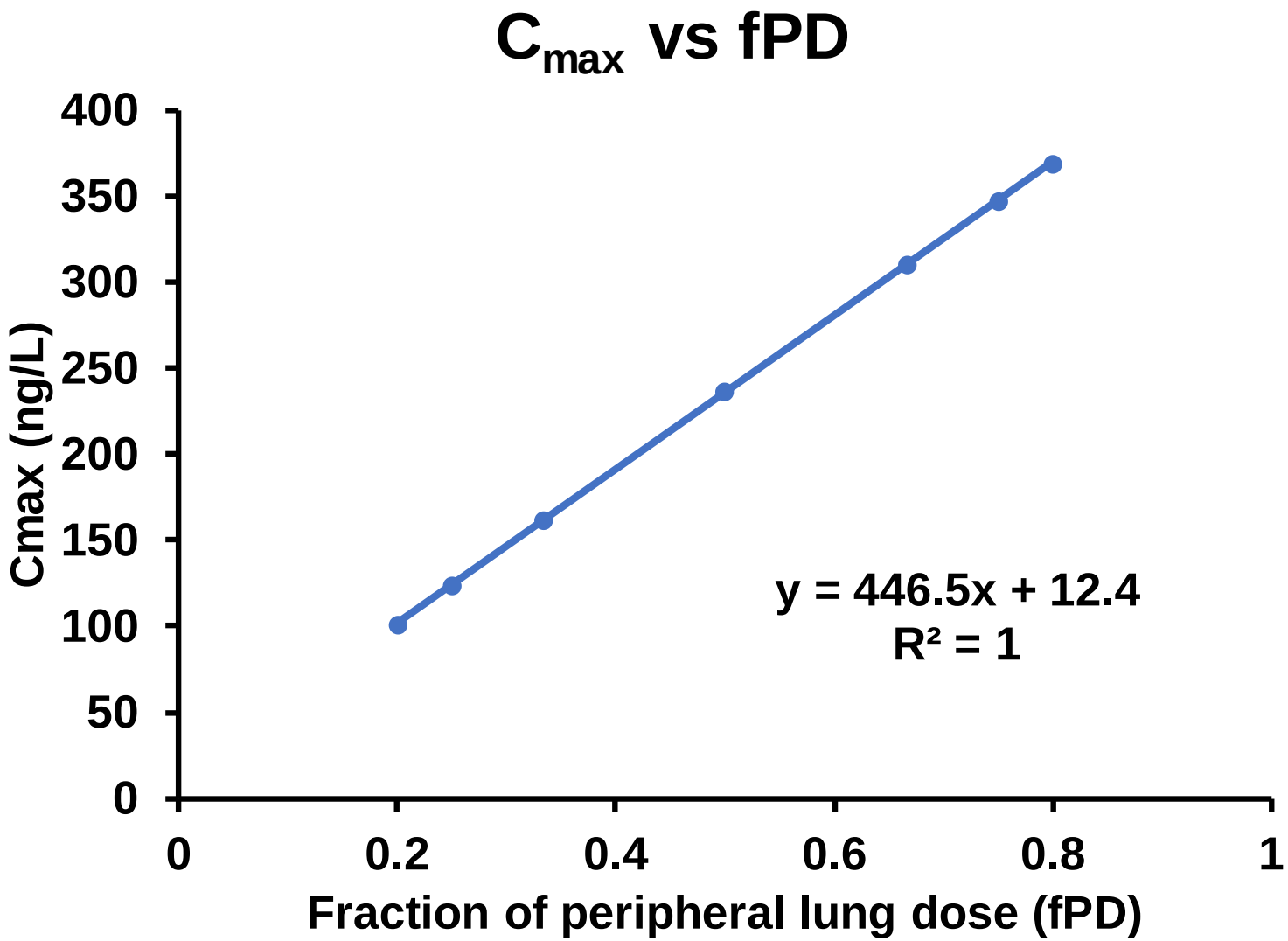


- Model was validated by predicting the PK of A-4.5 µm and B-3.8 µm
- Predicted Cmax and AUC within two-fold range of the observed data

Is C_{max} sensitive to C/P?



Is C_{max} sensitive to C/P?



Take home message

- Population PK indicated biphasic absorption profile for FP
- Semi-physiological modeling linked biphasic behavior to pulmonary fate of FP in central and peripheral lung regions
- The developed semi-physiological model confirmed that Pop PK and NCA are sensitive to
  - Dose
  - Residence time
  - Regional deposition
- Work underlines that *in vitro* tests plus PK may be sufficient for BE assessment of slowly dissolving OIDPs

Acknowledgements

PhD advisor:
Dr. Günther Hochhaus

Co-advisor:
Dr. Jürgen Bulitta

Group members:
Dr. Mong-Jen Chen
Dr. Uta Schilling
Stefanie Drescher, Pharm.D
Elham Amini, Pharm.D
Simon Berger, Pharm.D

Dr. Mike Hindle (VCU)
Dr. Rob Price/Dr. Jag Shur (Bath)

FDA Collaborators:
Dr. Denise Conti
Dr. Renish Delvadia
Dr. Minori Kinjo
Dr. Bavna Saluja
Murewa Oguntimein, M.H.S.