Use of Mechanistic Modelling to Determine the Sensitivity of *in vitro* CQAs to Regional Lung Deposition and Predict PK for OIDPs

2021 CRCG Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches Workshop

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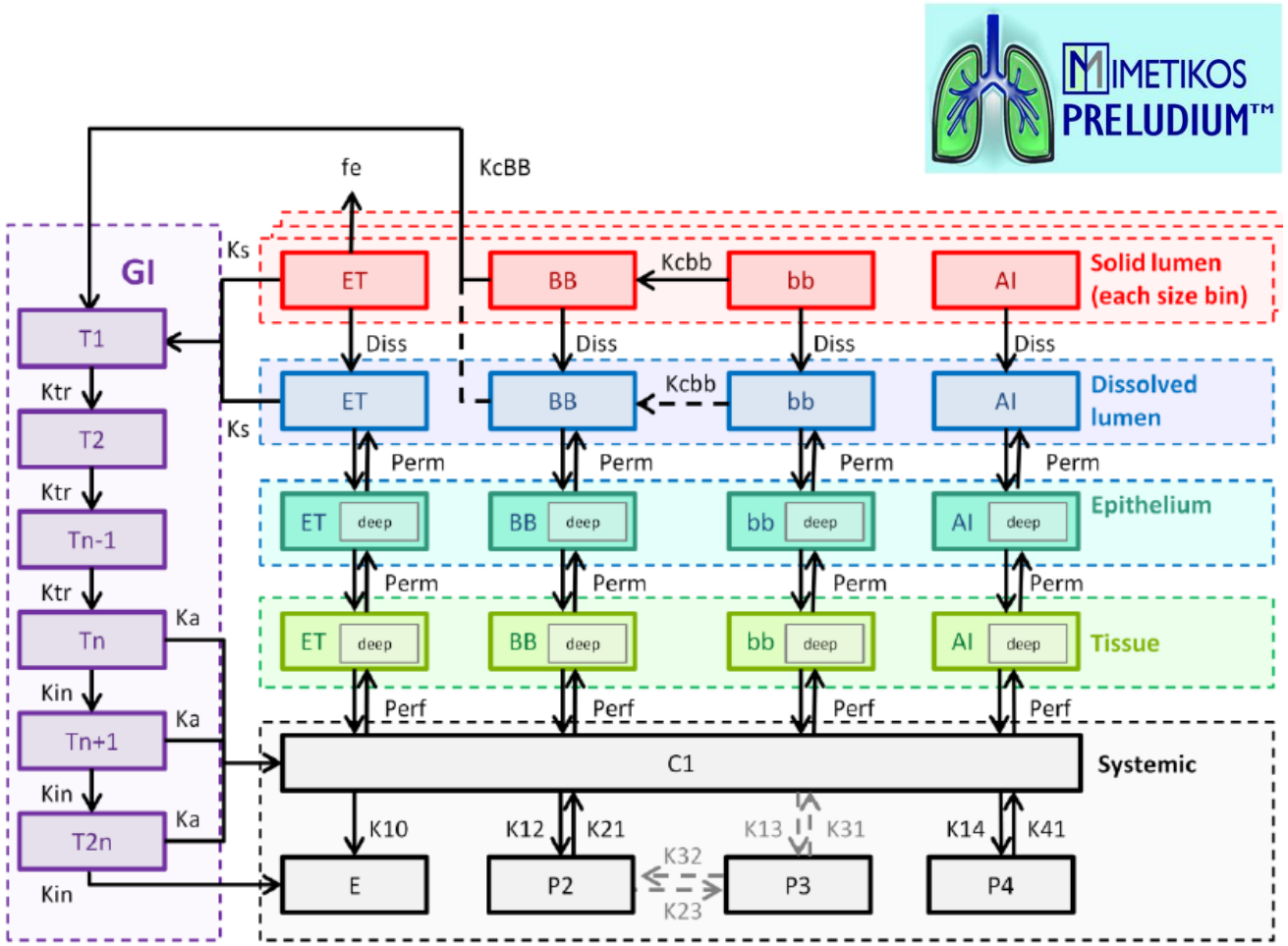
Physiological Based Pharmacokinetic Model (PBPK)

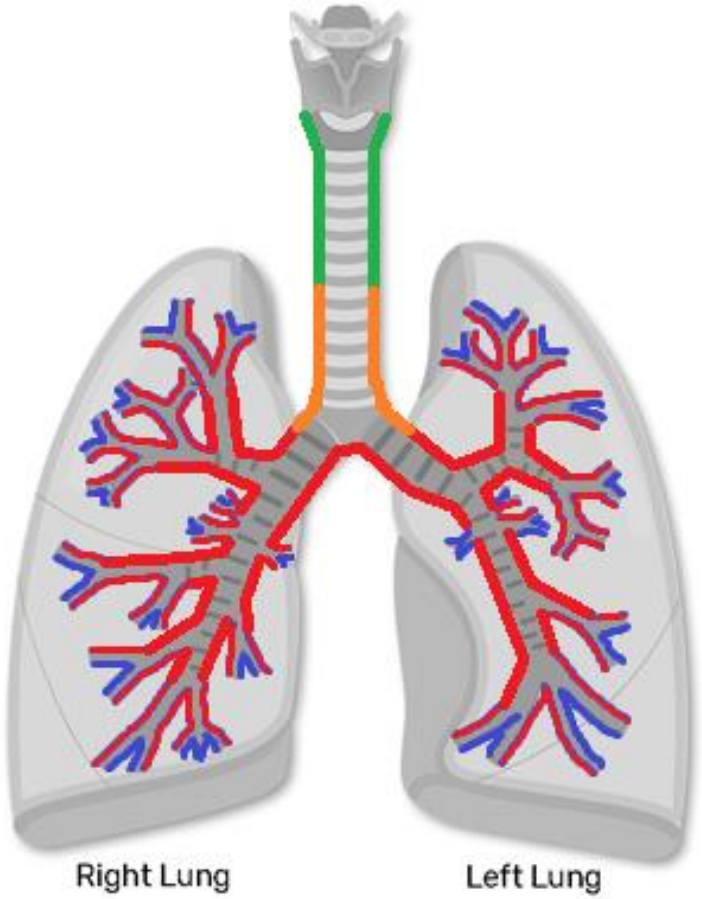
PBPK simulated in Mimetikos Preludium™



In Silico Deposition Model

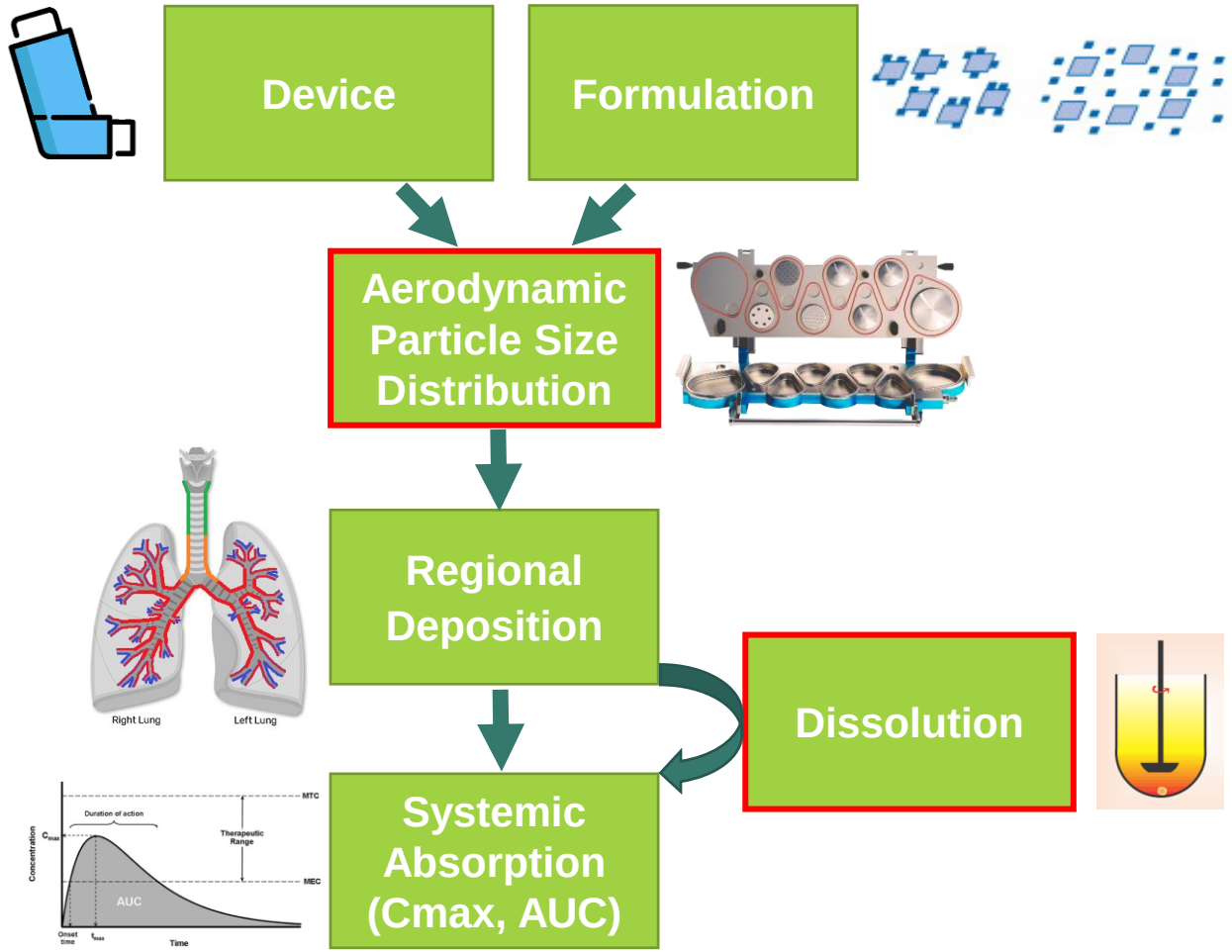
Regional deposition simulated in Mimetikos Preludium™

- **Aerosol deposition in human respiratory tract calculated:**
  - ET: Mouth-Throat
  - BB: Tracheobronchial
  - Bb: Bronchiolar
  - AI: Alveolar Interstitial
- **Post deposition effects simulated.**
  - Lung and systemic properties
  - Compound and formulation properties



PBPK Modelling of Device and Formulation Differences

Mechanistic modelling PK outputs reflect differences in formulation and device

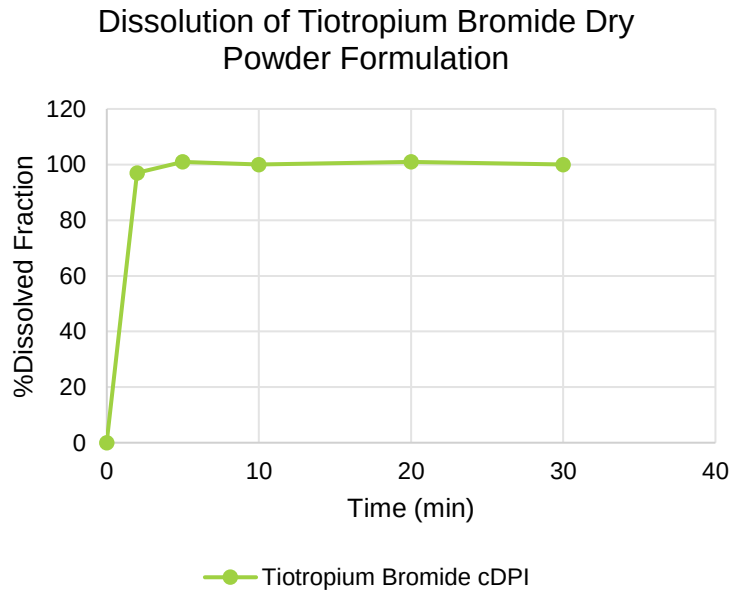


PBPK Model Parameterisation: Tiotropium Capsule Dry Powder Inhaler

Mechanistic modelling of physiochemical and compartmental parameters for simulation of PK

Compartmental Parameter	Value
Vc (L)	11.94
Ke (h^{-1})	3.85
CL (L h^{-1})	46.00
K12 (h^{-1})	7.0375
V2 (L)	201.08
K21 (h^{-1})	0.4179
CLd2 (L h^{-1})	84.03

Physiochemical Parameter	Value
Mw (g/mol)	392.5
Diffusivity (cm^2 min^{-1})	4.1 E4
Solubility in PBS Ph 7.4 (µg mL^{-1})	3.5 E4
Density (g cm^{-3})	1.50
LogP/Kow	-2.2
Unbound concentration, Vu	3.87 mL/g
Tissue to plasma partition coefficient, Kp (Vu*Fup)	1.08 mL/g

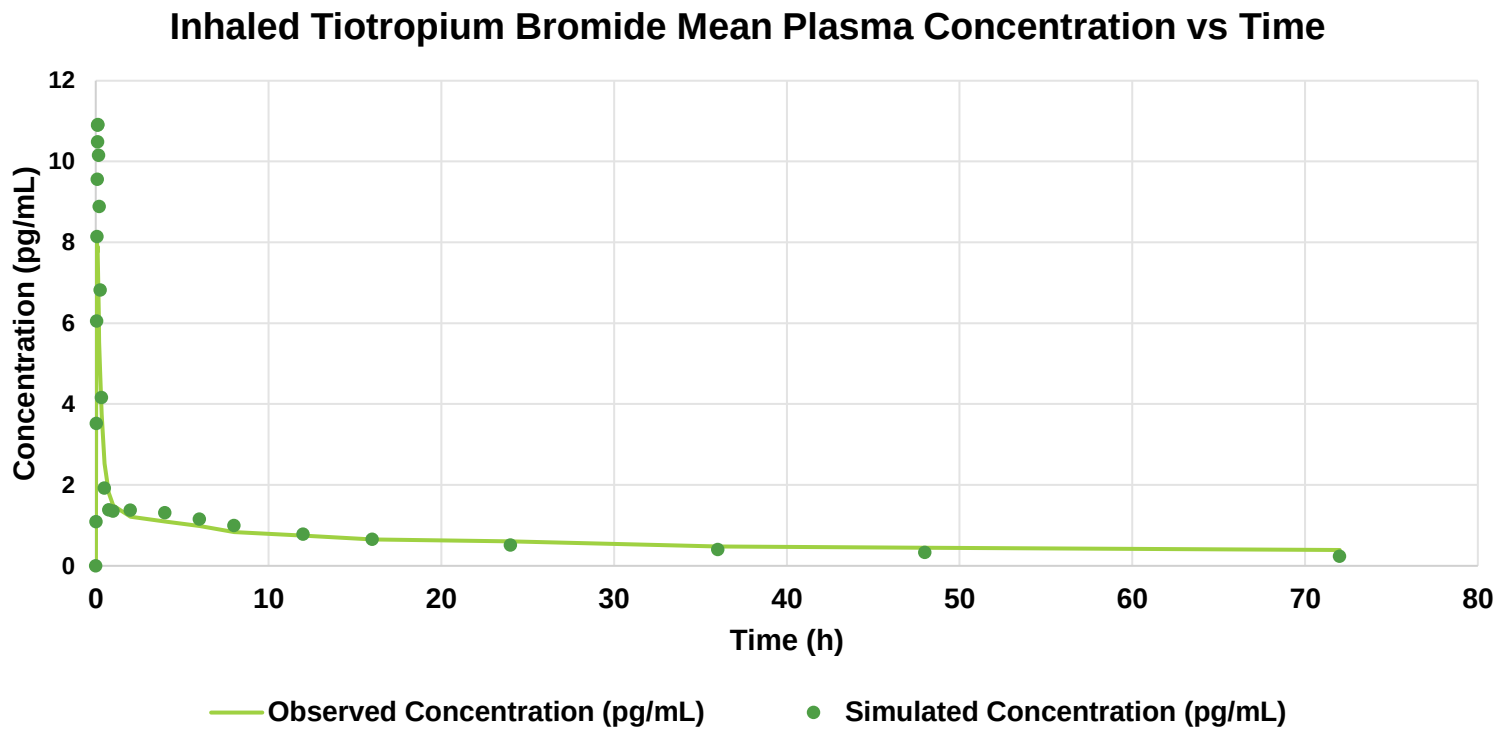


Tiotropium is a hydrophilic drug with moderate permeability, high solubility and fast dissolution

Türck et al, Journal of Clinical Pharmacology, 2004

PK Study of Inhaled Tiotropium cDPI

Simulated PK profile via mechanistic modelling aligns closely with observed data

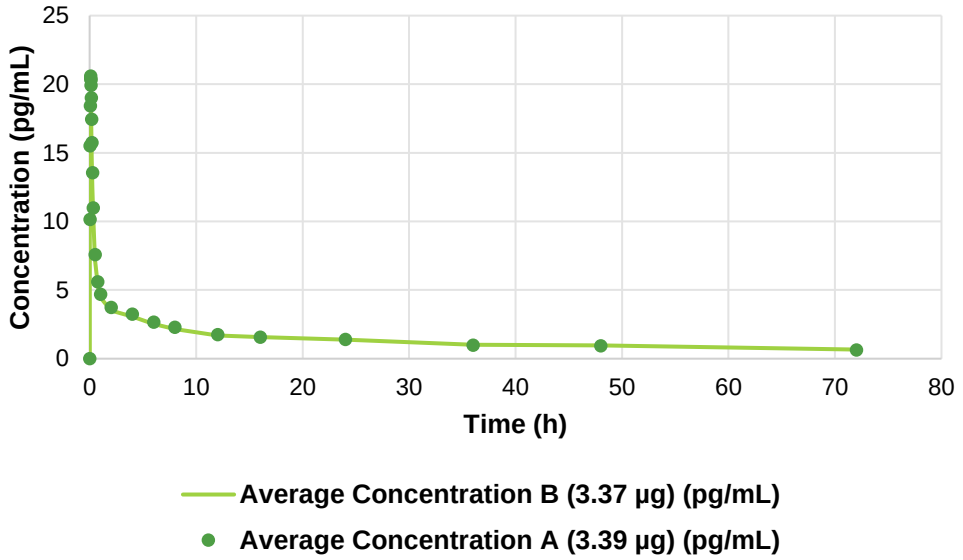


	Tiotropium observed	Tiotropium simulated	Log Ratio Sim v Obs
C_{max} (pg\mL)	8.7	10.9	1.1
$AUC_{0\text{-}72h}$ (pg.hr\mL)	36.0	39.8	1.0
T_{max} (hr)	0.1	0.1	1.0

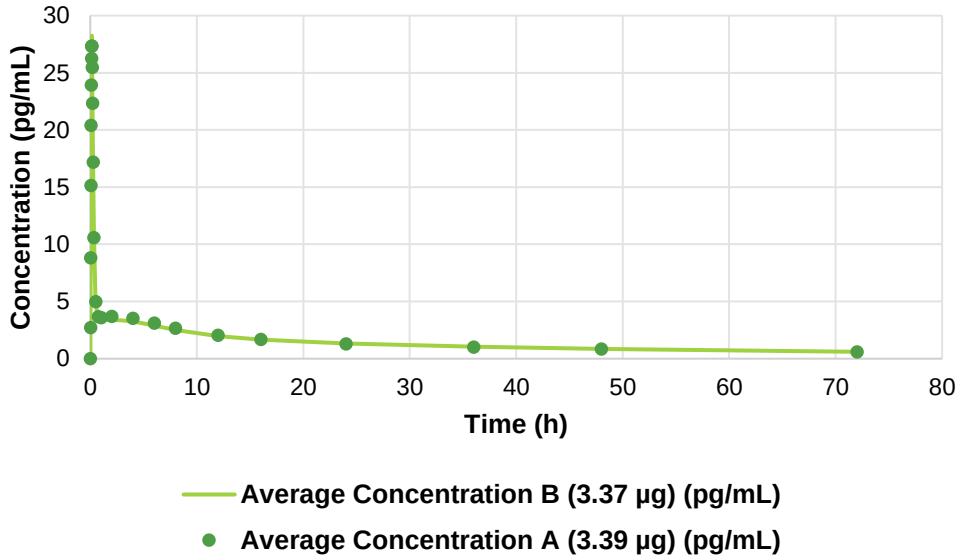
PK Simulation of Similar Tiotropium Capsule Dry Powder Formulations

In vivo PK of formulations with similar FPD can be reliably simulated using mechanistic modelling

Mean Tiotropium Plasma Concentration - (Observed)



Mean Tiotropium Plasma Concentration - (Simulated)



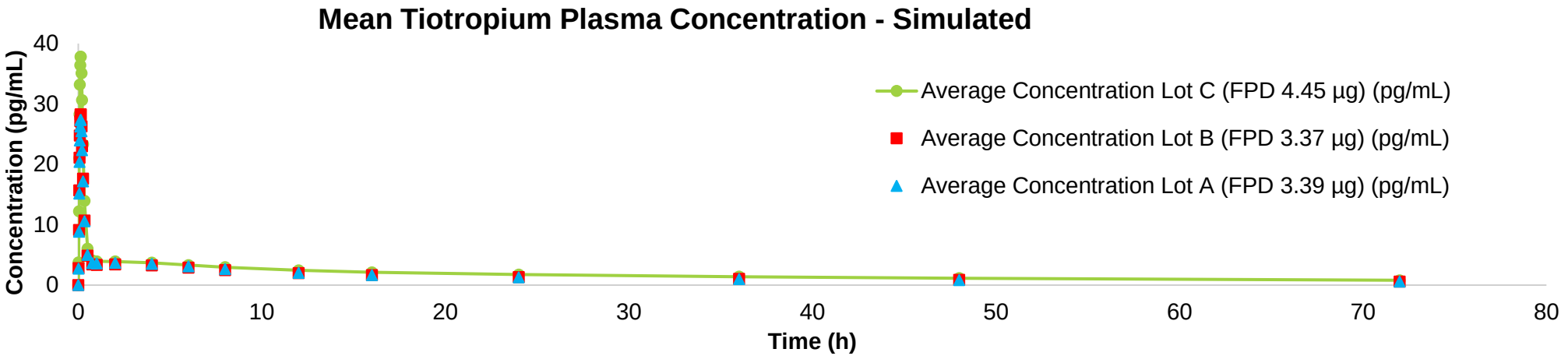
	Obs Lot A (FPD 3.39 µg)	Obs Lot B (FPD 3.37 µg)	Log Ratio
Cmax (pg\mL)	22.41	21.71	0.99
$AUC_{0\text{-}72\ h}$ (pg.hr\mL)	99.84	100.47	1.00
Tmax (hr)	0.1	0.1	1.00

	Sim Lot A (FPD 3.39 µg)	Sim Lot B (FPD 3.37 µg)	Log Ratio
Cmax (pg\mL)	27.35	28.26	1.01
$AUC_{0\text{-}72\ h}$ (pg.hr\mL)	102.22	101.77	0.99
Tmax (hr)	0.1	0.1	1.00

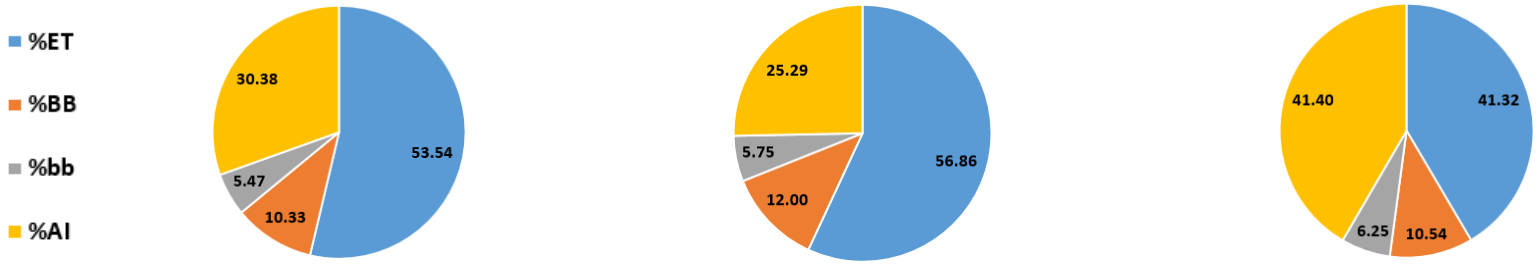
Log Ratio A sim/obs	Log Ratio B Sim/obs
1.06	1.08
1.00	1.00
1.00	1.00

Simulation of PK Using Different Tiotropium cDPI Formulations

Simulated C_{max} and AUC_t are elevated in formulations with higher fine particle dose (FPD)



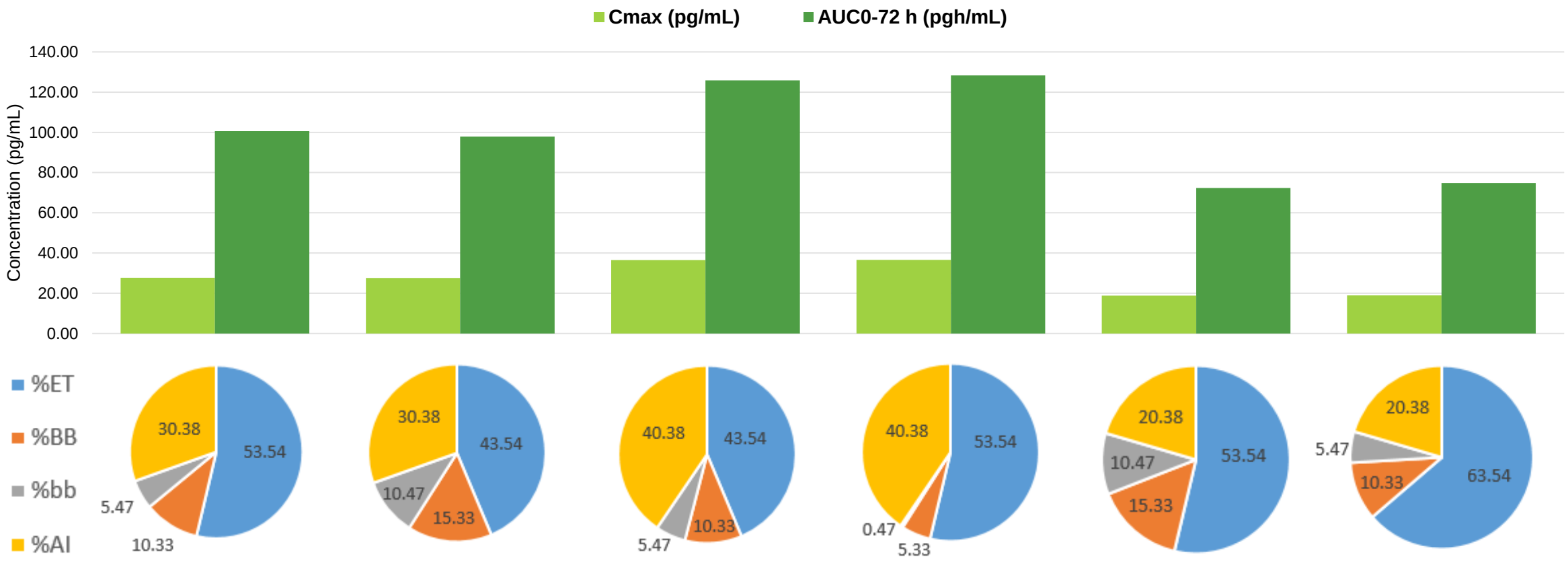
	Sim Lot A (FPD 3.39 µg)	Sim Lot B (FPD 3.37 µg)	Sim Lot C (FPD 4.45 µg)
Cmax (pg\mL)	27.35	28.26	37.81
$AUC_{0\text{-}72\ h}$ (pg.hr\mL)	102.22	101.77	129.72
Tmax (hr)	0.13	0.13	0.13



Simulated regional lung deposition distribution

Mechanistic Modelling of Altered Regional Deposition

Cmax and AUC0-72h are driven by alveolar-interstitial deposition of Tiotropium

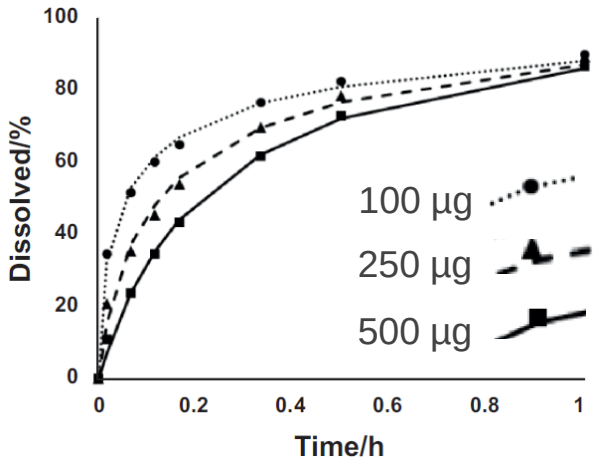


Simulated regional lung deposition distribution

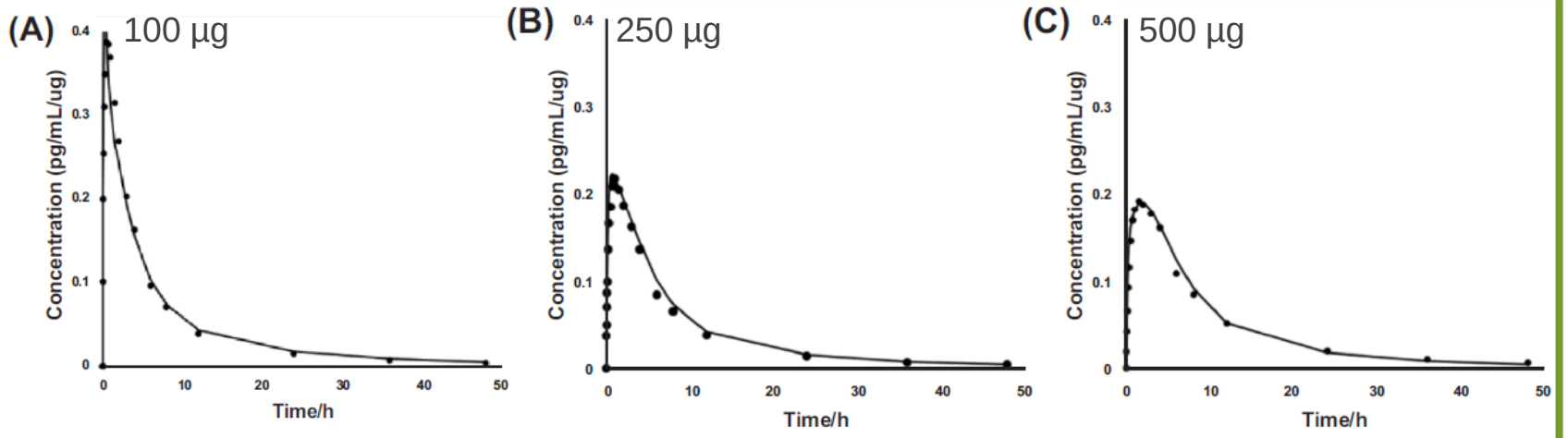
PK Simulation of Fluticasone Propionate Dry Powder Formulation

PK outcome for poorly soluble compounds correlates with dissolution profile

Dissolution (*in vitro*)



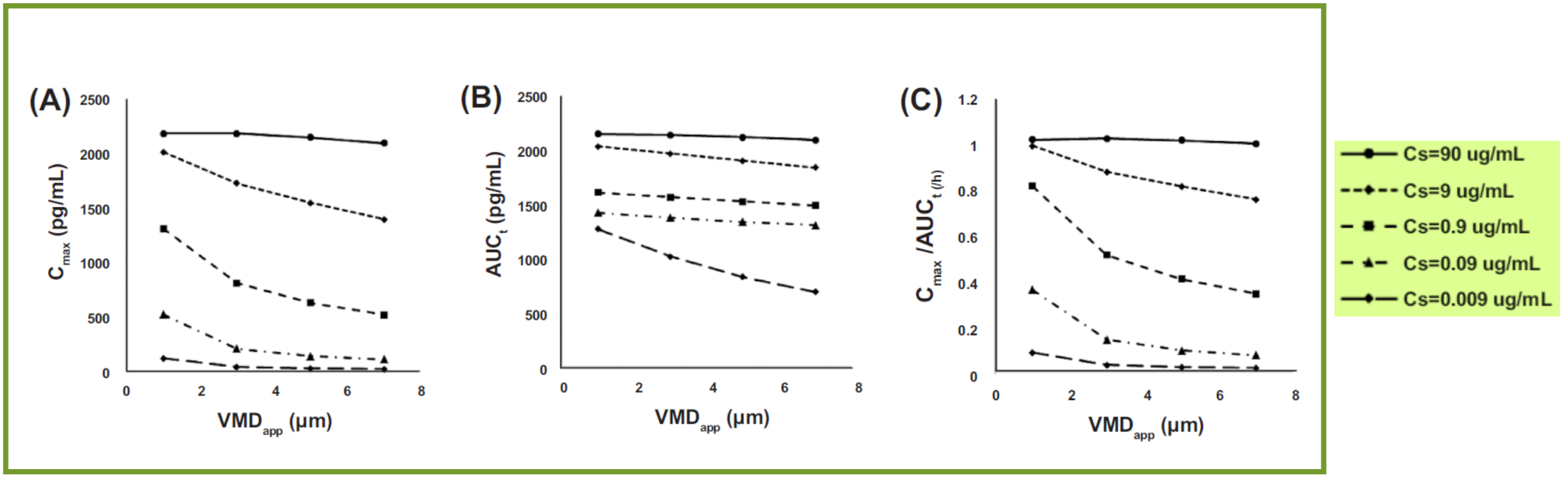
PK plasma curve (*in vivo*)



Bäckman and Olsson, *Respiratory Drug Delivery 2020.*

Exploring the *in vivo* PK Profile Sensitivity of Fluticasone Propionate

Simulated PK is sensitive to changes in dissolution for a poorly soluble inhaled drug



Bäckman and Olsson, *Respiratory Drug Delivery 2020.*

Conclusions

1. Preludium *in silico* model can reliably simulate PK profiles of inhaled formulations as supported by successful validation using both highly and poorly soluble OIDPs.
2. Mechanistic modelling can demonstrate the impact of changes to formulation and device on the systemic absorption of inhaled Tiotropium capsulated dry powder.
3. Regional lung deposition of Tiotropium is sensitive to changes in *in vitro* particle size distribution and PK is sensitive to changes in regional lung deposition.
4. The PK outcome following inhalation of a poorly soluble compound is sensitive to changes in dissolution as well as particle size distribution.
5. Preludium can be used to understand the sensitivity of *in vivo* PK profiles to variations in *in vitro* product attributes of inhalers.

Acknowledgements

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