Pharmacokinetic Comparison of Locally Acting Dry powder Inhalers

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In collaboration with
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DIA 2018 Workshop:
Generic Drug-Device Combination Complex Products
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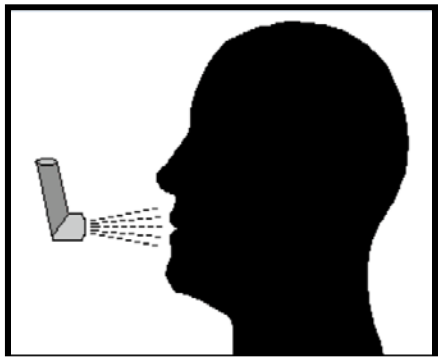
UF UNIVERSITY of FLORIDA

Background

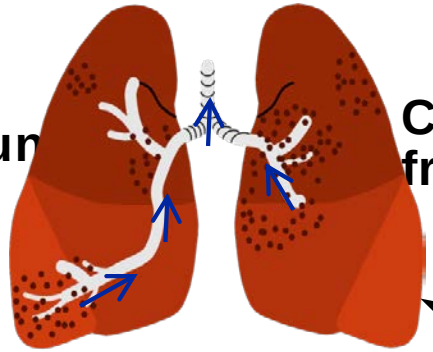
- There is a need for generic forms of topical asthma medication (Advair is ~$ 2000/per patient year)
- Pressure to streamline generic approval is high.
- FDA is currently very active in providing guidance information and participating in discussions with stakeholders. (June 21st 2013, FDA Meeting on Bioequivalence,…… GDUFA Meetings, DIA 2018…..)

Topics related to Bioequivalence

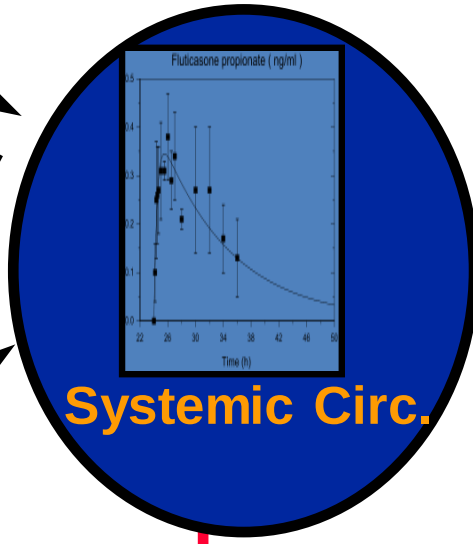


10 - 60 %
Deposited in lun

Cl_{muc}



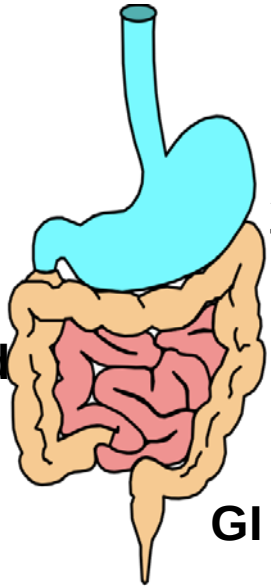
Complete absorption
from the lung



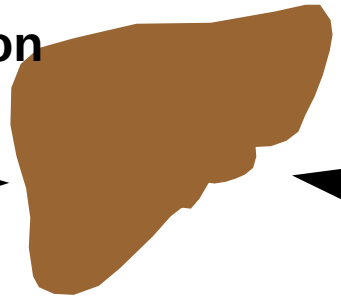
Lung

Mouth and pharynx

Orally bioavailable
fraction



Absorption
from gut



Liver

Systemic
side effects

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

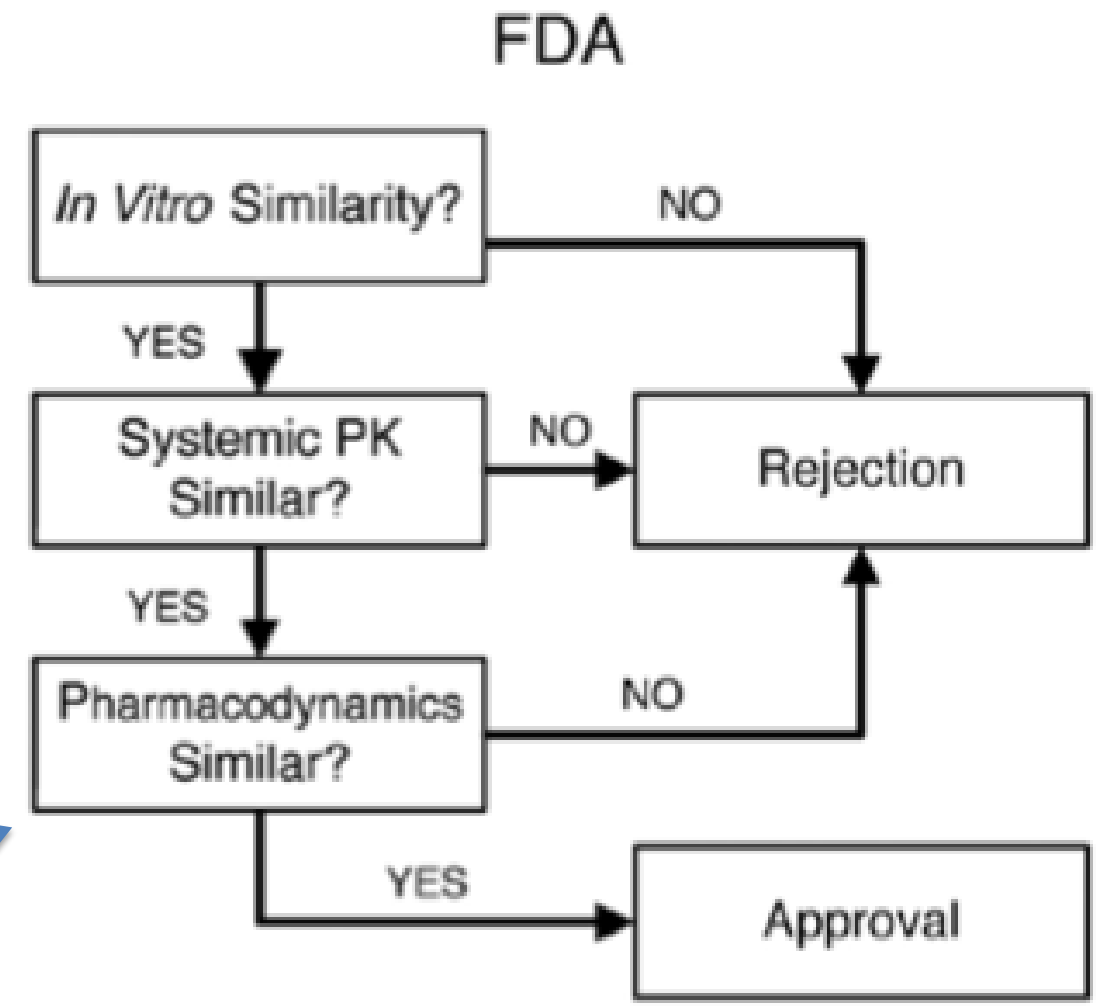
GI tract

First-pass
inactivation

Relevant Questions

1. What is the dose available to the lung?
2. What is the regional distribution of the deposited dose within the lung?
3. How long drug the drug stay in the lung?
4. What is the systemic exposure?

Current FDA Recommendation



expensive, risky,
cannot differentiate between doses

Need

- **Alternative approaches**
  - to replace pharmacodynamic studies with sensitive and accurate alternative approaches
  - thereby allowing higher resolution in decision making

Strategy

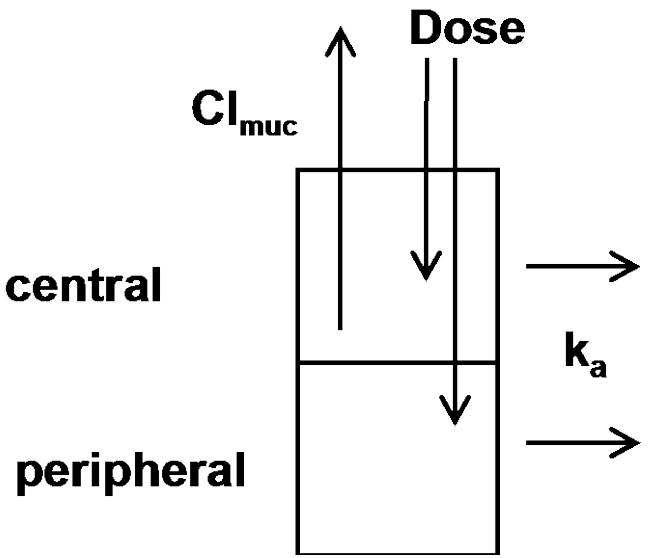
suggested at "PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (2009)"

- **Perform**
  - In vitro studies
  - Pharmacokinetic studies to probe equivalence in lung dose, residence time and regional deposition.

Hypothesis

For slowly dissolving drugs, PK should allow one to assess differences in:

- **Lung dose**
- **Lung residence time** (absorption)
- **Regional deposition** (more central deposited drug will be removed more efficiently by mucociliary clearance



If this can be shown:

Clinical studies are not necessary

Simulations: AUC affected by C/P ratio

drug is slowly dissolving, such as FP

Simulations (same Dose)

	Brand	Generic	Generic	Generic
C/P Ratio	45/55	45/55	63/37	22/78
Variability	30%	30%	30%	30%
N	30	30	30	30
Bioequivalence Trials*		82%	6%	6%

*** % Trials with CI within 80-125%**

- **AUC should be sensitive to c/p ratio**
- **FDA provided contract to demonstrate in vivo**

Goal of Study

Probe whether PK is sensitive to differences in the c/p ratio for slowly dissolving drugs (FP).

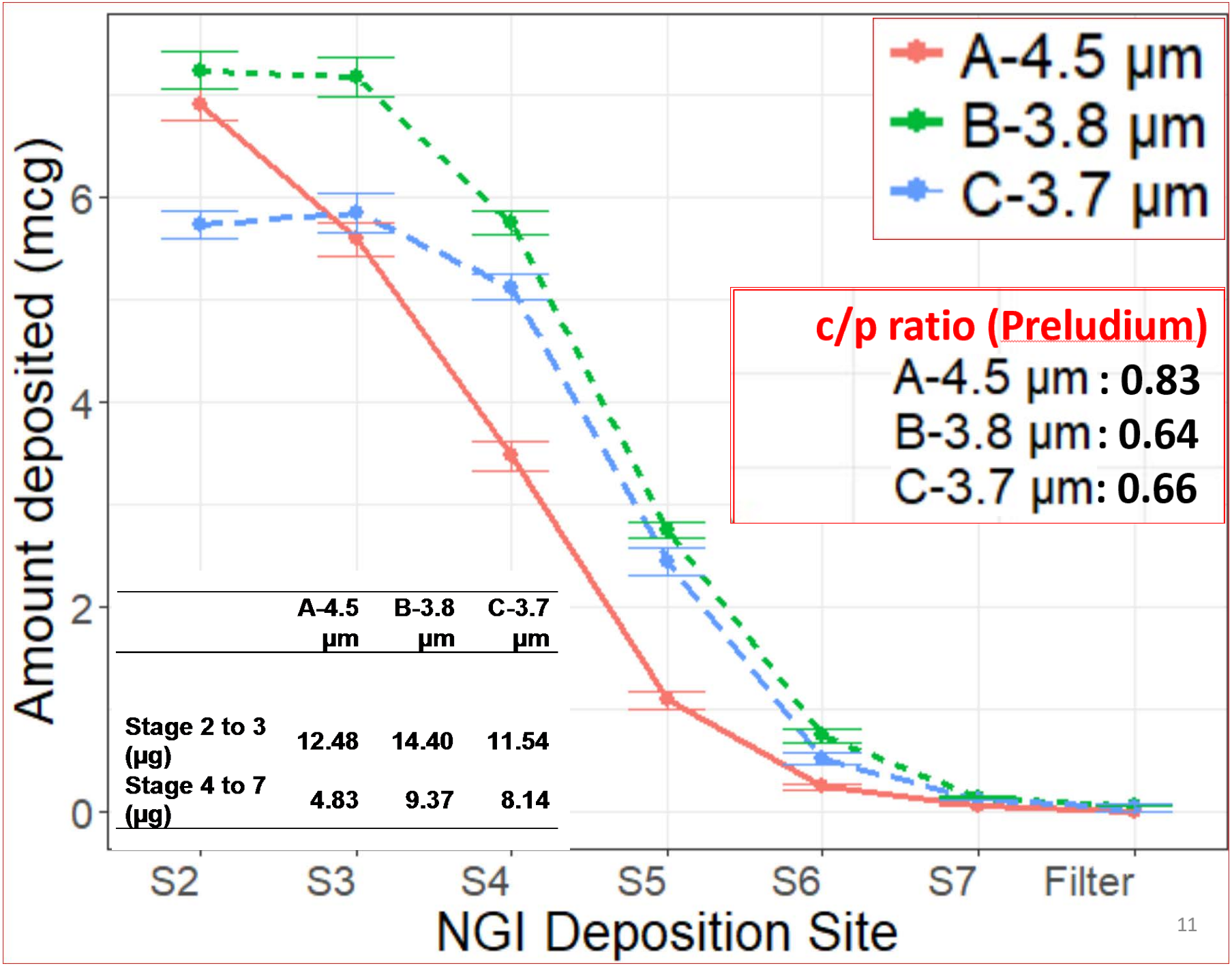
- **Develop three DPI-FP formulations. If possible:**
  - Same dose
  - Same dissolution rate
  - Difference in central to peripheral lung deposition.
- **Characterize through in vitro experiments**
  - Ex throat dose
  - Cascade impactor profile
  - Dissolution rate
- **Perform PK (4 way cross-over,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

Formulation Work

(Dr. Jag Shur, Robert Price, Univ of Bath)

Three formulations only differing in lactose fines

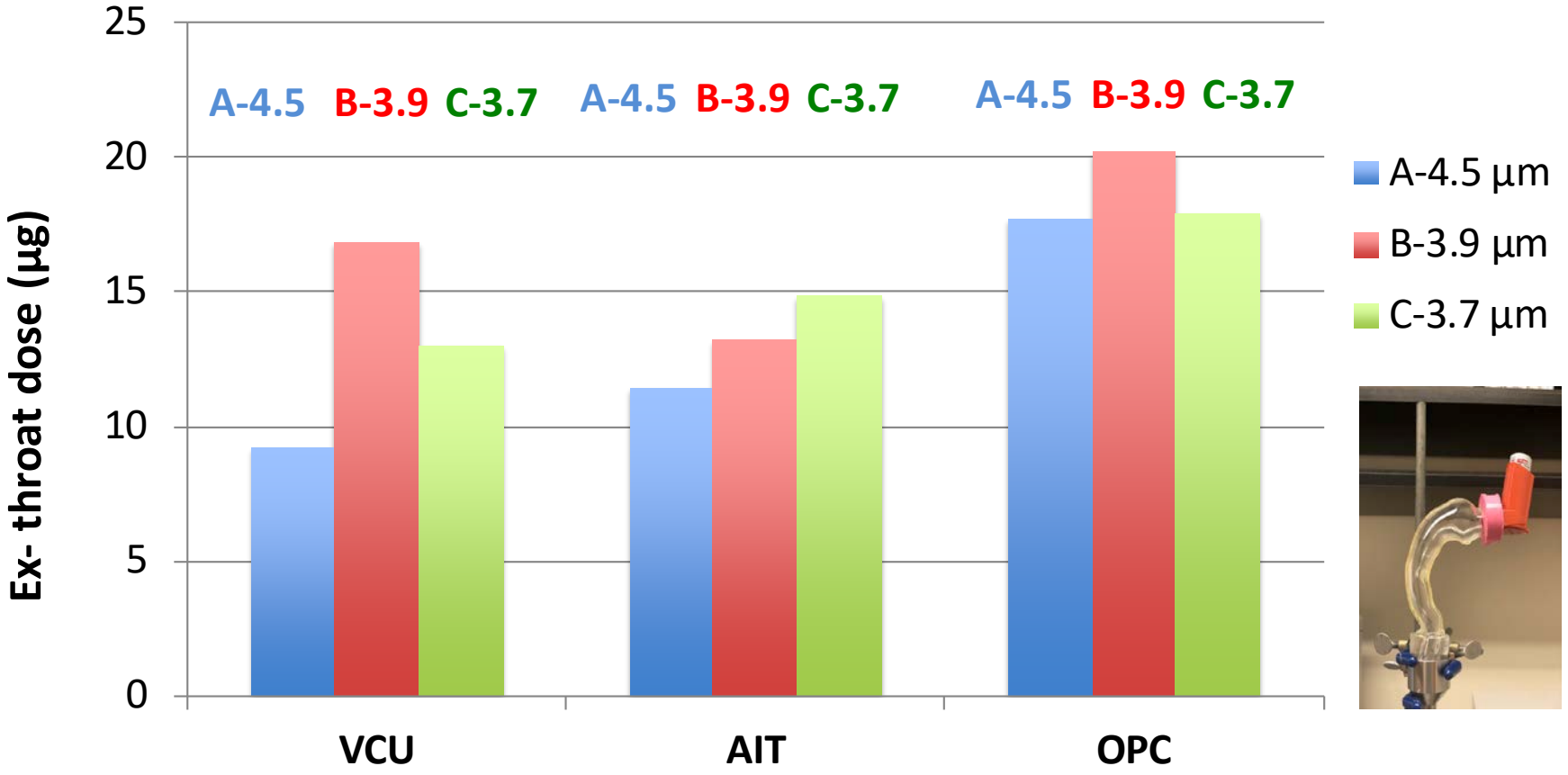
Product Name	Formulation (% w/w)	Lot Number
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 96.72 Lactohale LH300: 2.48	C-3.7µm Labelled as 15MM-015 In Appendixes
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 79.36 Lactohale LH201: 19.84	A-4.5µm Labelled as 15MM-017 In Appendixes
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 89.28 Lactohale LH230: 9.92	B-3.8µm Labelled as 15MM-016 In Appendixes



	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

Do formulations provide the same lung dose?

Ex-throat dose: anatomical throats, typical inhalation profile

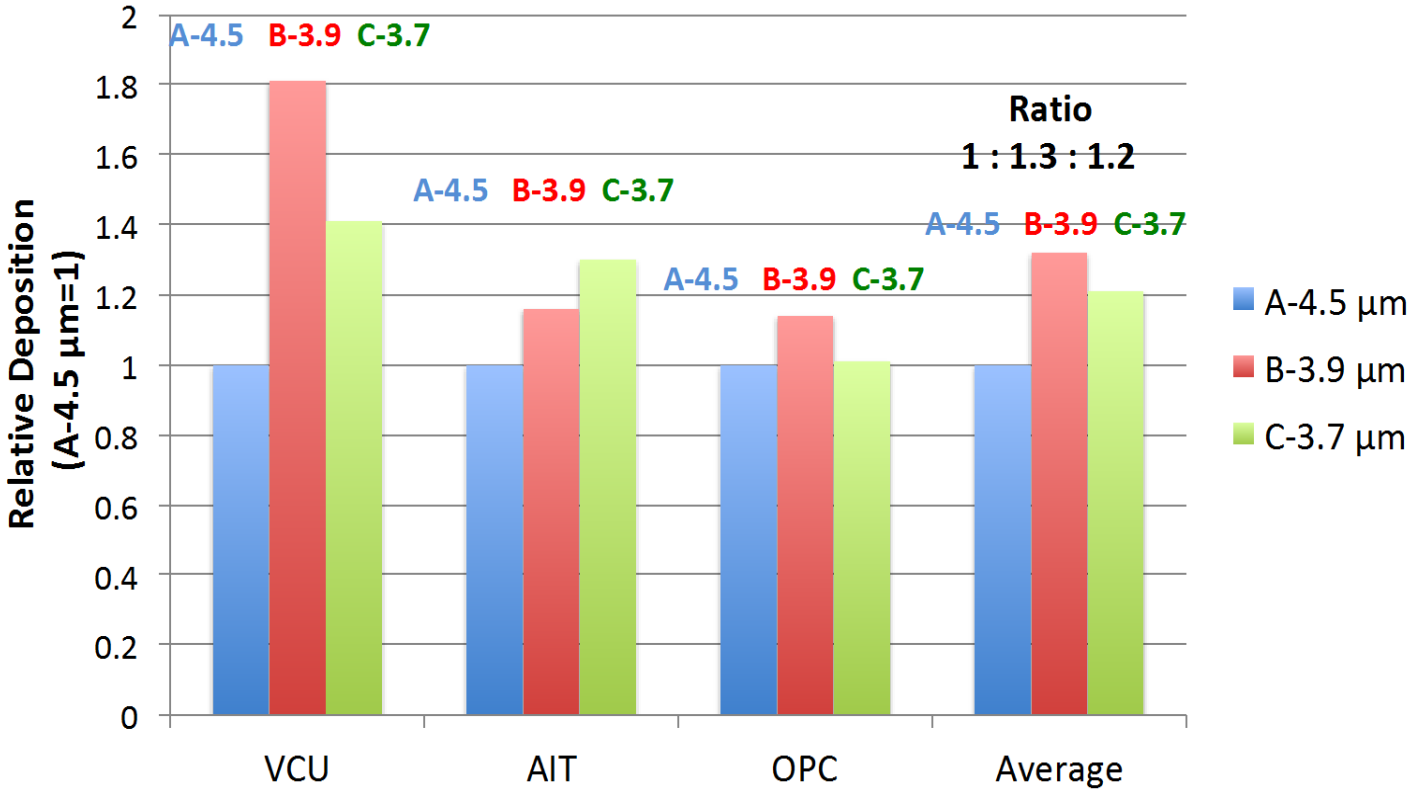


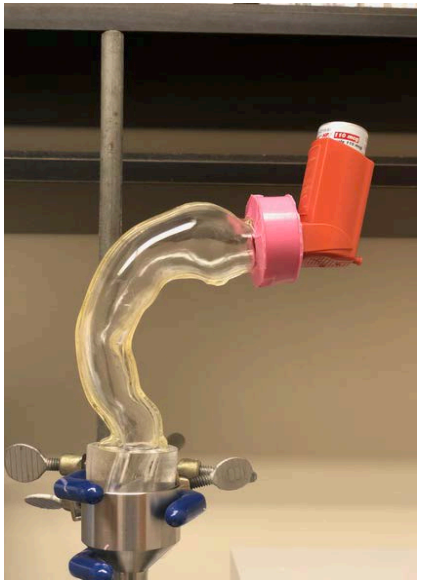
- **Throats differ in deposited amounts**
- **Projected Lung Doses will differ**
- **By which factor?**

Dr. Mike Hindle , VCU

Relative Ex-throat dose

(anatomical throats, typical inhalation profile)

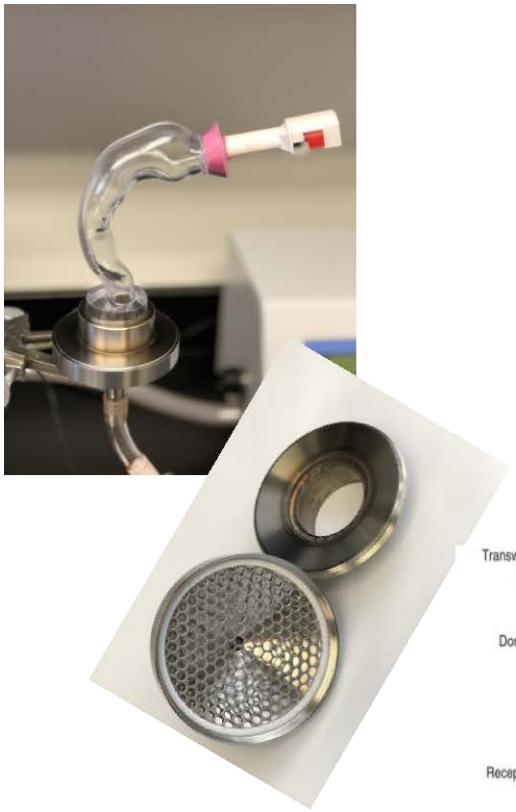


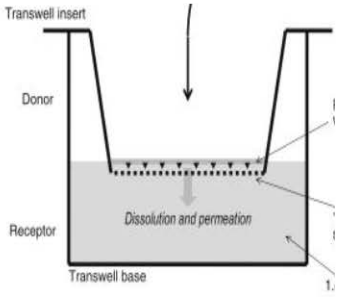


- Throats differ in rank-order and ratio
- For future: Design better throat???, use several throats???
- For now: Lung doses suggested by throats differ,
  but were supposed to be similar to test hypothesis.
- What correction factor should be applied?

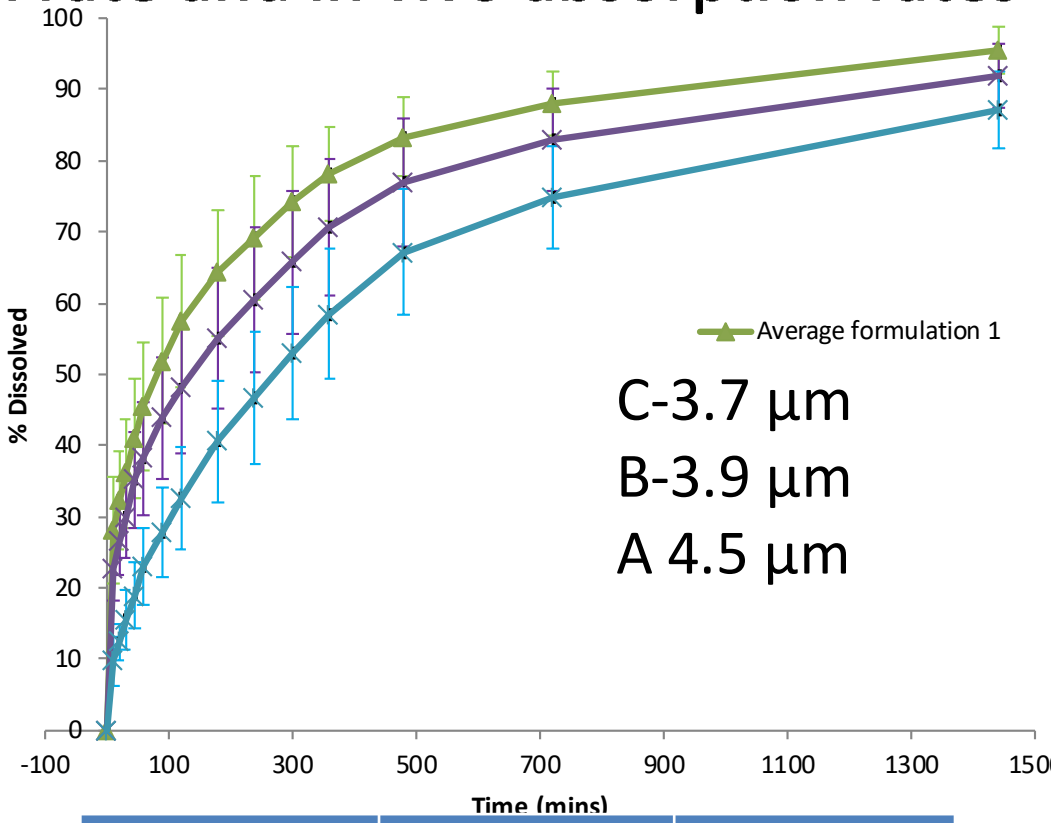
Do formulations provide same absorption rate?

In vitro methods: Dissolution rate and in vivo absorption rates





Arora, D., (2010)



Formulation	Parameter	Value
A-4.5 µm	MDT	15.4 hrs
B-3.9 µm	MDT	13.3 hrs
C-3.7 µm	MDT	10.3 hrs

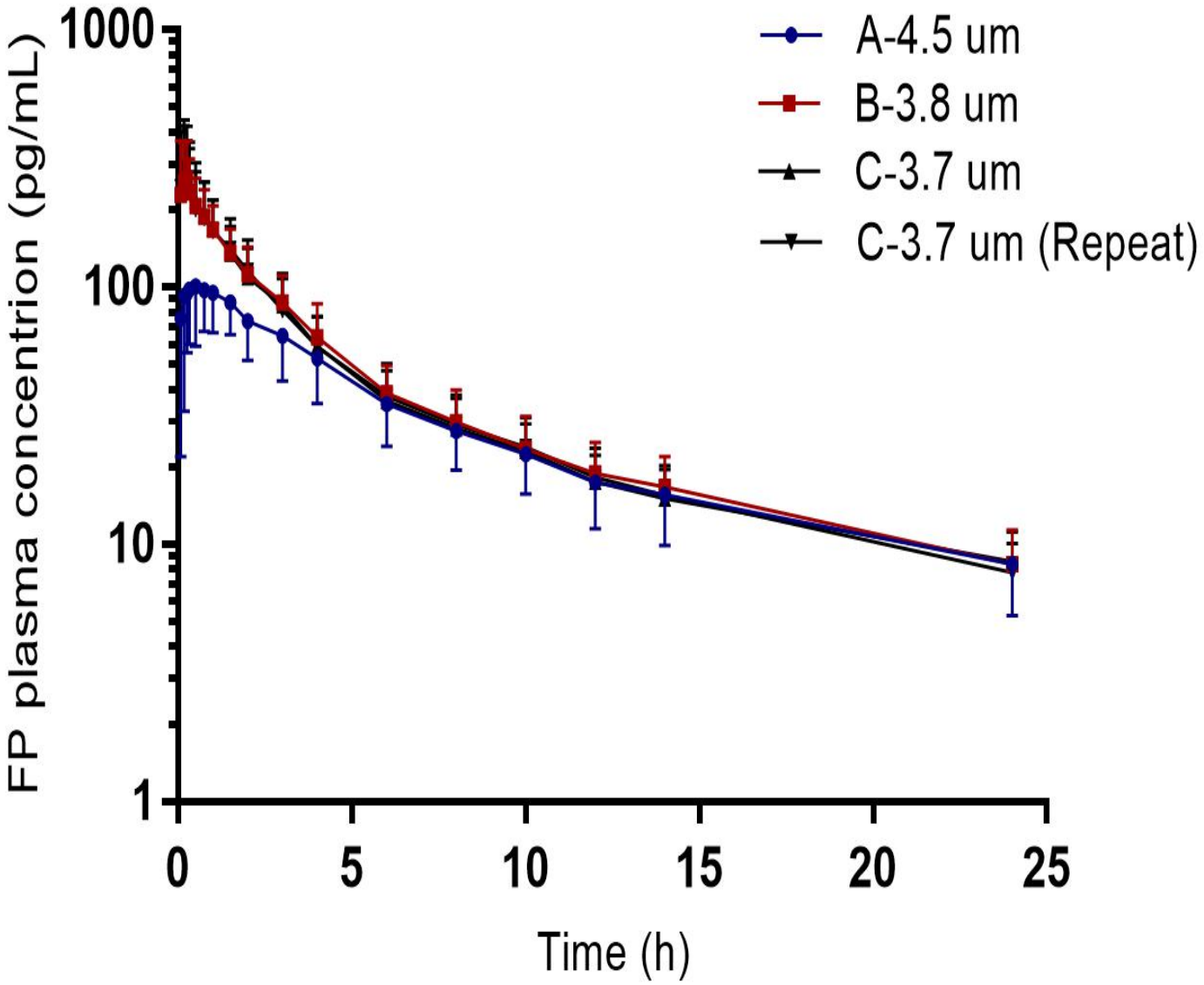
In vitro assessment

- Formulations might provide different lung dose
- Formulations might show differences in absorption kinetics
- Formulations might differ in the c/p lung deposition ratio.

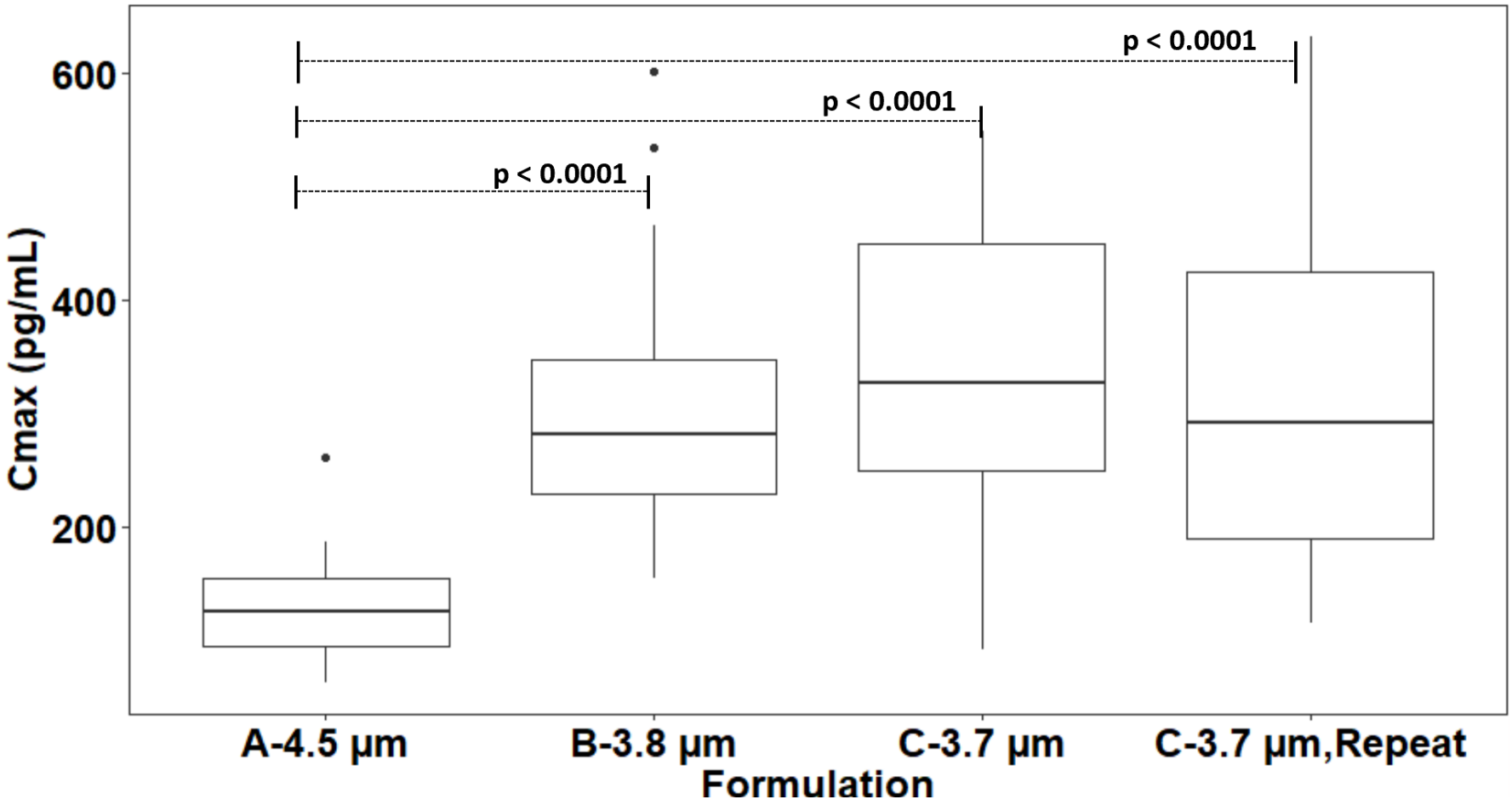
PK Study Design

- 4-way, cross-over, double blind in 24 healthy volunteers (informs intra-subject variability)
- DPI formulations with Plastiape: A-4.5 µm, B-3.8 µm, C-3.7 µm, and CR-3.7 µm (repeat)
- Dose: 5 * 100 µg
- Record individual inhalation profiles
- LC-MS/MS Assay sensitivity: 1 pg/mL
- Non-compartmental Analysis + Compartmental Analysis (population-PK)

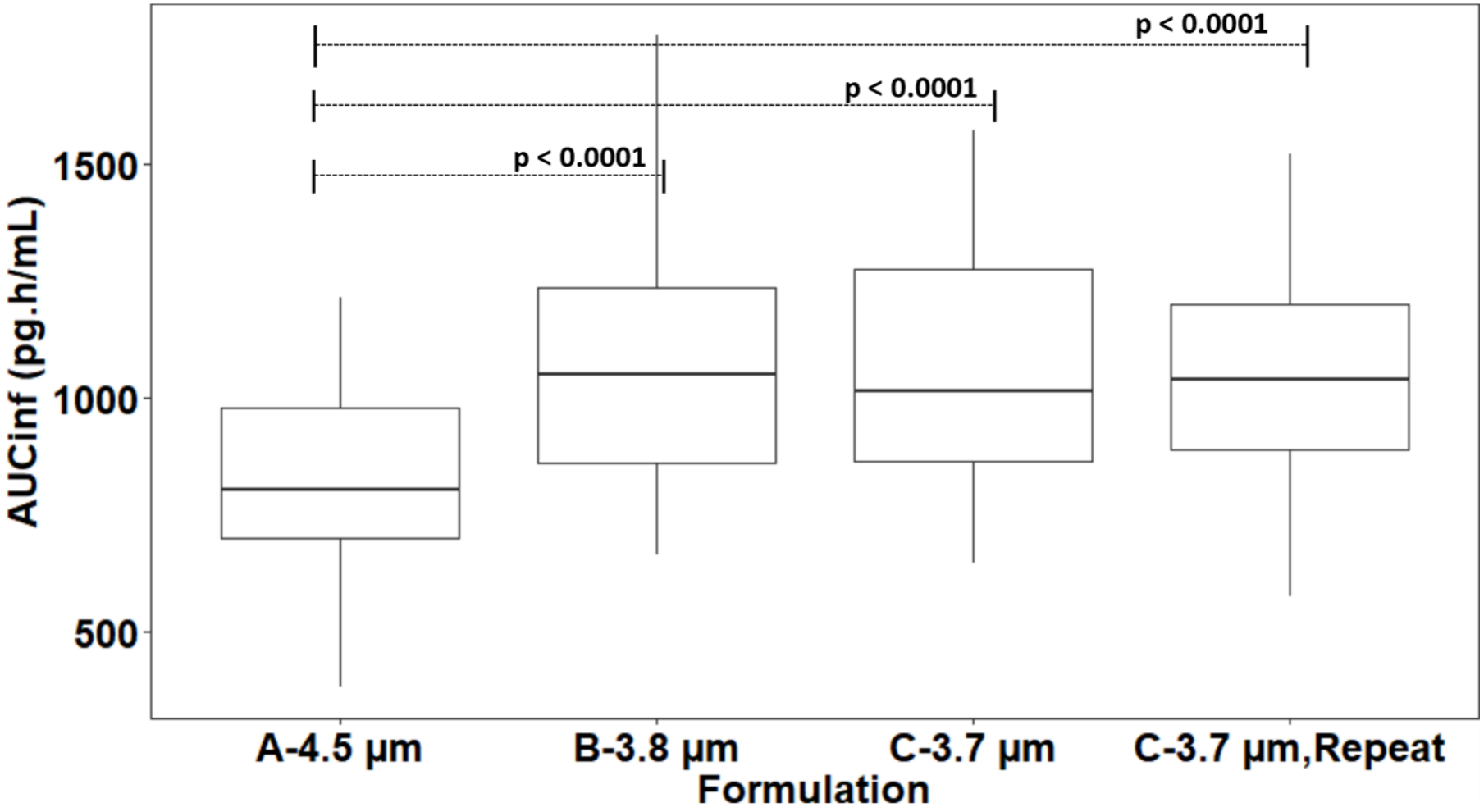
Before dose normalization



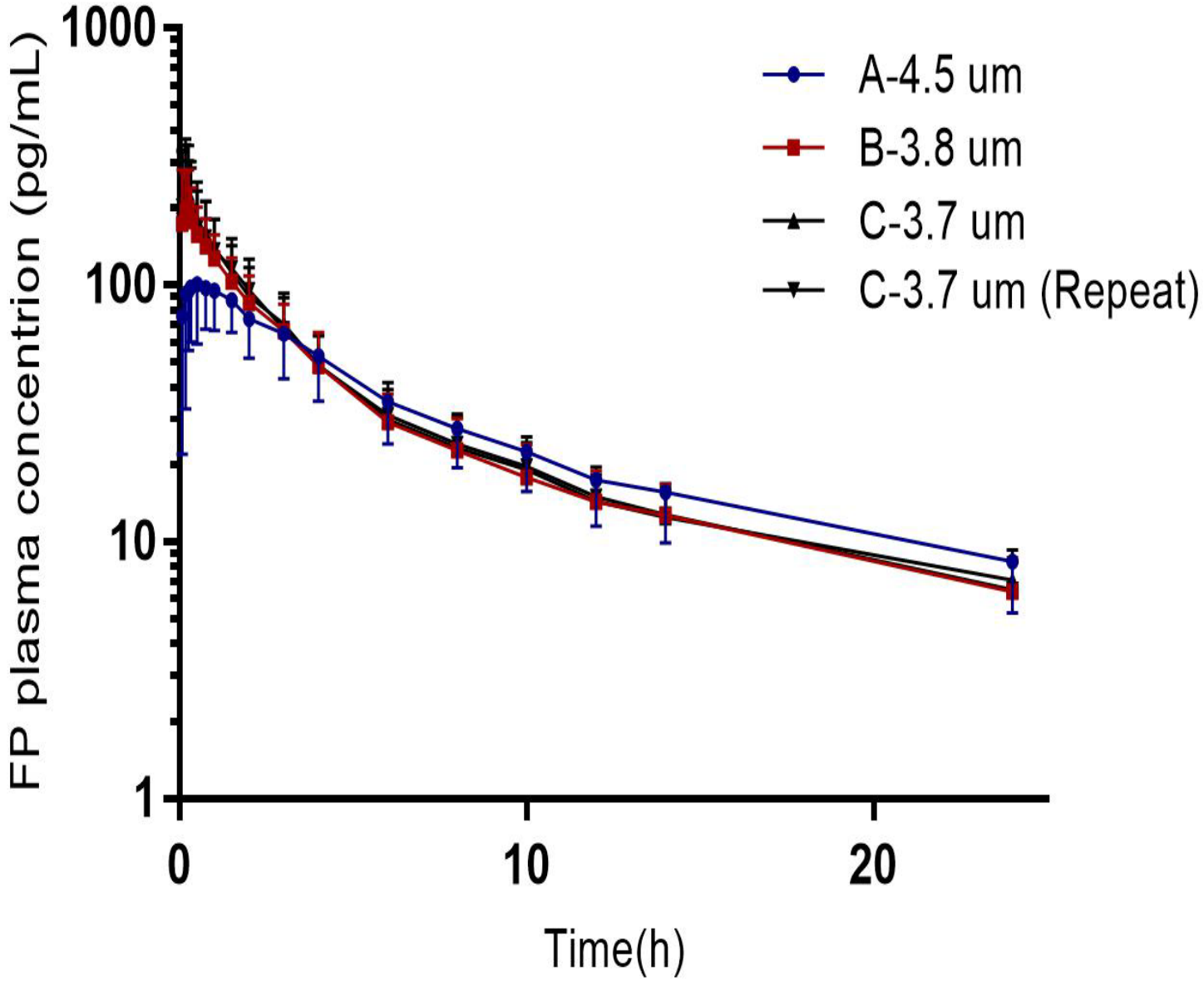
Peak concentrations in plasma (Cmax)



Area under the plasma concentration time curves (AUC)

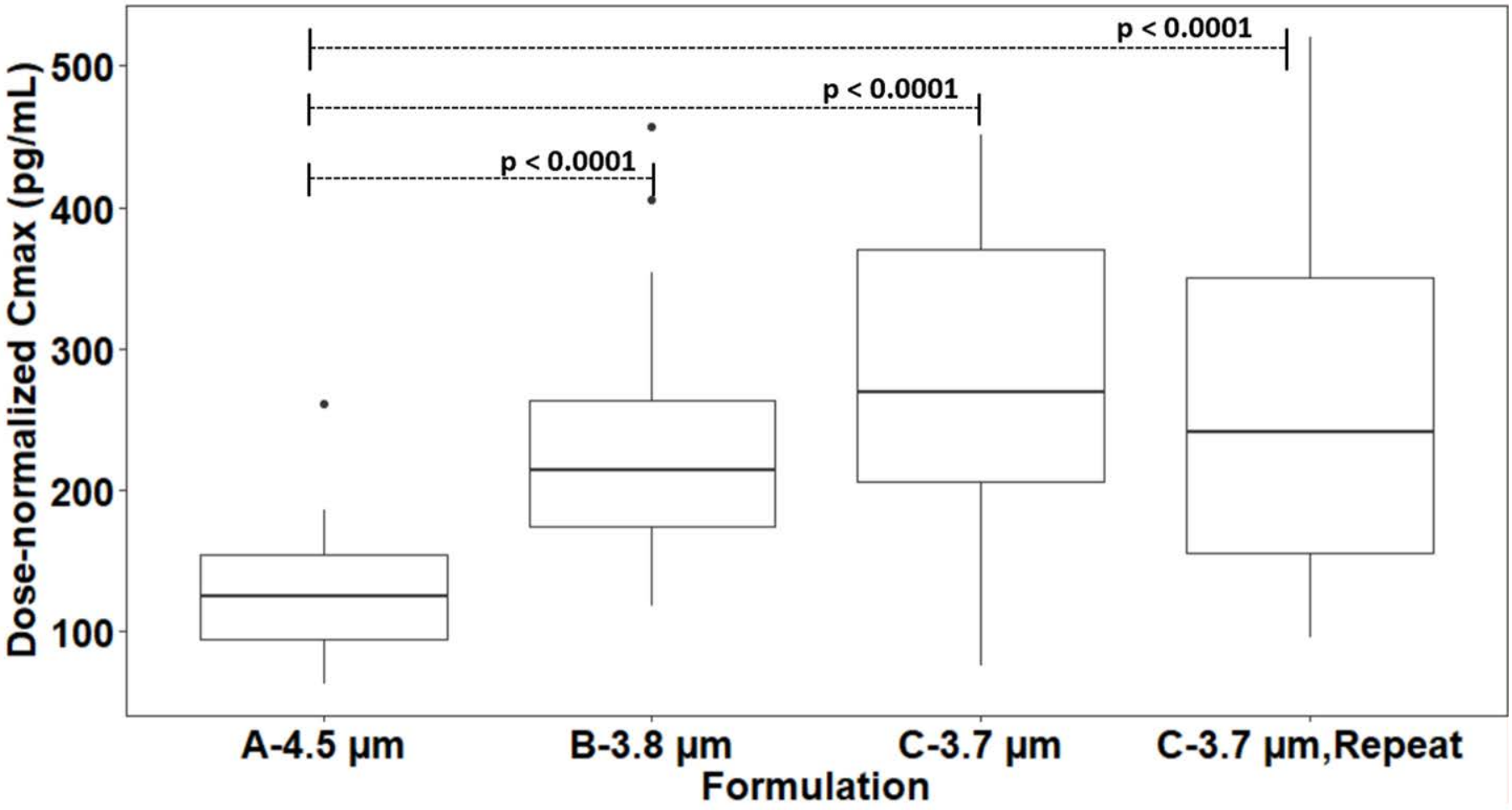


After Dose Normalization:



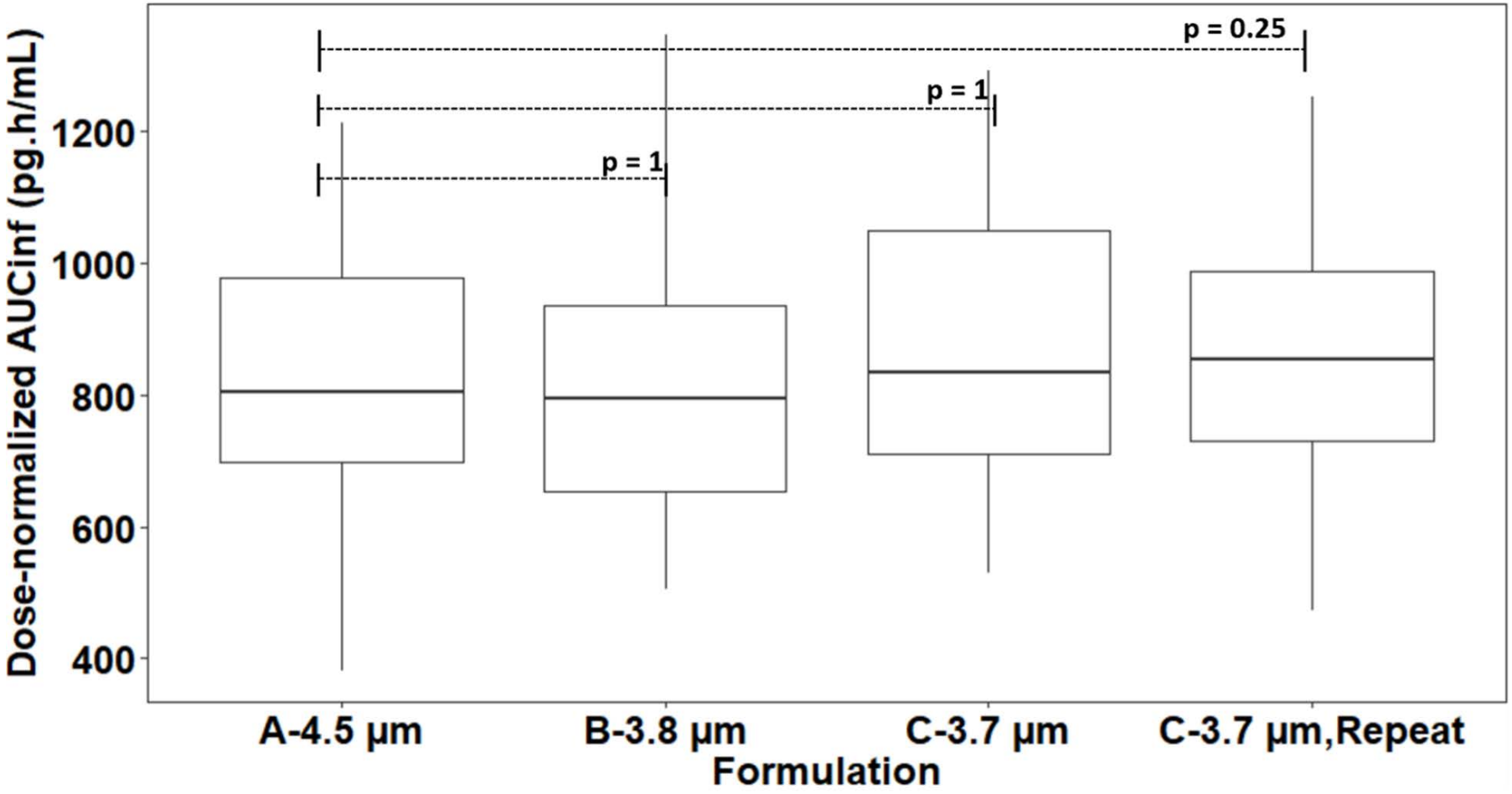
Peak concentrations in plasma (Cmax)

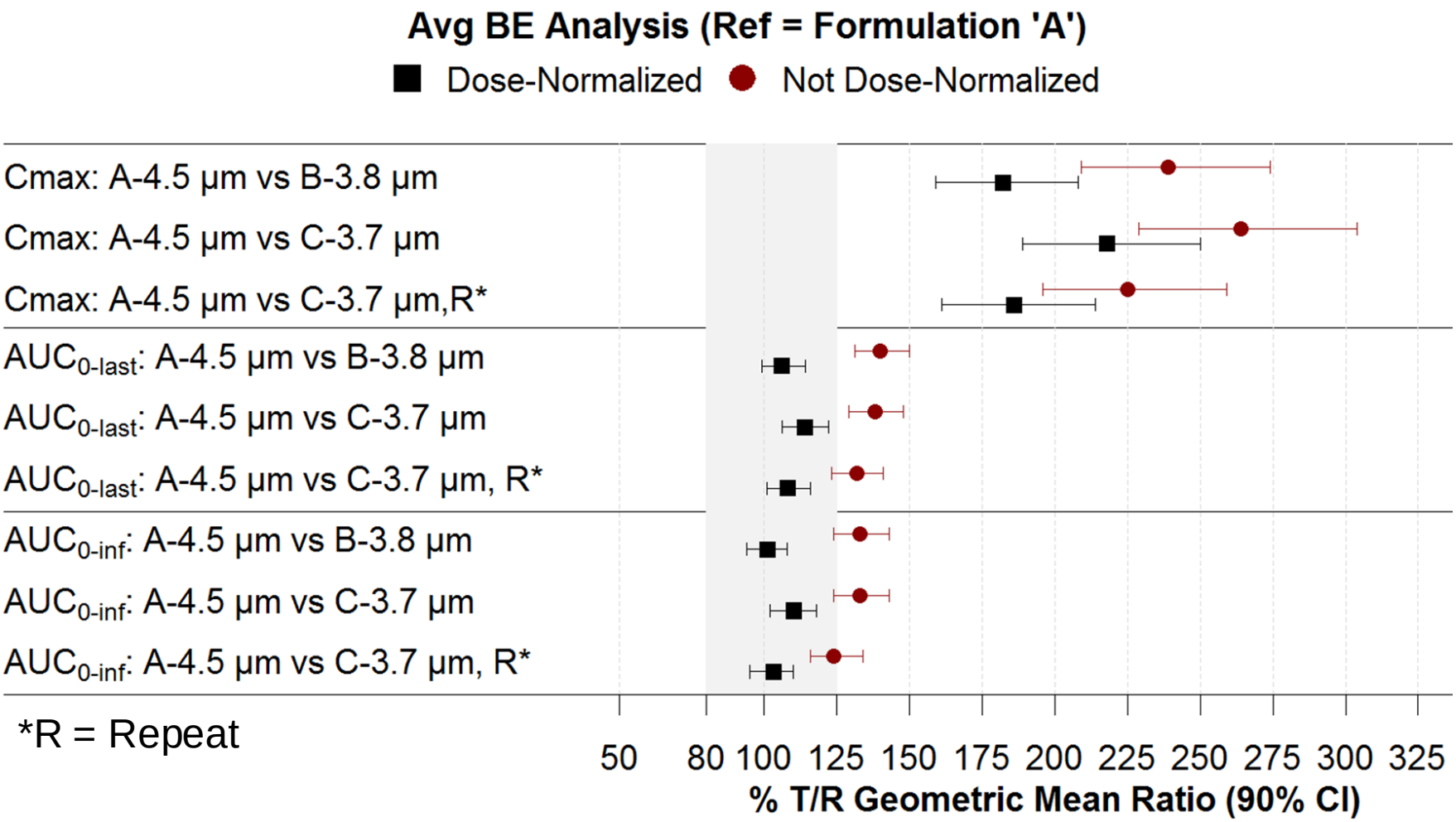
- after dose normalization -



Area under the plasma concentration time curves (AUC)

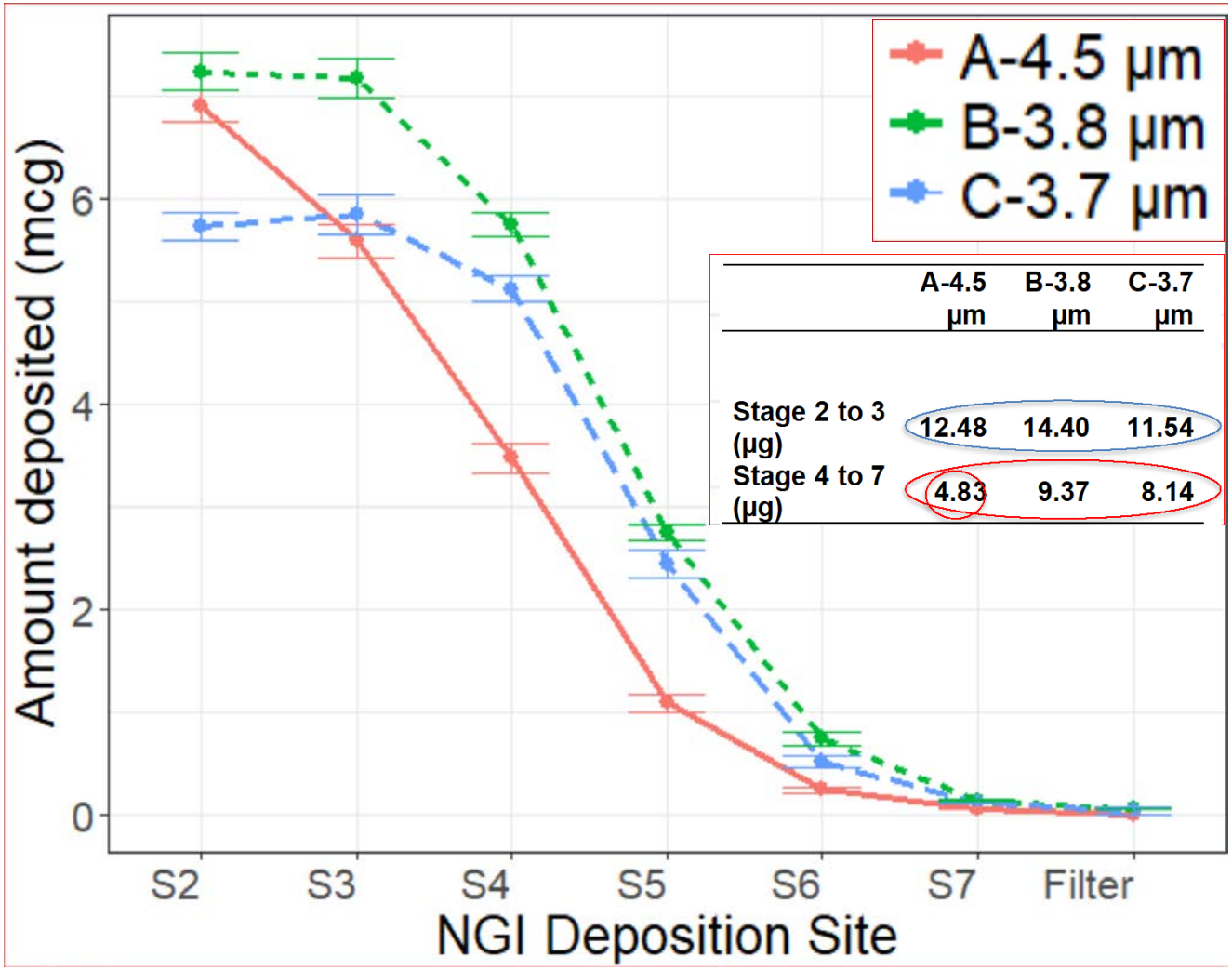
- after dose normalization -




Avg BE Analysis (Ref = Formulation 'A')
Dose-Normalized
Not Dose-Normalized
Cmax: A-4.5 µm vs B-3.8 µm
Cmax: A-4.5 µm vs C-3.7 µm
Cmax: A-4.5 µm vs C-3.7 µm,R*
AUC0-last: A-4.5 µm vs B-3.8 µm
AUC0-last: A-4.5 µm vs C-3.7 µm
AUC0-last: A-4.5 µm vs C-3.7 µm, R*
AUC0-inf: A-4.5 µm vs B-3.8 µm
AUC0-inf: A-4.5 µm vs C-3.7 µm
AUC0-inf: A-4.5 µm vs C-3.7 µm, R*
50 80 100 125 150 175 200 225 250 275 300 325
% T/R Geometric Mean Ratio (90% CI)

*R = Repeat

Why is the difference in AUC after dose normalization so small?

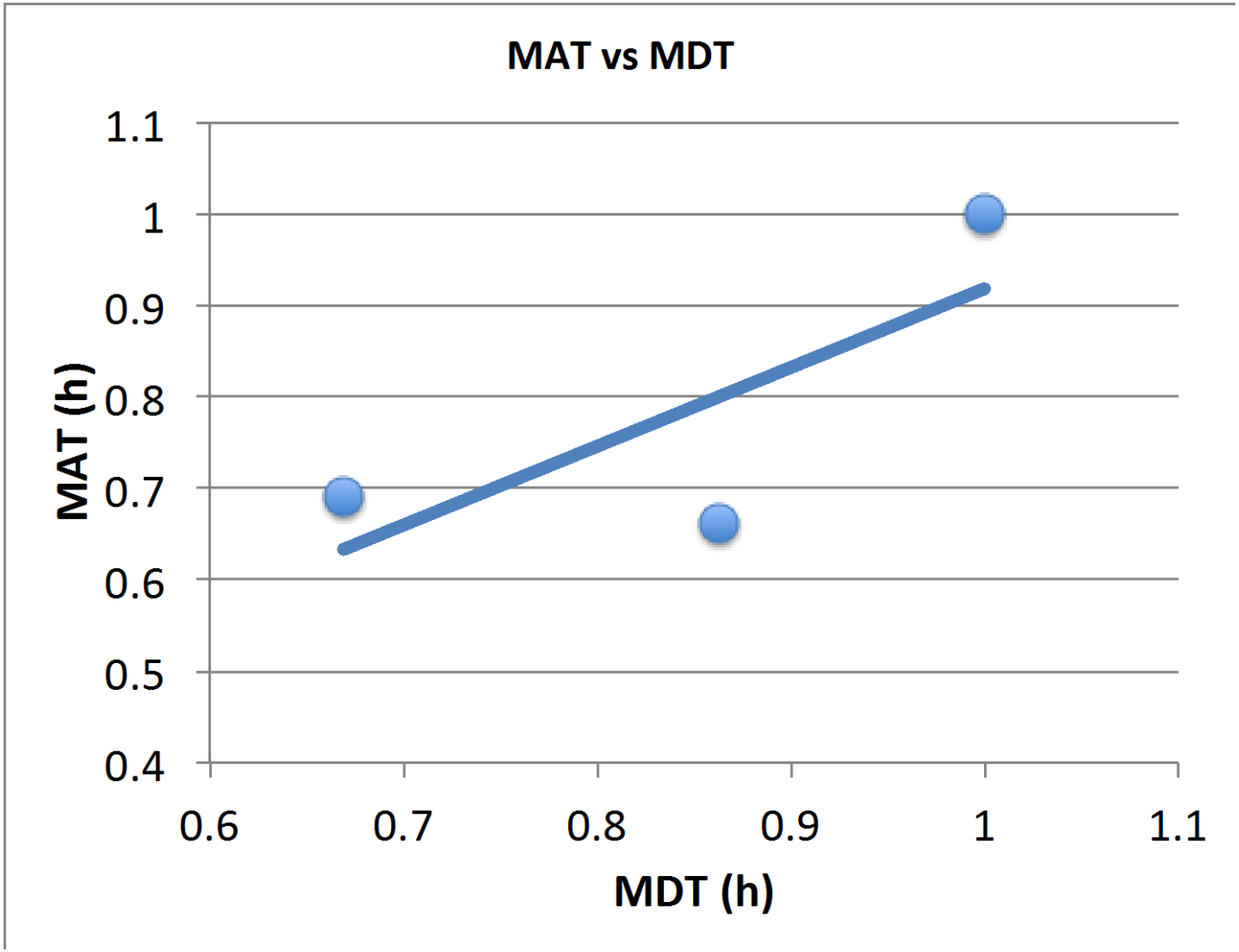


	A-4.5 µm	B-3.8 µm	C-3.7 µm
Stage 2 to 3 (µg)	12.48	14.40	11.54
Stage 4 to 7 (µg)	4.83	9.37	8.14

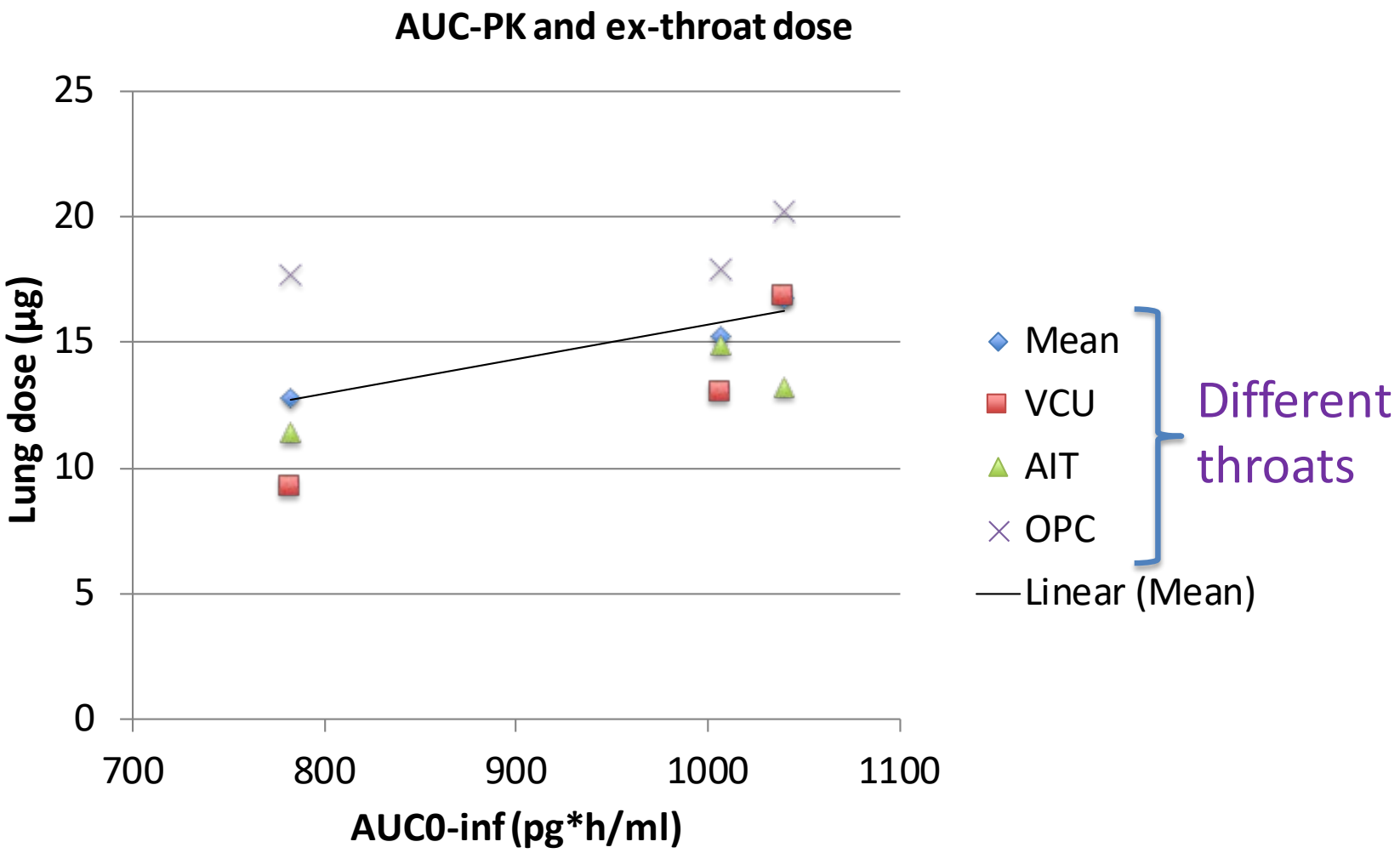
- Formulations differ mainly in "peripheral" stages
- "Central" stages are similar
- Differentiation through mucociliary is difficult

In vitro/in vivo Correlations?

Mean absorption time (MAT) vs. Mean Dissolution Time (MDT)



In vitro/ in vivo Correlations



Conclusions from non-compartmental PK analysis (NCA)

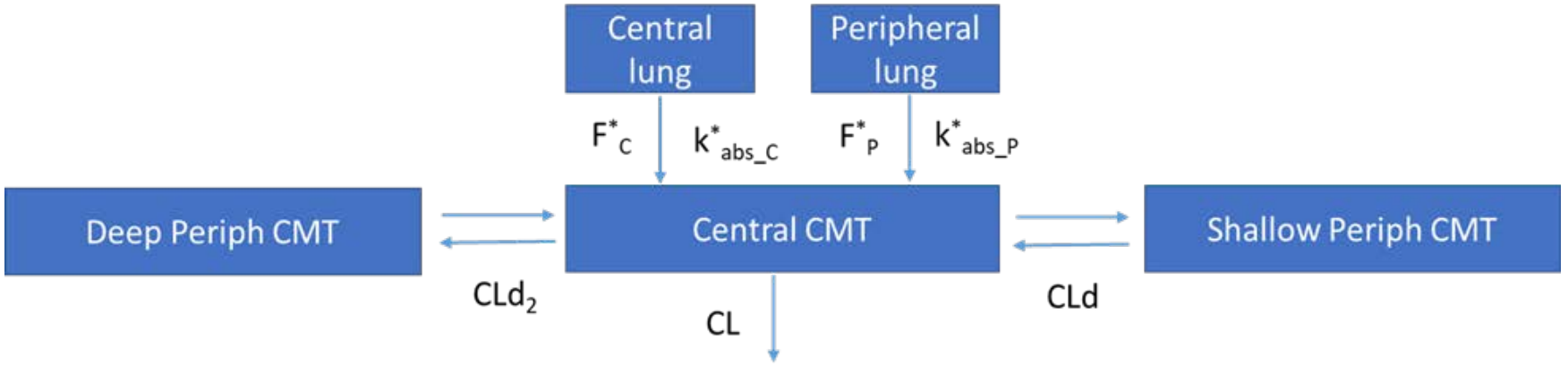
- PK-NCA is able to detect differences **Lung Dose**
- PK-NCA is able to detect differences in pulmonary **Residence Time**
- There was a significant difference between dose normalized AUC0-t of A-4.5µm and C-3.7 µm
- However, the inability to show bio-IN-equivalence after dose normalization did **not fully support the conclusion** that the PK can identify differences in the **c/p ratio** when analyzed via NCA methods.
  - The difference in the central deposition was too small.

Conclusions from non-compartmental PK analysis (NCA)

- Overall, the relationship between dissolution rate and absorption rate is indicated.
- Study found a correlation between systemic exposure and ex-throat based lung dose.
- However, significant variability was found across throats. More work (including pop PK modeling) is necessary.

Population PK Modeling

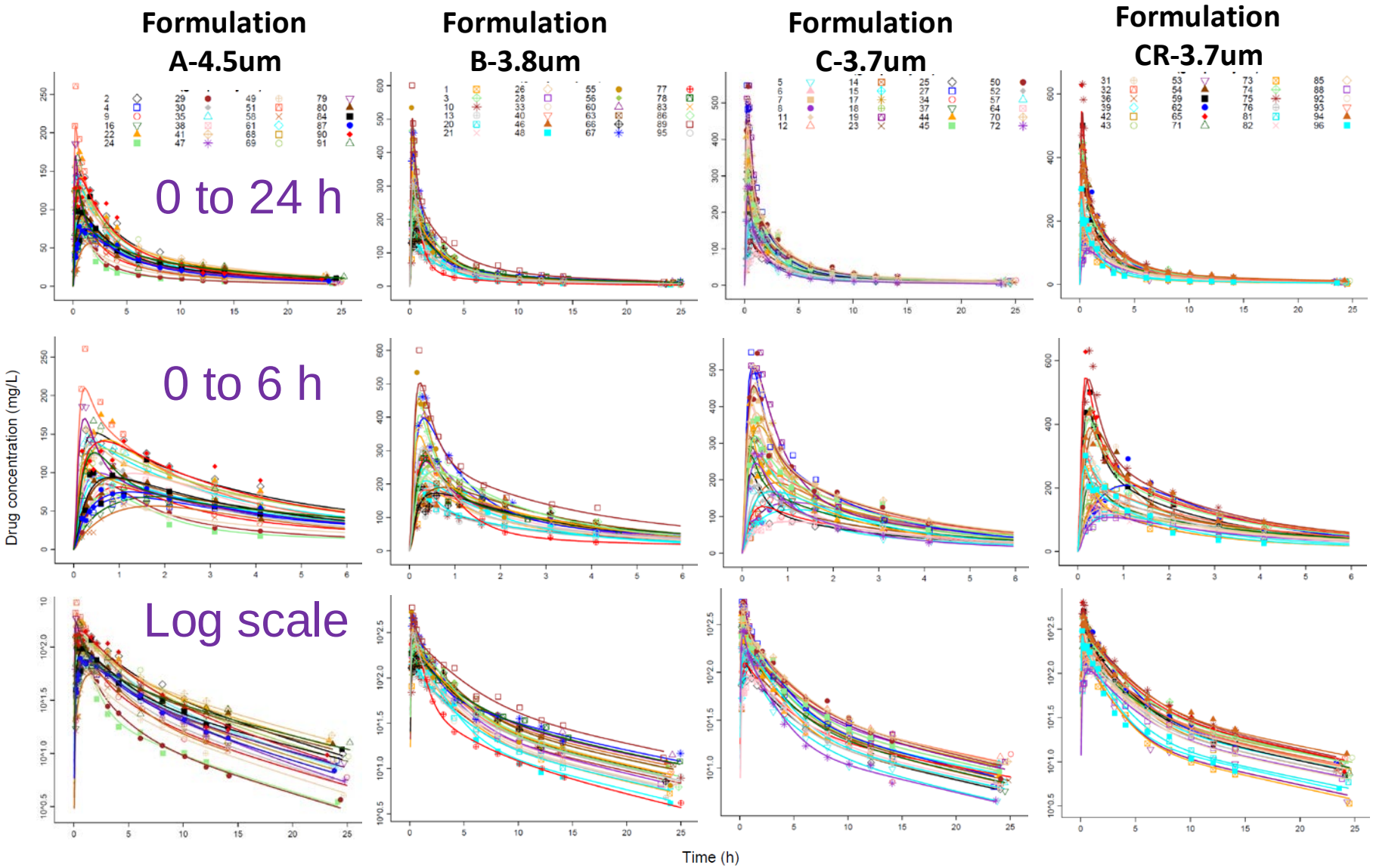
PK Compartmental Model Structure



F_c: Absorbed dose fraction from central lung
F_p: Absorbed dose fraction from peripheral lung
k_{abs_c}: Absorption rate from central lung
k_{abs_p}: Absorption rate from peripheral lung

- Two parallel first-order absorption processes from the central lung (slow) and peripheral (fast) lung; first-order elimination process
- F_c, F_p, k_{abs_c}, k_{abs_p} were estimated for **each** formulations
- Body weight was selected as covariate for CL, CL_D, CL_{D2}, V_1, V_2, and V_3
- Peak inspiratory flow rate (PIFR) was identified as an information covariate for F_c and F_p

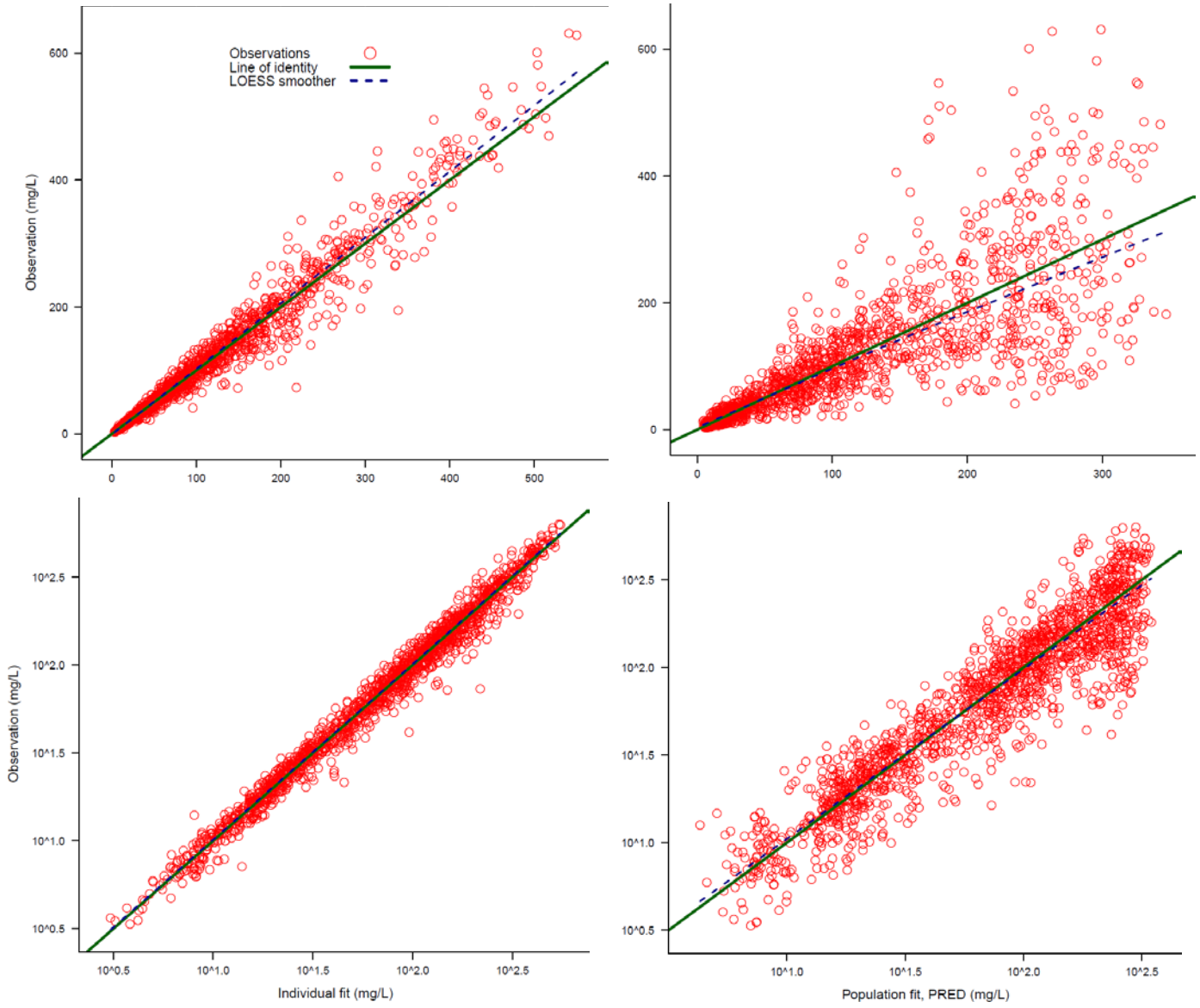
Excellent Individual curve fits



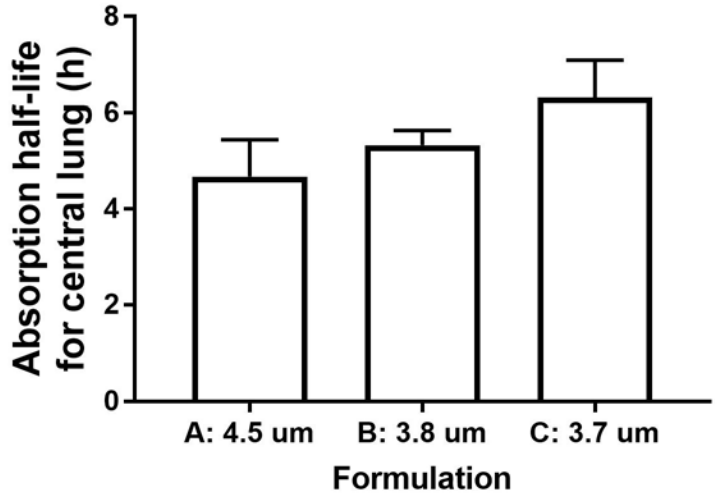
Unbiased and reasonably precise curve fits

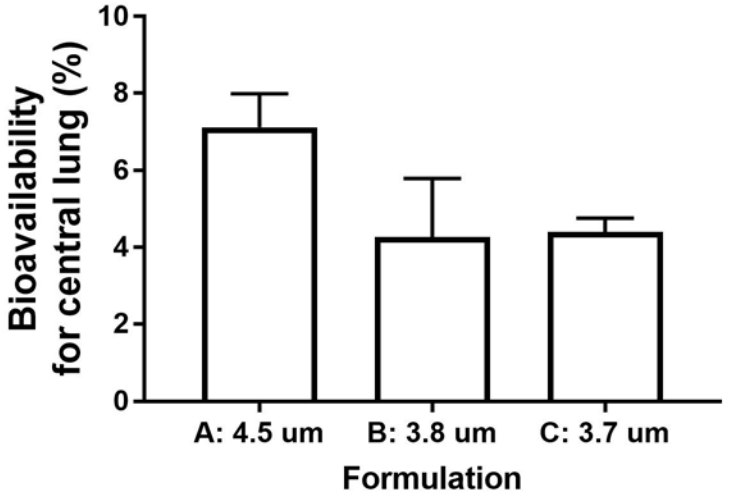
Individual fit

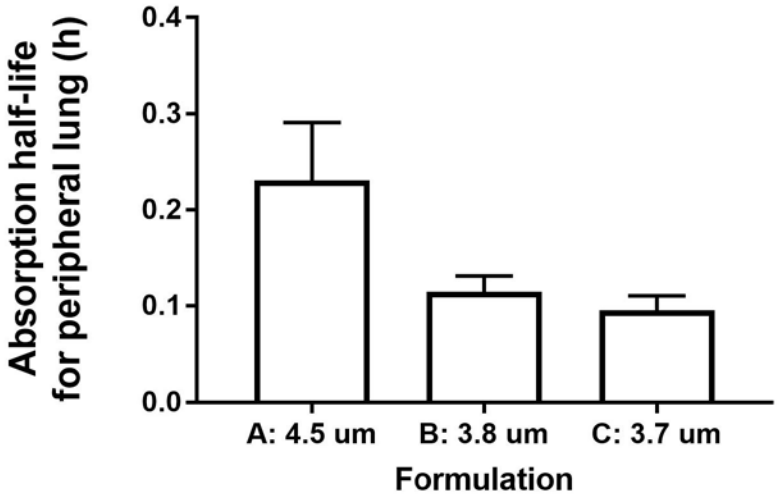
Population fit

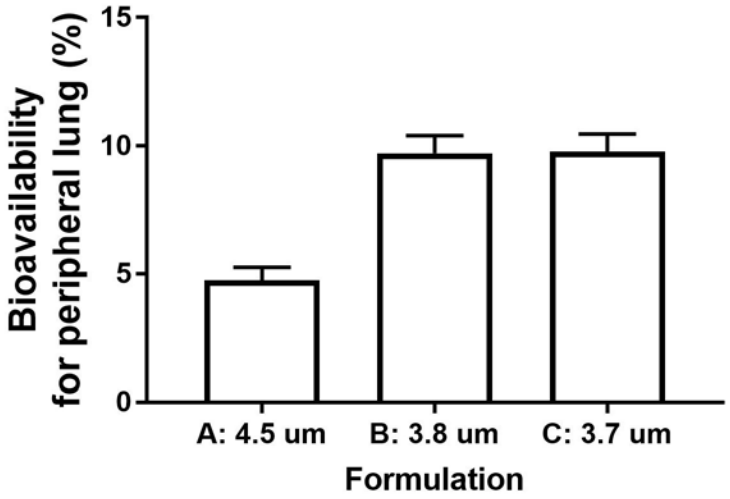


Population mean PK parameters and between subject variability estimates









Population mean PK parameters and between subject variability estimates

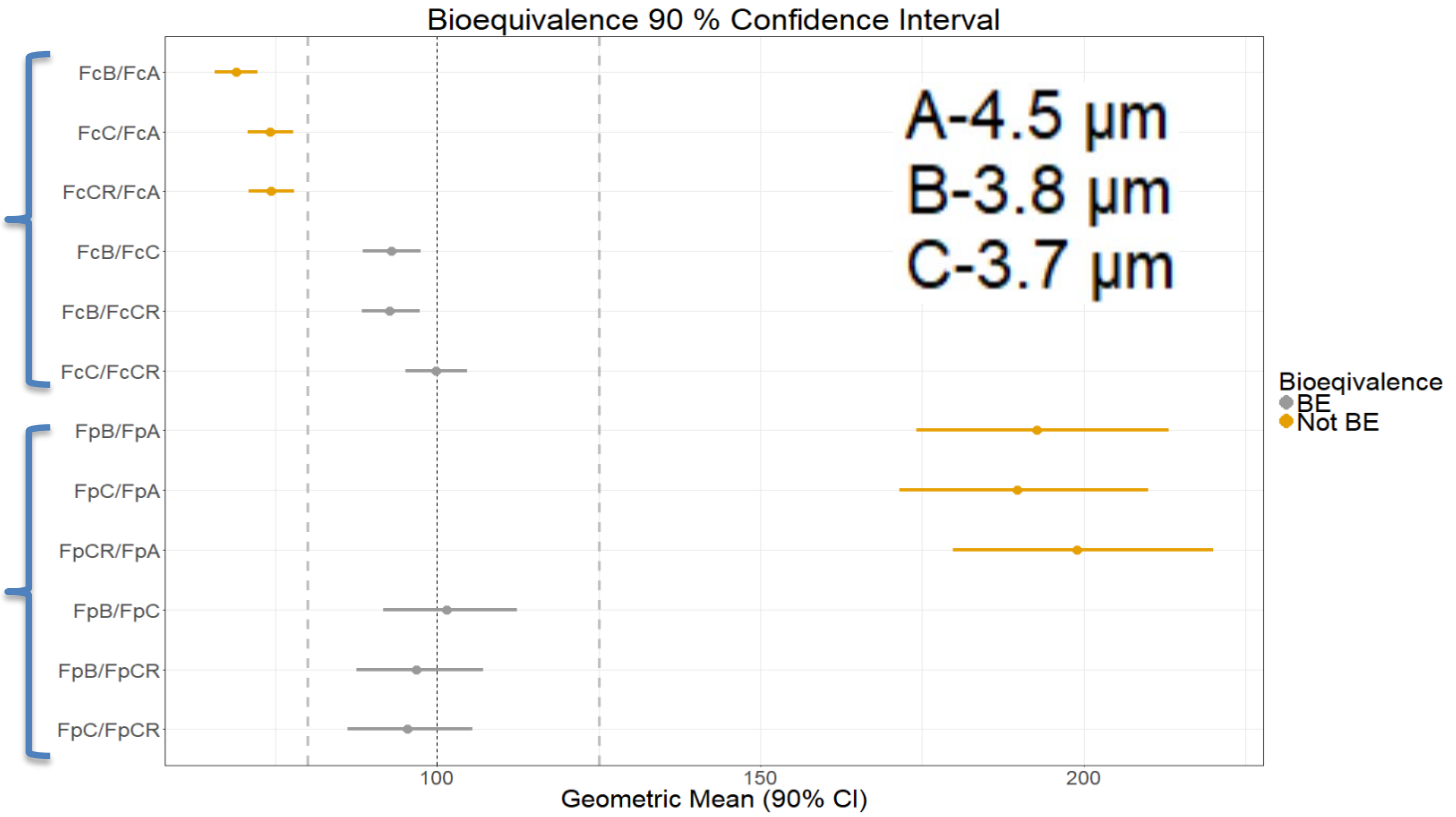
Parameters	Symbol	Unit	Formulation A	Formulation B	Formulation C
			Mean (SE%)[a]	Mean (SE%)[a]	Mean (SE%)[a]
Absorption half-life for central lung	$t_{1/2\_c}$	h	4.68 (16.3%)	5.33 (5.8%)	6.31 (12.4%)
Absorption half-life for peripheral lung	$t_{1/2\_p}$	h	0.231 (26.1%)	0.115 (14%)	0.0954 (16%)
Bioavailability for central lung	**F_c**	**-**	**0.0713 (12%)**	**0.0426 (36%)**	**0.044 (8.3%)**
Bioavailability for peripheral lung	**F_p**	**-**	**0.0474 (11%)**	**0.0972 (7%)**	**0.0978 (7%)**

Pop-PK BE Approach based on Individual Subject Estimates in DPI study

Comparison of Absorbed Doses from the Central (Fc) and Peripheral (Fp) Lung based on population PK modeling

Fc ratios between formulations

Fp ratios between formulations



FcA: absorbed dose from central lung for Formulation A-4.5 µm;
FcB: absorbed dose from central lung for Formulation B-3.8 µm;
FcC: absorbed dose from central lung for Formulation C-3.7 µm;
FcCR: absorbed dose from central lung for Formulation C-3.7 µm-repeated;
FpA: absorbed dose from peripheral lung for Formulation A-4.5 µm;
FpB: absorbed dose from peripheral lung for Formulation B-3.8 µm;
FpC: absorbed dose from peripheral lung for Formulation C-3.7 µm;
FpCR: absorbed dose from peripheral lung for Formulation C-3.7 µm-repeated.

Population PK Modeling

Bootstrap analyses /
simulation estimation studies

Bias and Imprecision of Population Parameter Estimates

Parametric Bootstrap using 200 simulation-estimation studies [a]

Each dataset contain n=24 subject, all initial estimates poor (at least 2-fold off)

Parameters	Symbol	Unit	Form. A	Form. B	Form. C
Absorption half-life for central lung	$t_{1/2\_c}$	h	3% (17%)	34% (42%)	42% (44%)
Absorption half-life for peripheral lung	$t_{1/2\_p}$	h	16% (18%)	17% (13%)	17% (15%)
Bioavailability for central lung	**F_c**	**-**	**-3% (11%)**	**-10% (17%)**	**-10% (12%)**
Bioavailability for peripheral lung	**F_p**	**-**	**18% (13%)**	**15% (14%)**	**17% (13%)**

Parametric bootstrap demonstrated that the population means for Fc and Fp could be estimated without bias (±18%, or better) and with small (i.e. good) imprecision (≤17%) even at n=24.

Pop-PK BE Approach #2: Nonparametric bootstrapping method to assess 90% CI

Nonparametric bootstrap to estimate the median and 90% confidence interval for the population mean Fc(A)/Fc(B) and Fp(A)/Fp(B) ratios between formulations

Nonparametric Bootstrap Based on 200 Replicates of datasets with n=24 subject

A-4.5 µm
B-3.8 µm
C-3.7 µm

Parameter	Symbols	Ratio of geometric means (90% Conf. Int) [a]		
		A vs. B	A vs. C	B vs. C
Peripheral lung	F_p	47 (41 - 54)	47 (42 - 53)	100 (88 - 115)
Central lung	F_c	164 (124 - 224)	170 (134 - 215)	104 (78 - 136)
Overall	$F_c + F_p$	84 (72 - 97)	84 (73 - 95)	102 (90 - 114)

→ CI would be narrower for n=48

[a] Bioequivalence was calculated by the bioavailability of test formulation divided by that of reference formulation. To be bioequivalent, this number is needed to be in the range of 80 -125%.

→ Population-PK indicated BE for peripheral lung and total lung dose between the similar formulations B and C.

→ BE for central lung could have been established in a study with more than 24 subjects using this population modeling based approach.

Overall conclusions

- Pop-PK was able to estimate differences in the c/p ratio based on human PK data.
- Combination of pop-PK and standard bioequivalence assessments represents novel approach to evaluate BE of slowly dissolving inhalation drugs.
- In vitro experiments support findings.
- Peak inspiratory flow rate was identified as an influential covariate.

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- Jag Shur, Rob Price (University of Bath)
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Backup slides

Population mean PK parameters and between subject variability estimates

Parameters	Symbol	Unit	Formulation A		Formulation B		Formulation C	
			Mean (SE%)[a]	BSV[b] (SE%)	Mean (SE%)[a]	BSV[b] (SE%)	Mean (SE%)[a]	BSV[b] (SE%)
Absorption half-life for central lung	$t_{1/2\_c}$	h	4.68 (16.3%)	40.6% (69%)	5.33 (5.8%)	4.9% (240%)	6.31 (12.4%)	31.1% (77%)
Absorption half-life for peripheral lung	$t_{1/2\_p}$	h	0.231 (26.1%)	84.2% (38%)	0.115 (14%)	52.0% (60%)	0.0954 (16%)	91.2% (29%)
Bioavailability for central lung	**F_c**	**-**	**0.0713 (12%)**	**30.3% (86%)**	**0.0426 (36%)**	**20% (111%)**	**0.044 (8.3%)**	**4.4% (168%)**
Bioavailability for peripheral lung	**F_p**	**-**	**0.0474 (11%)**	**21.6% (89%)**	**0.0972 (7%)**	**25.3% (47%)**	**0.0978 (7%)**	**30.7% (25%)**
Clearance	CL	L/h	71 (fixed)	19.6% (23%)	Disposition parameters (i.e. CL and V) were shared across all formulations.			
Distribution clearance to shallow peripheral compartment	CL_D	L/h	297 (19.1%)	87.8% (23%)				
Distribution clearance to deep peripheral compartment	CL_{D2}	L/h	32.3 (6.5%)	10% (fixed)				
Volume of distribution for central compartment	V_1	L	124 (6.5%)	10% (fixed)				
Volume of distribution for shallow peripheral compartment	V_2	L	111 (6.0%)	14% (261%)				
Volume of distribution for deep peripheral compartment	V_3	L	410 (6.9%)	10% (fixed)				

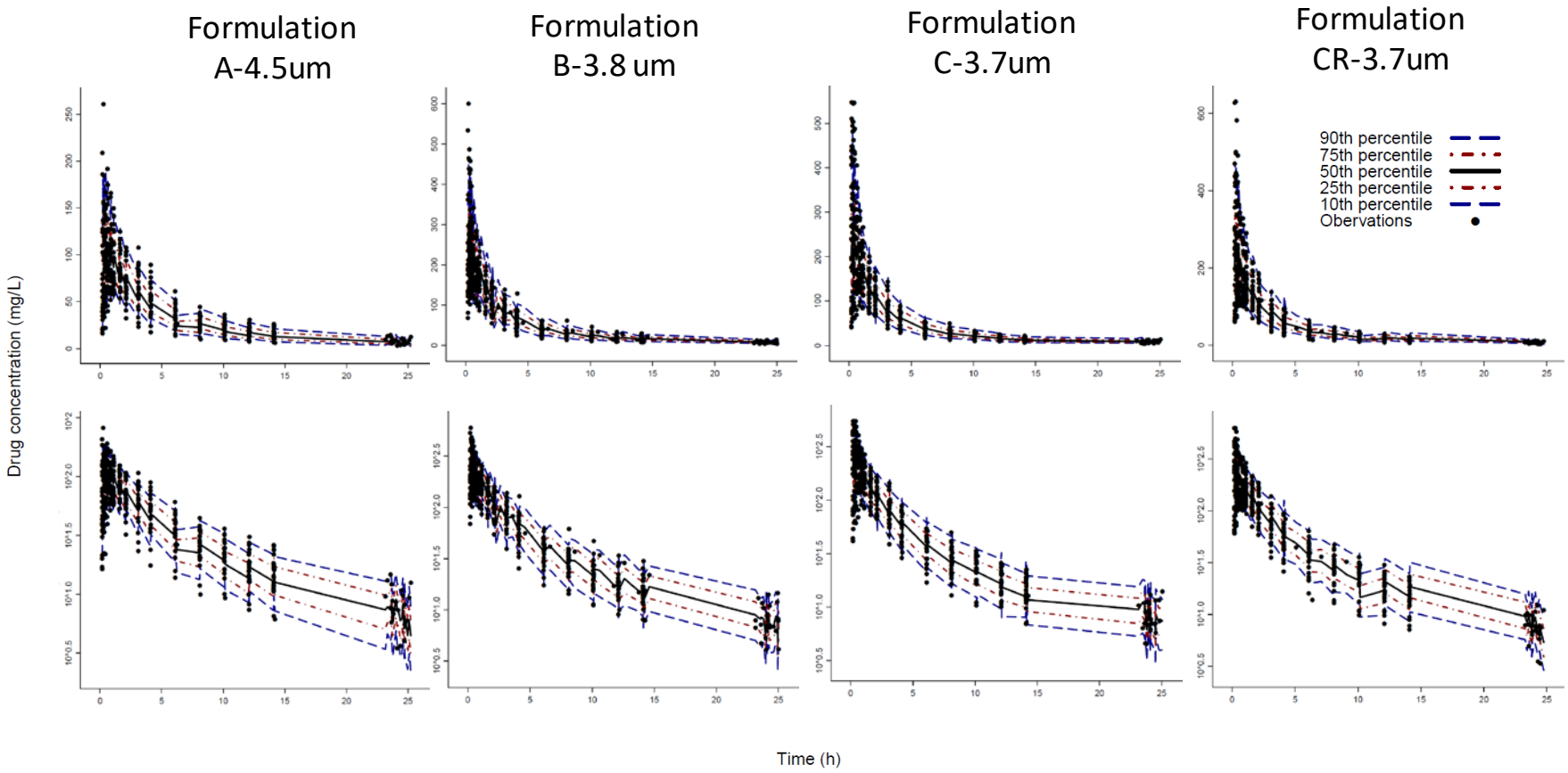
The additive and proportional residual errors of plasma concentrations were 0.602 ng/mL and 16.1%.

The slope factor for central and peripheral lung were 0.686 and 1.14, these values were used in building PIFR covariate model.

[a] Numbers shown in parentheses were imprecision for each parameter estimate.

[b] BSV: between subject variability expressed as apparent coefficients of variation.

Visual Predictive Check



→ Population PK model had adequate predictive performance.

Bias and Imprecision of Population Parameter Estimates

Parametric Bootstrap using 200 simulation-estimation studies [a]

Each dataset contain n=24 subject, all initial estimates poor (at least 2-fold off)

Parameters	Symbol	Unit	Formulation A		Formulation B		Formulation C	
			Mean[b]	BSV[c]	Mean[b]	BSV[c]	Mean[b]	BSV[c]
Absorption half-life for central lung	$t_{1/2\_c}$	h	3% (17%)	14% (25%)	34% (42%)	332% (57%)	42% (44%)	16% (31%)
Absorption half-life for peripheral lung	$t_{1/2\_p}$	h	16% (18%)	-11% (18%)	17% (13%)	-8% (22%)	17% (15%)	-6% (14%)
Bioavailability for central lung	**F_c**	-	**-3% (11%)**	**27% (28%)**	**-10% (17%)**	**38% (50%)**	**-10% (12%)**	374% (62%)
Bioavailability for peripheral lung	**F_p**	-	**18% (13%)**	**23% (28%)**	**15% (14%)**	**17% (18%)**	**17% (13%)**	**14% (12%)**
Clearance	CL	L/h	- [d]	-12% (19%)				
Distribution clearance to shallow peripheral compartment	CL_D	L/h	-14% (17%)	-18% (15%)				
Distribution clearance to deep peripheral compartment	CL_{D2}	L/h	-1% (9%)	- [d]				
Volume of distribution for central compartment	V_1	L	6% (8%)	- [d]				
Volume of distribution for shallow peripheral compartment	V_2	L	7% (10%)	4% (46%)				
Volume of distribution for deep peripheral compartment	V_3	L	-18% (14%)	- [d]				

Disposition parameters (i.e CL and V) were shared across all formulations.

Parametric bootstrap demonstrated that the population means for Fc and Fp could be estimated without bias (±18%) and with small / good imprecision (≤17%) even at n=24.

[a] Each dataset include 24 healthy volunteers under 4 occasions.
[b] Numbers shown in parentheses were imprecision for each parameter estimate.
[c] BSV: between subject variability.
[d] Not applied, since this parameter was fixed to IV data in humans for CL and to 10% CV for between subject variability.

Two very small variabilities (i.e. BSV) were significantly biased. → No impact