The Potential of Pharmacokinetic Bioequivalence (BE) Studies in Detecting Regional Deposition with Orally Inhaled Drug Products

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop
Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches
Topic 1: Nasal & Inhalation Products

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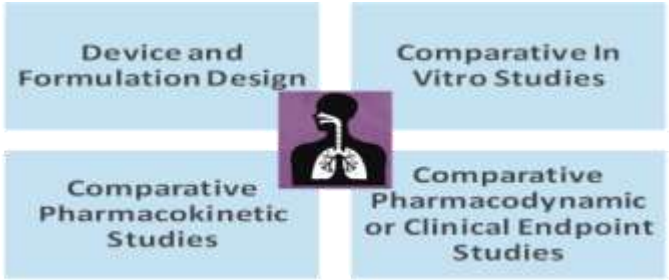
Learning Objectives

- Function of the comparative clinical endpoint (CCEP) bioequivalence (BE) study in establishing equivalence in local drug delivery
- Current thinking on challenges with using pharmacokinetic (PK) BE studies as part of an alternative approach for assessing equivalence in regional deposition
- Explore whether PK studies can detect differences of orally inhaled drug products (OIDPs) in the lung regional deposition [i.e., the central to peripheral (c/p) drug deposition ratio]

Aggregate Weight of Evidence Approach for Establishing BE for Orally Inhaled Drug Products (OIDPs)



- Currently recommended for locally acting **dry powder inhaler (DPIs)** and **metered dose inhaler (MDIs)**
- Incomplete understanding of the relevance of results from BE studies to drug concentrations at local site of action
- Uncertainties regarding sufficiency of correlation of in vitro to in vivo PK data to establish BE
- Comparative PD BE Study with clinical endpoints is currently the only tool addressing local action in the lungs

In Vivo Study Issues Related to Locally Acting Assessment

In Vivo Comparative BE Study with Clinical Endpoints for OIDPs

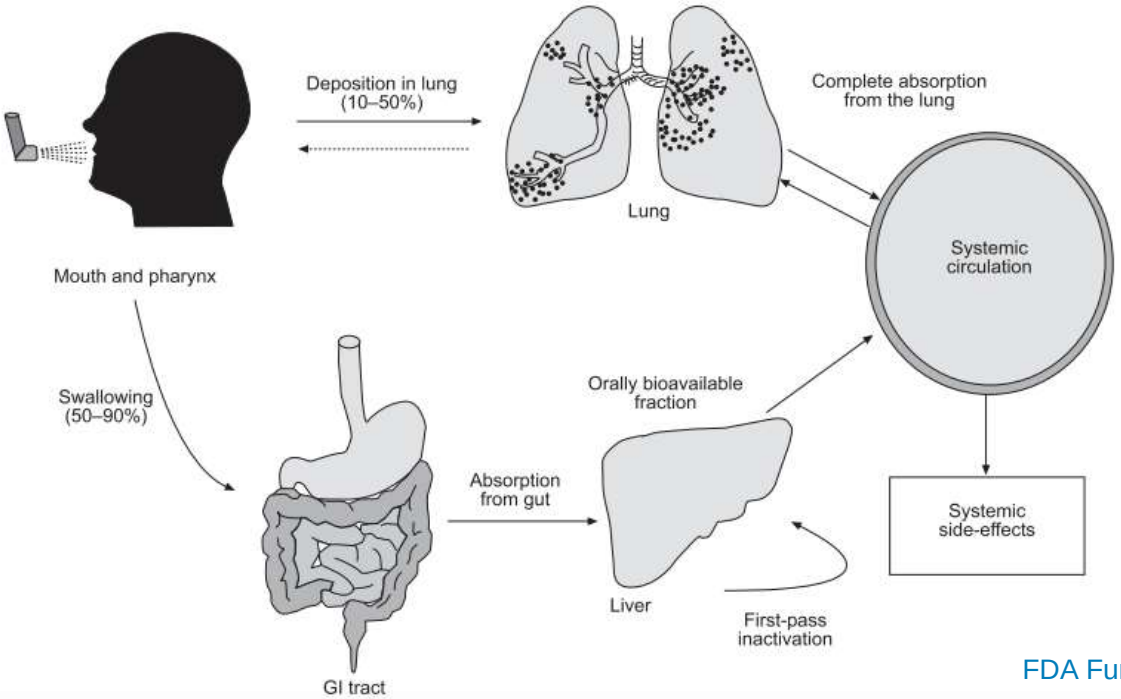
- Less sensitive and expensive
- Large sample size
- Long study duration

In Vivo PK BE Studies for OIDPs

- Currently limited to assessment of systemic exposure
- Assesses plasma concentrations that are downstream of local delivery and site of action, but PK studies may detect differences in the pulmonary available dose and the pulmonary mean residence time
- May provide information related to local activity, and potential as a tool to assess equivalence in local drug delivery in the lungs
- Recently, FDA posted draft guidance on Beclomethasone Dipropionate (available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020911.pdf) that proposes an alternative approach to the comparative clinical endpoint BE study, including additional supportive in vitro, in silico, and in vivo studies

Project: PK Study to Detect Drug Deposition in the Lung

Fate of Inhaled Drugs After Administration



Overall Objectives

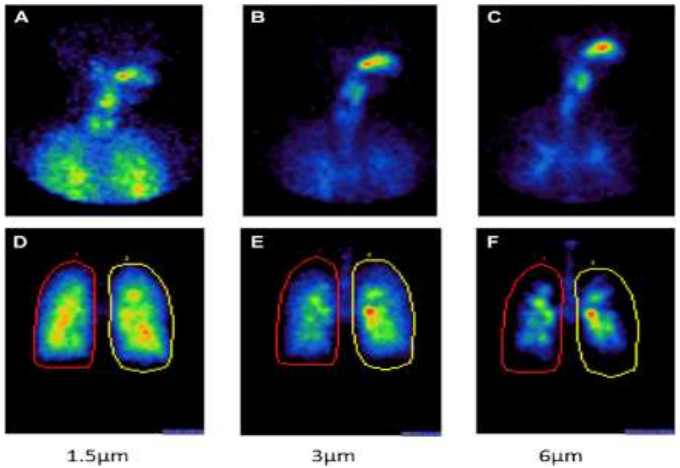
- To evaluate if PK is sensitive to DPI formulations that differ in c/p lung deposition ratio
- To perform an in vivo PK study in healthy adult subjects after a single-dose of different orally inhaled formulations using a DPI

FDA Funded Projects: FY13 Contract # HHSF223201110117A
FY16 Contract # HHSF223201610099C
(Awarded to University of Florida)

Main Hypothesis

- **For slowly dissolving drugs**
  - Fluticasone Propionate (FP)

	Central deposit	Peripheral deposit
Absorption	Slow	Fast
Mucociliary clearance	Yes	No
Mass median aerodynamic diameter (MMAD)	↑	↓
Cmax	↓	↑
AUC	↓	↑



PK may be able to provide information on regional deposition

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Study Design

1. Prepare three DPI formulations

- Same amount and particle size for active pharmaceutical ingredients (API),
- Vary lactose fines
- Same dose and dissolution rate
- May differ in regional deposition

2. In vitro characterization

- APSD
- Anatomical throats, inhalation profiles
- Dissolution

3. Conduct PK study

4. Analyze data

- Non-Compartmental Analysis

Formulation Design

Composition of DPI Formulations (Collaboration with University of Bath)

Formulation	FP (% w/w)	SV003 (% w/w)	LH300 (% w/w)	LH201 (% w/w)	LH 230 (% w/w)	MMAD (um)
A (017)	0.80	79.36	-	19.84	-	**4.5**
B (016)	0.80	89.28	-	-	9.92	**3.8**
C (015)	0.80	96.72	2.48	-	-	**3.7**

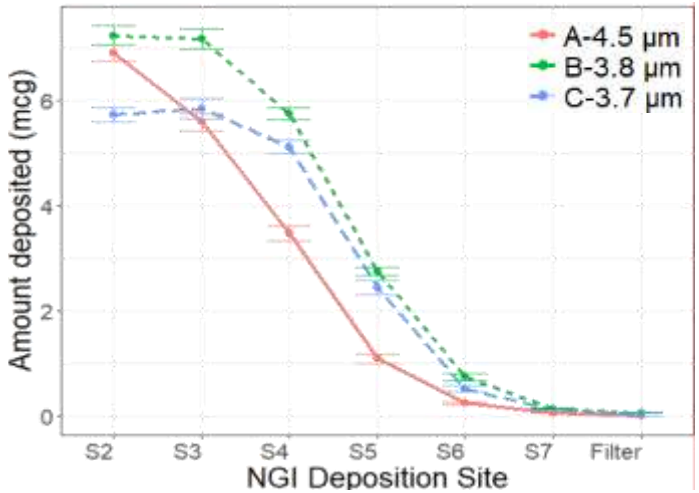
- FP (API) PSD D50 = 2.1 μm
- Lactose monohydrate (carrier excipient)

Lactose Monohydrate	Grade	D_{50} (μm)
SV003	Sieve	64.33
LH201	Milled	22.63
LH230	Milled	8.06
LH300	Micro-fine	3.53

Key In Vitro Results

APSD Parameters

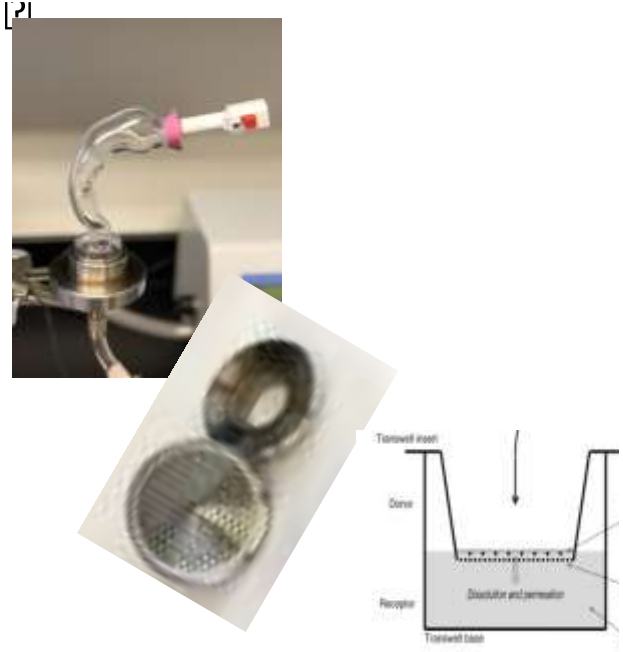
- Direct manipulation of fine particle mass (FPM) and mass median aerodynamic diameter (MMAD) through addition of lactose fines
- Cascade impactor performance of DPI formulations, compendial Next Generation Impactor (NGI), 60 L/min
- Drug deposited on NGI stages 2 and 3 was similar across the three formulations, but smaller amount of drug deposited on stage 4-7 and micro orifice collector (MOC) for formulation A-4.5

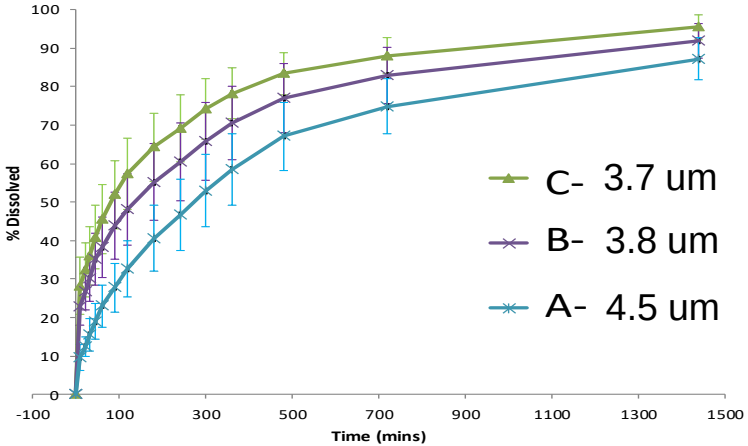


Günther Hochhaus and Jürgen Bullita. "Pharmacokinetic Comparison of Locally Acting Dry Powder Inhalers." In: DIA Meeting on Complex Drug-Device Generic Combination Products, Oct 9-10, 2018, Silver Spring, MD, USA. Podium Presentation

Key In Vitro Results

Dissolution Test 1 (University of Florida method using Transwell® Insert)





Mean dissolution time

Formulation	Value
A-4.5 um	15.4 hrs
B-3.8 um	13.3 hrs
C-3.7 um	10.3 hrs

Slowest dissolution rate for FP DPI formulation A-4.5

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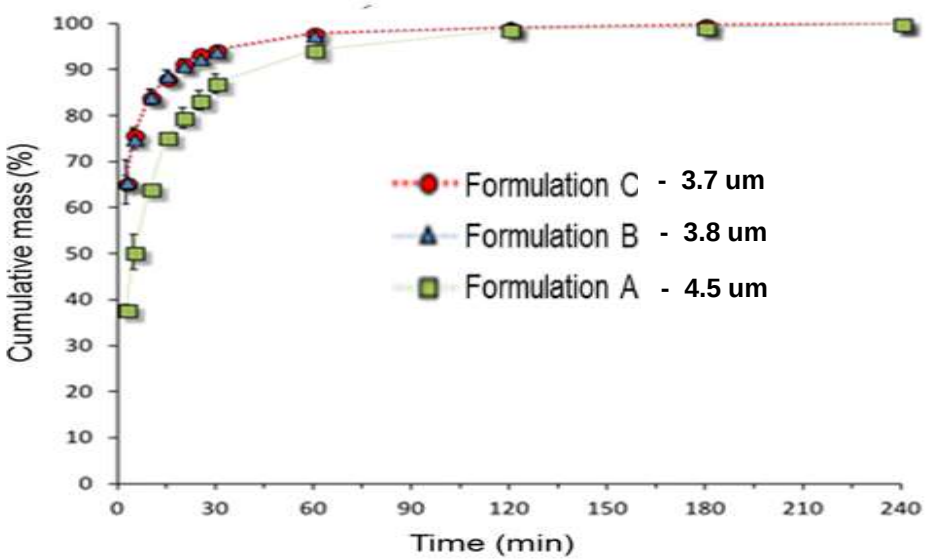
Key In Vitro Results

Dissolution Test 2 (University of Bath method using Apparatus V, Paddle-over-disk)



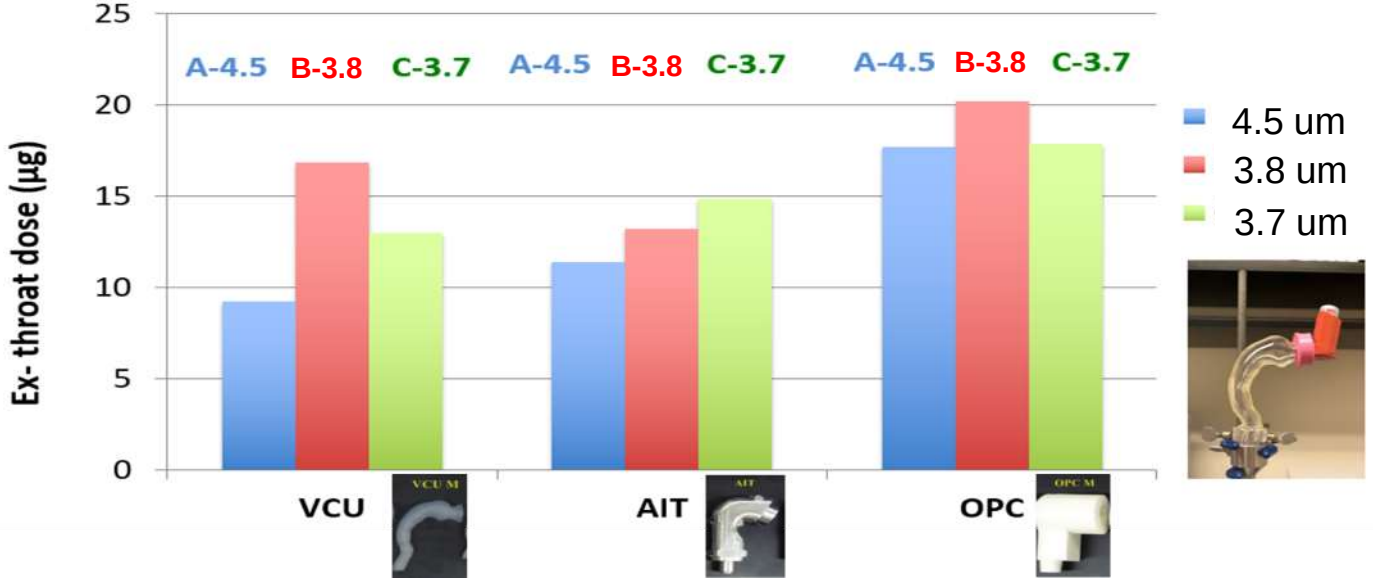
Similar to the method using Transwell® insert, formulation A-4.5 has a slower dissolution rate compared to formulations B and C

Susan Boc, et al. Investigation of Pharmacokinetic Sensitivity to Lung Deposition of Locally-Acting Orally Inhaled Drug Products. In: 2019 APPS PharmSci 360 Annual Meeting, Nov 3-6, 2019, San Antonio, TX, USA. Poster

Key In Vitro Results

Estimated Lung Dose (Collaboration with Virginia Commonwealth University)

- Three anathomical throats, typical inhalation profile



The absolute amounts and the ratios between the FP DPI formulations differed between MT models.

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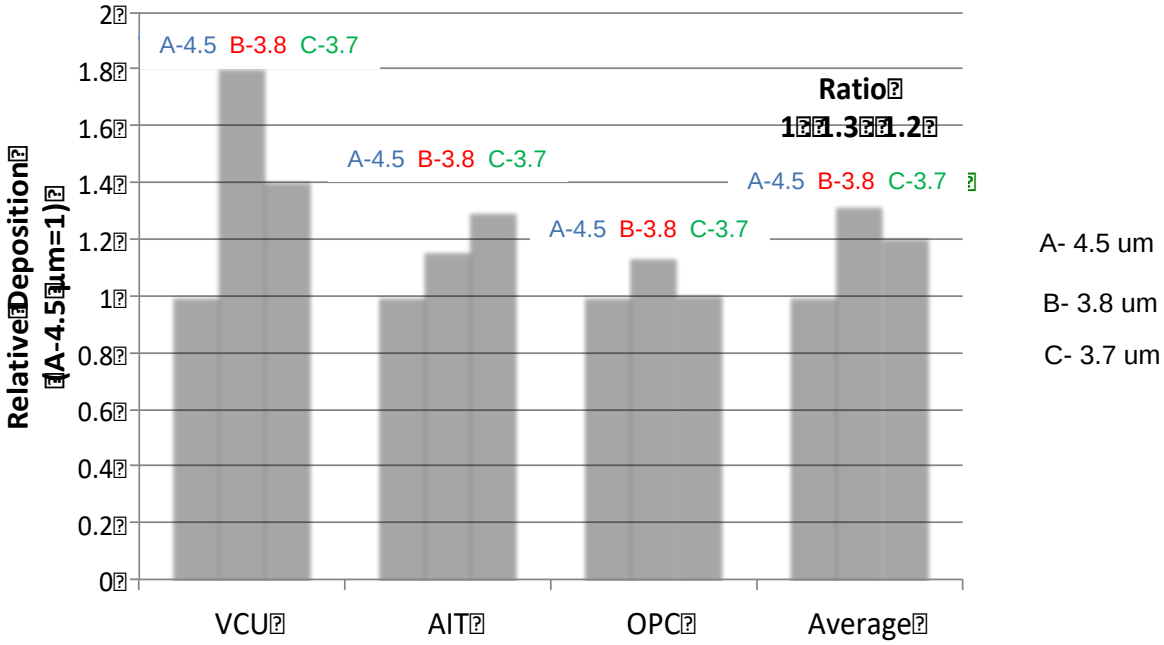
Key In Vitro Results

Relative Lung Dose

- Correction factor to account for different dose reaching the lung



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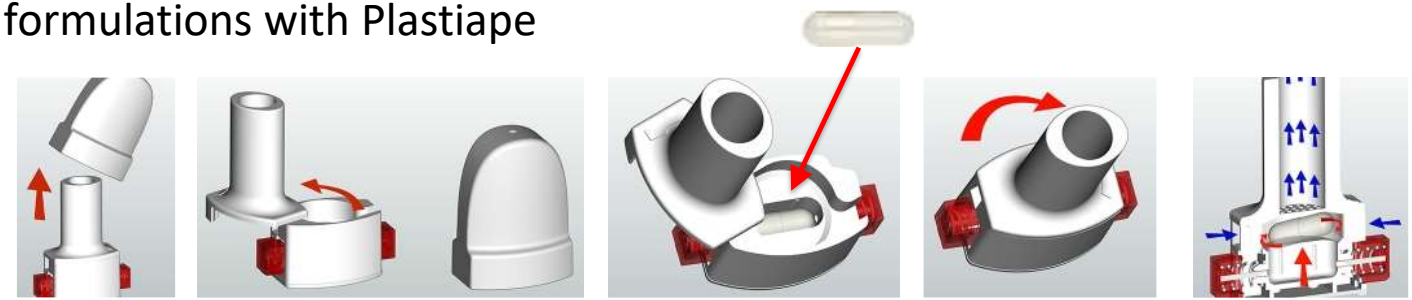
PK Study Design

- Four-way, randomized, single-center, double-blind, cross-over in 24 healthy subjects
- DPI formulations with Plastiape



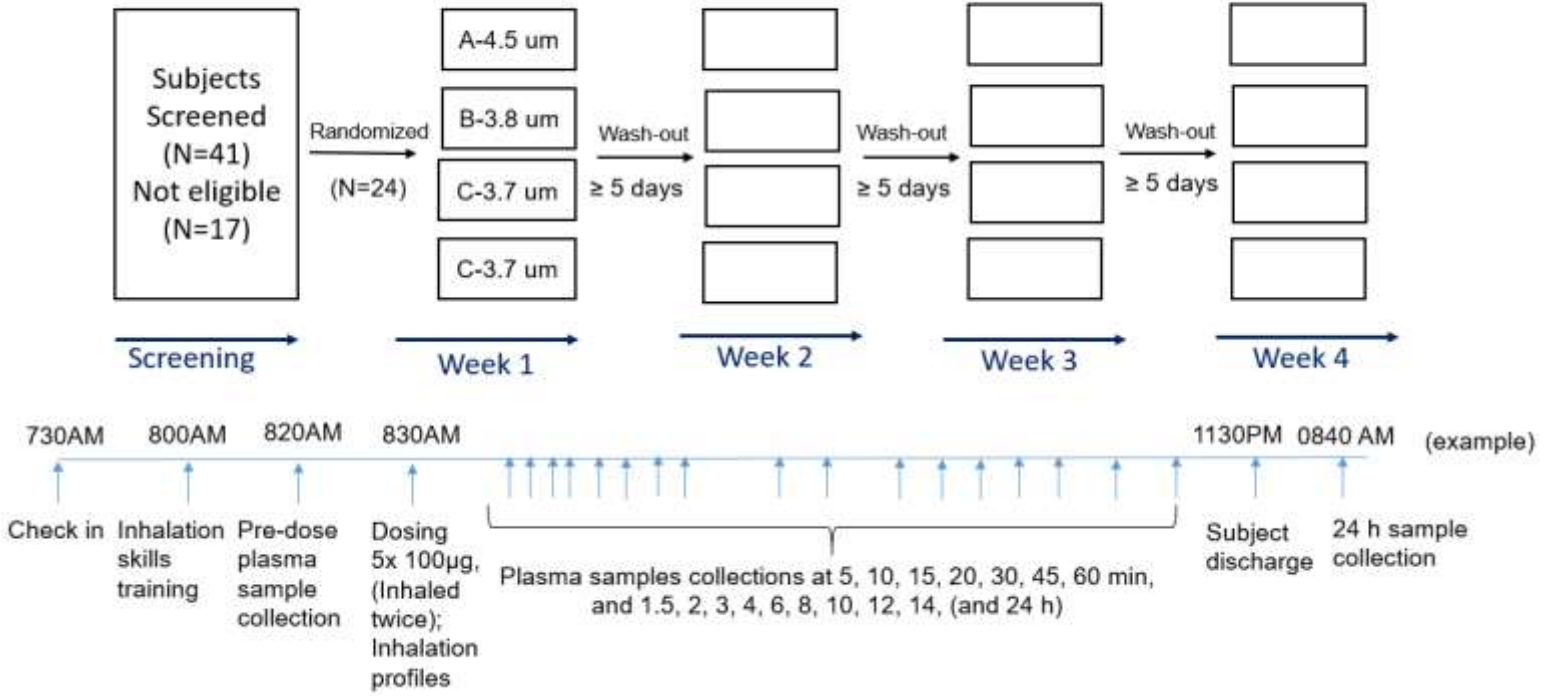
http://plastiape.com/en/content/1635/dry-powder-inhaler-rs01-how-use

- One single-dose of 500 µg FP (5 capsules of 100 µg FP)
- Record individual inhalation profiles
- LC-MS/MS assay sensitivity: 1 pg/mL
- Non-Compartmental Analysis

Günther Hochhaus and Jürgen Bullita. "Pharmacokinetic Comparison of Locally Acting Dry Powder Inhalers." In: DIA Meeting on Complex Drug-Device Generic Combination Products, Oct 9-10, 2018, Silver Spring, MD, USA. Podium Presentation

PK Study Design

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



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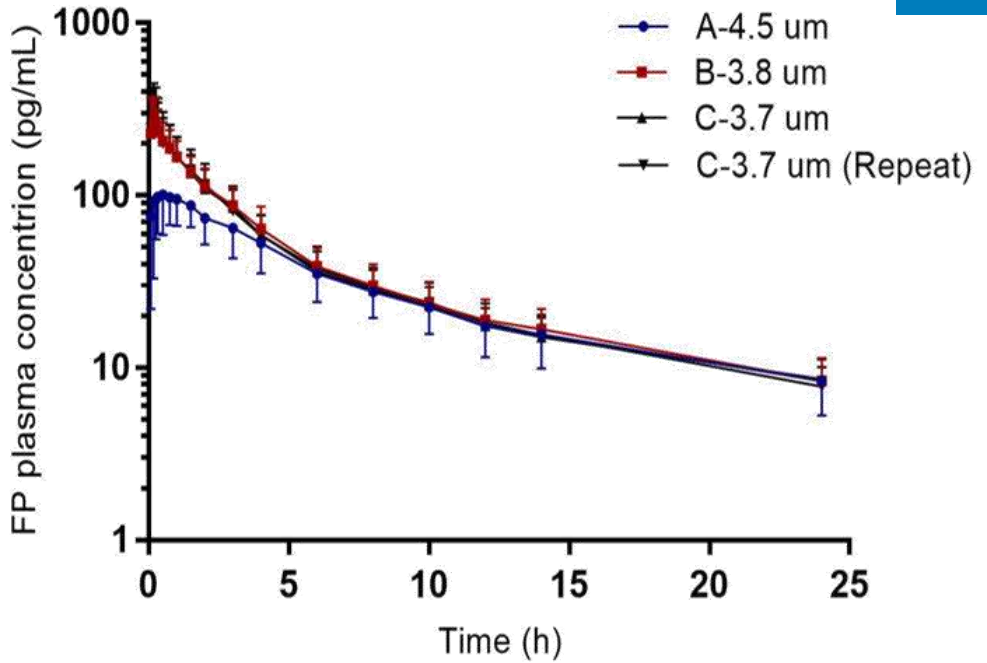
Key PK Results

Mean (± SE) FP Plasma Concentration-Time Profiles

(before lung dose normalization)



- Formulation B and C were nearly identical for PK profiles
- Cmax and AUC of Formulation A are smaller than B and C

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Key PK Results

Mean (± SE) FP Plasma Concentration-Time Profiles

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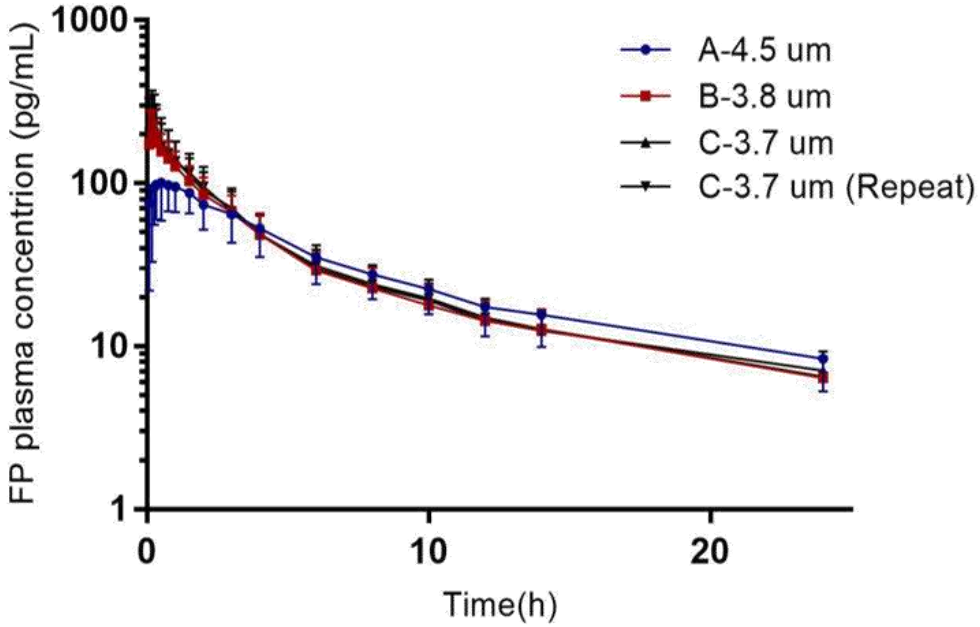

Cmax of Formulation A are smaller than B and C

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Key PK Results

Peak Plasma Concentrations (Cmax)

(after lung dose normalization)

- Cmax of Formulation A is statistically significantly different than Formulations B and C
- Strong indication that absorption rate of Formulation A is slower compared to Formulations B and C

Area Under the Curve (AUC)

(after lung dose normalization)

- AUC of Formulation A is NOT statistically significantly different than Formulations B and C.
- Weak indication that deposition of Formulation A is more centrally than Formulations B and C.

C_{max} differences may indicate differences in regional lung deposition.

Key PK Conclusions for FP DPI

- PK was able to detect differences between formulations which differ in **formulation factors**
- PK was able to detect differences in **lung dose**
- PK was able to detect differences in **pulmonary residence time**
- There was a trend that PK can also identify differences in **regional deposition** (c/p ratio), but the AUC difference was small when the dose normalization factors were applied
  - The inability to show bio-IN-equivalence after dose normalization did **not fully support** the conclusion that PK can identify differences in the c/p ratio when analyzed via NCA methods (the difference in the central deposition was too small)

Additional Conclusions

- Given the same qualitative and quantitative excipient (lactose) concentrations, differences in lactose fines that impacted the MMADs were able to **alter** *in vitro* performance parameters and *in vitro* dissolution profiles
- These differences in product performance were detectable with *in vivo* PK metrics (Cmax and AUC), although the relationship with these metrics and regional deposition still requires further study

Lesson Learned and Closing Remarks

1. The selected mouth-throat model may be critical for estimating the in vitro total lung dose
2. Consideration should be made for how to control for potential differences in delivered dose in vivo (e.g., dose normalization) between products or formulations
3. When designing a study to evaluate whether a PK metric may be informative on regional drug deposition in the lung, efforts should be made to reduce potential variability (e.g., proper staff training, study design, number of doses, realistic respiratory pattern)
4. The results from this study suggest that PK parameters **may be sensitive** to differences in regional drug deposition. This may be product-dependent, and the sensitivity may vary between different PK parameters
5. This research is just **one example** for how a PK study may be designed to evaluate its sensitivity in detecting regional drug deposition between different products
6. If you have a different study design that you believe is scientifically justified and you wish to include it as part of your alternative BE approach to conducting a CCEP study, the Agency **highly encourages** you to submit a pre-ANDA Product Development Meeting

Acknowledgements

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Challenge Question #1

The CCEP BE study is included in the weight of evidence approach because it may provide information regarding

A. Safety

B. Efficacy

C. Equivalence in Local Drug Delivery

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Questions?


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