Assessing Central and Peripheral Pulmonary Deposition of Three Fluticasone Propionate Dry Powder Inhaler Formulations with Different Aerodynamic Particle Size Distributions in Healthy Subjects via Population Pharmacokinetics Modeling

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Introduction

- The current approval pathway for generic inhalation drugs in the US is challenging, as it involves within FDA's *weight-of-evidence* approach in vitro, pharmacokinetic and clinical/pharmacodynamic studies
- The following questions need to be addressed for demonstrating pulmonary bioequivalence (BE):
  - Are the doses available to the lung equivalent for test (T) reference (R) products?
  - Are the pulmonary residence times equivalent?
  - Are the regional deposition profiles equivalent?
- Most subject matter experts will agree that PK can evaluate equivalence of pulmonary available doses and lung residence times.

Objectives

To test whether PK can provide information on regional deposition of slowly dissolving corticosteroids by testing DPI formulations that differ in particle size distribution.

Methods

DPI Formulations: With the intention of designing formulations with different central to peripheral deposition ratios, but otherwise similar properties, three fluticasone propionate (FP) DPI formulations (A-4.5 µm, B-3.8 µm and C-3.7 µm) were developed at the University of Bath (Table 1) using the same batch of FP but different lactose fines. Capsule based formulations were prepared under cGMP by Catalent Pharma solutions (Morrisville, NC, USA). Standard next generation impactor studies (NGI) were performed for the three formulations.

Pharmacokinetic Study design: The data were collected from a single-dose (500 µg from capsule based Plastiape Monodose DPI device), double-blinded, four-way, crossover clinical study in 24 healthy subjects. C-3.7 µm was given twice to assess intra-subject variability.

Dosing and Sampling: Each subject inhaled 5 doses of the study medication (5x 100 µg capsules) per visit and inhaled at least twice per FP capsule. Complete inhalation profiles were captured during dosing. Blood samples were obtained at pre-dose and up to 24 hours after dosing and measured by a sensitive HPLC/MS/MS method (sensitivity of 1 pg/ml).

Modeling: The population pharmacokinetic (popPK) model depicted in Fig. 2 was best to describe data for the three formulations within S-ADAPT (version 1.57). Doses absorbed with fast and slow absorption rates were determined for the formulations in individual subjects and subsequently compared with standard bioequivalence methodology to test whether formulations were bioequivalent.

Results

Figure 1: NGI

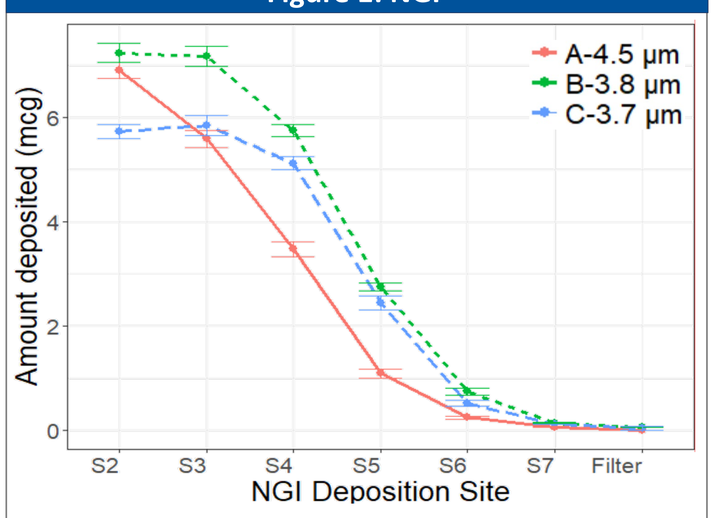

Figure 1: Cascade impactor performance actuated into the NGI with a flow rate of 60 L/min

Table 1: NGI

	A-4.5 µm	B-3.8 µm	C-3.7 µm
MMAD (µm)	4.5	3.8	3.7
GSD	1.9	2.0	2.1
FPD < 5µm (µg)	12.2	18.7	15.8
FPD < 3µm (µg)	5.3	10.0	8.6
Stage 2 to 3 (µg)	12.5	14.4	11.5
Stage 4 to 7 (µg)	4.8	9.4	8.1

Table 1: Summary of the in vitro characterization of the formulations

The amount of drug deposited on Stage 2 to 3 (11.5 to 14.4µg) were similar (Fig.1, Table 1), while the mass deposited on Stages 4 to 7 was substantially smaller for formulation A-4.5 µm (4.8 µg) as compared to the other two (8.1 µg and 9.4 µg).

Figure 2: Model structure

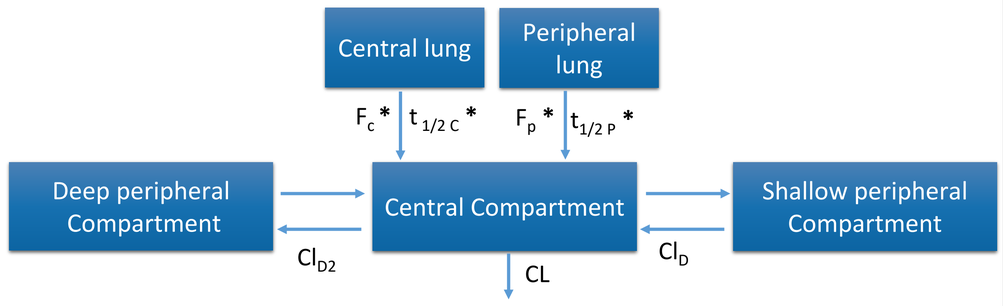

Figure 2: F_c and F_p are the absorbed dose (%) and $t_{1/2\,C}$ and $t_{1/2\,P}$ are the absorption half-life (hours) from the central and peripheral lung, respectively. CL_D and CL_{D2} are the distribution clearance into the shallow and deep peripheral compartment, CL is the elimination clearance from the central compartment.
Parameter labelled with a star (*) were estimated for each formulation separately.

Biphasic pulmonary absorption was described by two parallel first-order processes (one slow, central, and one fast, peripheral absorption process).

Table 2: Model Lung Estimates

Parameters	Symbol	Unit	A-4.5 µm	B-3.8 µm	C-3.7 µm
Absorbed dose in Central Lungs	FC	%	6.4	4.4	4.8
Absorbed dose in Peripheral Lungs	FP	%	5.1	9.9	9.9
Absorption half-life for central lung	$t_{1/2\,C}$	h	6.2	7.9	9.1
Absorption half-life for peripheral lung	$t_{1/2\,P}$	h	0.24	0.11	0.10

Table 2: The summary of estimated pulmonary absorbed doses and absorption half-lives for three tested FP DPI

Pulmonary absorbed dose and absorption half-live are presented in Table 2 and illustrated in Fig. 4.
Formulation A-4.5 µm differed in F_p and $t_{1/2\,P}$ from the other two formulations as for A-4.5 µm less drug was absorbed from the peripheral lung more slowly (Fig. 4), quite in agreement with in vitro dissolution tests (data not shown).

Figure 3: Individual Estimates of Regional Absorbed Dose

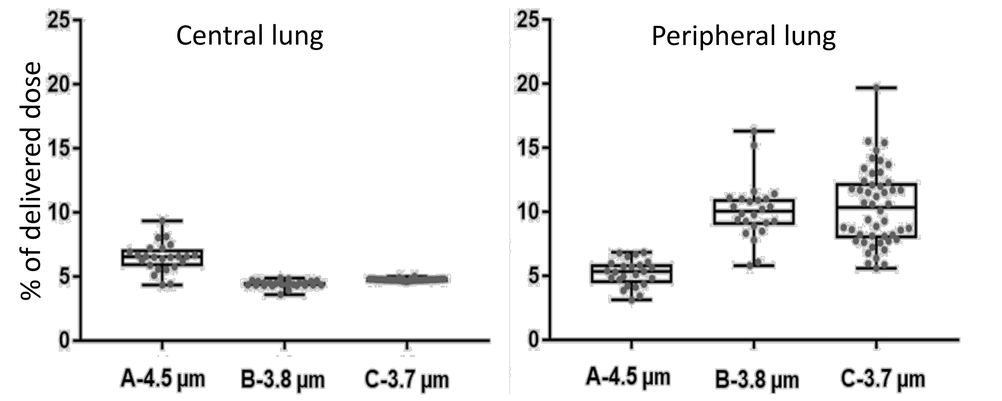

Figure 3: Individual model prediction of the absorbed doses in the central and peripheral regions of the lungs for formulations A-4.5 µm, B-3.8 µm and C-3.7 µm.

In agreement with NGI data, the compartmental analysis (Fig. 4) suggested central depositions of the three formulations to be rather similar, while peripheral deposition was smaller for formulation A-4.5 µm than for B-3.8 µm and C-3.7 µm (Table1 and 2; Figure 1 and 3). A-4.5 µm lacked bioequivalence (Table 5).

Table 5: 90% Confidence Interval for BE testing

	Test	Lower bound	Point Estimate	upper bound	Conclusion
Central lung (F_C)	B-3.8 µm vs. A-4.5 µm	65.7	69.0	72.4	Not BE
	C-3.7 µm vs. A-4.5 µm	70.8	74.3	77.9	Not BE
	C-3.7 µm vs. B-3.8 µm	88.5	92.8	97.4	BE
Peripheral lung (F_P)	B-3.8 µm vs. A-4.5 µm	174.1	192.6	213.1	Not BE
	C-3.7 µm vs. A-4.5 µm	175.6	194.3	214.9	Not BE
	C-3.7 µm vs. B-3.8 µm	89.7	99.2	109.8	BE

Table 5: Absorbed doses from central (Fc) and peripheral (Fp) lung based on population PK modeling.

B-3.8 µm and C-3.7 µm were bioequivalent for both Fc and Fp
A-4.5 µm vs B-3.8 µm and A-4.5 µm vs. C-3.7 were not bioequivalent

Figure 4: Visual Predictive Check

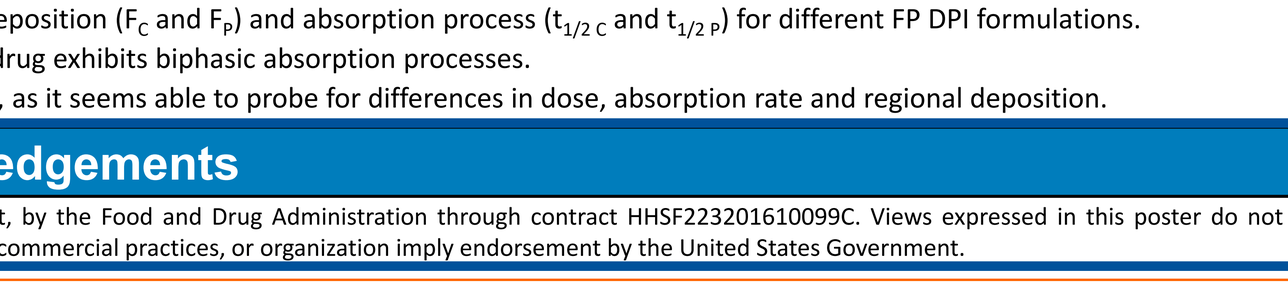

Figure 3: The visual predictive check of the performance of the proposed PopPK model for three formulations

Figure 4: Excellent curve fits of PopPK model. Formulation A-4.5 µm shows a smaller bioavailability as compared to the other two formulations.

Figure 5: Suggested Alternative BE Methodology using Population PK

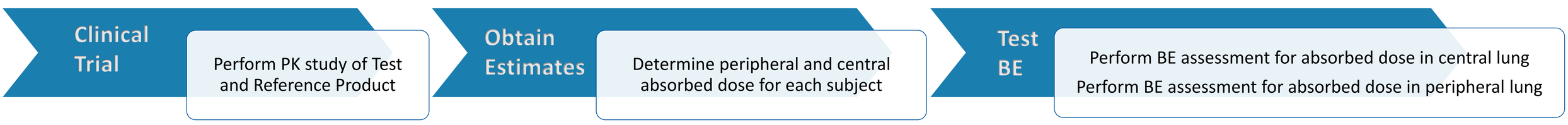

Figure 5 : Working flow of proposed novel PopPK alternative BE methodology.

Conclusions

- The developed PopPK model appears sensitive to quantitatively detect differences in regional lung deposition (F_C and F_P) and absorption process ($t_{1/2\,C}$ and $t_{1/2\,P}$) for different FP DPI formulations.
- Presented here is a new way of looking for regional deposition differences of inhalation drugs if the drug exhibits biphasic absorption processes.
- This novel approach (Figure 5) could provide supportive information for bioequivalence assessments, as it seems able to probe for differences in dose, absorption rate and regional deposition.

Acknowledgements

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