Unraveling the Pulmonary Fate of Fluticasone and Friends: Meeting the Physiologic and Pharmacokinetic Challenges

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SUMMARY

The ability of pharmacokinetic (PK) studies to evaluate the pulmonary fate and to assess pulmonary bioequivalence (BE) of fluticasone propionate (FP) inhalation products without the need to perform comparative clinical endpoint studies is still debated among stakeholders. This paper discusses the physiological basis and possible justification for using PK as a potential tool to assist in BE decision-making for FP inhalation products. Results of a study that evaluated the PK of three different FP dry powder inhaler (DPI) formulations through both non-compartmental and compartmental analysis are described. They showed agreement with the *in vitro* characteristics of the formulations, underlining that PK may be able to provide comparative information on the pulmonary available dose, pulmonary residence time and regional lung deposition (the key attributes for determining pulmonary BE) while relating observed PK differences to the *in vitro* properties of the formulations and their regional lung deposition, dissolution and permeability.

INTRODUCTION

Access to generic versions of locally acting orally inhaled drug products (OIDP), such as fluticasone propionate (FP), is still very limited. Due to the complexity of locally acting OIDPs, the US FDA currently recommends that BE demonstration follows the *weight of evidence approach*. This includes, in addition to information related to formulation sameness and device similarity, *in vitro* and PK studies, and the use of comparative clinical endpoint or pharmacodynamic (PD) studies, even though such studies often lack adequate dose-response relationships. Within the last 10 years, a number of workshops [1–3] discussed potential alternative approval pathways. GDUFA-sponsored projects, including those for FP, were initiated to evaluate their feasibility, including studies to evaluate PK as a potential tool to assist in BE decisions.

Pulmonary bioequivalence of fluticasone propionate: What needs to be shown?

The pulmonary fate of inhaled fluticasone propionate when delivered for example using a DPI, is determined by a complex series of events that can be modulated by device, drug, formulation and patient characteristics (Figure 1). Together they influence (1) the release of the drug/formulation from the DPI drug storage compartment (e.g. capsule, blister, reservoir), (2) de-agglomeration of the drug/excipient (e.g. lactose) complexes, (3) the dose emitted from the device, (4) deposition of the emitted dose within the airways (e.g. mouth–throat deposition; lung dose and regional lung deposition profile, e.g. central to peripheral deposition ratio) and (5) subsequent post-deposition events (mucociliary clearance from the central lung, dissolution in the epithelial lining fluid, absorption into lung tissue/vascular space and passage into the systemic circulation) (Figure 1). Based on clinical pharmacological principles, pulmonary bioequivalence should be achieved, in theory, if test (T) and reference (R) product (I) deliver the same lung dose (II) to the same regions of the lung followed by (III) dissolution of the deposited drug particles resulting at same/similar dissolution rates within the lung lining fluid so that the active drug has similar lung regional residence times. Methods comparing T and R products with respect to these three key characteristics should be suitable to assist in making bioequivalence decisions.

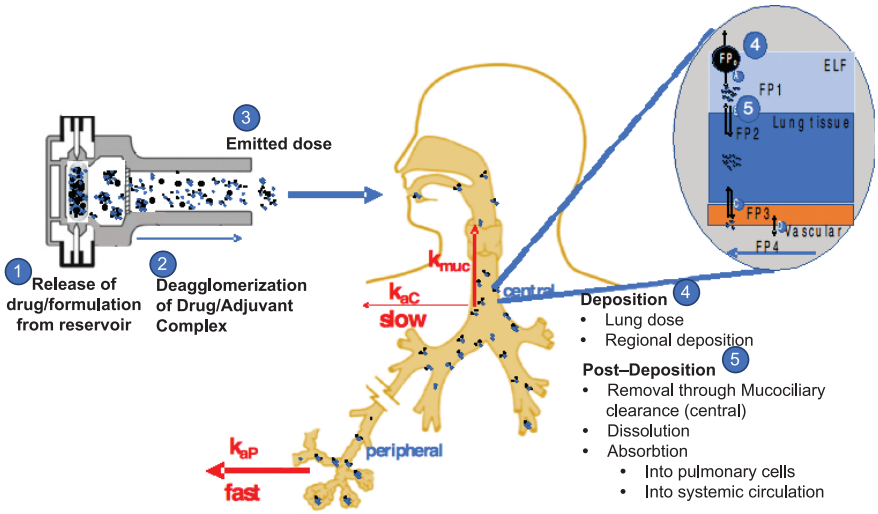

Figure 1. **Events and terms relevant to the fate and bioequivalence of FP (FP_0: FP particle; FP1: dissolved FP in epithelial lining fluid; FP2: dissolved FP in lung tissue; FP3: dissolved FP in extracellular/vascular space. k_{aC}: absorption rate constant for central lung, kmuc: rate constant for mucociliary clearance, k_{aP}: absorption rate constant for peripheral lung.**

Can pharmacokinetic studies provide sufficient information for assisting in making sound bioequivalence decisions?

Because the oral bioavailability of FP is negligible and all pulmonary deposited FP that escapes mucociliary clearance will dissolve and subsequently reach the bloodstream, the area under the FP plasma concentration time profile (AUC_{0-inf}) has been accepted by many stakeholders as a valid marker for the drug's pulmonary available dose [4]. Following the same reasoning, C_{max} and t_{max} ought to differentiate between formulations that differ with respect to their pulmonary residence times. Slowly dissolving FP deposited in the central regions of the lung will be subject to mucociliary clearance (k_{muc} in Figure 1). Considering two products that deliver the same amount of drug to the lung but differ in their central to peripheral deposition ratios, more FP will be removed from the central lung for the product that delivers more drug centrally. As a consequence, the amount of drug available to the lung will be smaller, less drug will be absorbed into the systemic circulation and AUC_{0-inf} will be smaller than for the product that delivers more to the peripheral region of the lung. In addition, products that differ in their regional deposition profile are also expected to show differences in pulmonary absorption characteristics (Figures 1 and 2), as peripherally deposited FP is likely to dissolve under sink conditions while the much lower permeability observed in the central lung should force FP to dissolve much more slowly under non-sink conditions (Figures 1 and 2). These differences in dissolution rates should lead to a biphasic absorption profile and differences in C_{max} and t_{max} estimates for products that differ in their central to peripheral deposition ratios.

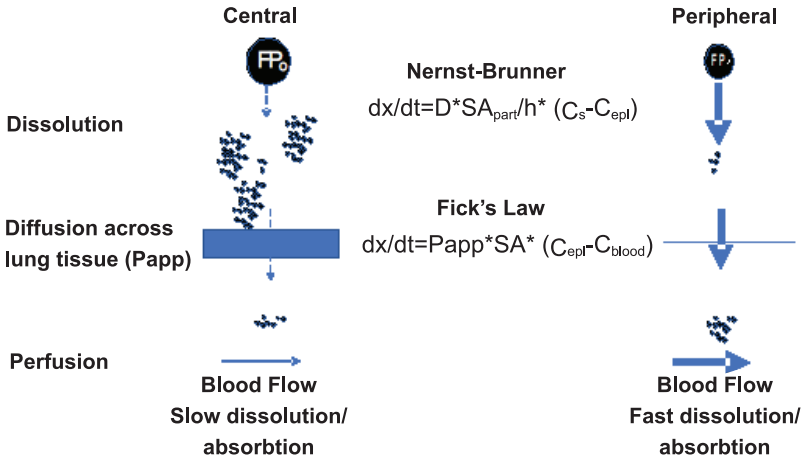

Figure 2. **Model of pulmonary dissolution and absorption showing the differences in the dissolution of FP from peripheral and central lung. SA_{part}: surface area of particles; C_S: solubility in epithelial lining fluid (epi); C_{epi}: Conc in epi; P_{app}: apparent permeability, SA: surface area of relevant lung region; C_{blood}: blood concentration.**

Arguments against the use of PK for BE assessment of FP

Although a significant number of stakeholder companies favor development of generic FP OIDPs without the need to perform comparative clinical endpoint BE studies, some do not (Table 1). Daley-Yates [5] referred to a range of *in vitro*, PK and pharmacodynamic (PD) endpoint studies that identified differences in the PK of FP from Advair® Diskus® and a reservoir powder inhalation device (RPID) while PD efficacy was equivalent. Similar discrepancies between results from PK and PD studies were highlighted for FP Diskus and Diskhaler® [5]. Kuehl and colleagues [6] compared the PK of a range of FP formulations with their pulmonary PD efficacy in dogs. Again, PK suggested differences across the formulations, while PD markers did not. Based on the inability of PK to suggest BE in such cases (Table 1), its ability to provide reliable information on the pulmonary fate of inhaled FP was therefore questioned, even though the PD marker was insufficiently sensitive to identify differences in each case (Table 1). Haughtie and colleagues recently reported equivalence in PK between T and R FP products [7], in agreement with PD results [8]. Furthermore, the ability of PK to provide reproducible results within FP Diskus batches, but identify differences across batches [9] indicates the robustness and sensitivity of the PK approach to allow conclusions on batch performance. Nevertheless, the continued discussions around the potential role of PK for assessing the pulmonary fate of FP underlined the need for a better understanding of FP's pulmonary fate based on well-designed PK studies with well characterized FP DPI formulations.

A study to further support the relevance of PK to assess the pulmonary fate of FP in DPI formulations

Within this GDUFA–sponsored FDA study, the potential role of pharmacokinetics to assess differences in the regional deposition of FP from three different formulations was evaluated under controlled conditions. Target formulations of FP were chosen that were likely to differ in lung dose, pulmonary residence time and/or regional deposition.

METHODS

The following three DPI FP blends were prepared: (1) Formulation A consisted of FP : Respitose SV003 : Lactohale LH201 in proportions by weight = 0.8:79.36:19.84 (2) Formulation B consisted of FP : Respitose SV003 : Lactohale LH230 in proportions by weight = 0.8:89.28:9.92 (3) Formulation C consisted of FP : Respitose SV003 : Lactohale LH300 in proportions by weight = 0.8:96.72:2.48. These formulations were characterized after delivery from a DPI using standard Next Generation Impactor–cascade impactor methods and Transwell® based dissolution tests to derive the mean dissolution time (MDT) as described previously [10]. After clinical protocol approval through the University of Florida and FDA Institutional Review Boards, formulations were delivered from a capsule based DPI device to 24 healthy volunteers at a single-dose of 5*100 μg FP within a double-blind, four-way crossover study where formulation C was repeated (CR). Eighteen blood samples were collected over a 24-hour time period and the FP concentrations in plasma were quantified via a validated LC-MS/MS assay, followed by non-compartmental and compartmental analysis using a population pharmacokinetic (popPK) approach within S-Adapt [11].

Table 1.

Results of *in vitro*, pharmacokinetic and clinical (PD) bioequivalence studies. Numbers in parentheses are literature references.

	In Vitro	PK	PD
Advair vs Wixela [7, 8]	equivalent	equivalent	equivalent
Diskus vs RPID [5]	good match	not equivalent	equivalent
Diskus vs Diskhaler [5]	small differences	not equivalent in healthy similar in asthmatics	equivalent
FP HFA vs FP CFC [5]	good match	not equivalent	equivalent
HFA vs CFC FP and Sal [12]	FP: similar Sal: similar	FP: similar Sal: different	equivalent equivalent
FP DPIs [6]		different	equivalent

Sal: Salmeterol; RPID: reservoir powder inhalation device, FPM: fine particle mass; HFA and CFC: Hydrofluoroalkane and chlorofluorocarbon propellants

RESULTS

Formulation A showed the largest *in vitro* mass median aerodynamic diameter (MMAD); the values for MMAD from each formulation were A: 4.5 μm, B: 3.8 μm and C: 3.7 μm. Estimates of the fine particle mass smaller than 3 μm (FPM <3 μm) for the three formulations (based on 100 μg FP per capsule) were 5.3, 10.0 and 8.6 μg for formulations A, B, and C respectively. Formulation A also showed the longest mean dissolution time (14.4, 13.2 and 10.8 hours for formulations A, B, and C, respectively). Non-compartmental analysis of the PK data (not subjected to lung dose normalization) revealed differences in AUC_{0-inf} (782, 1040, 980 and 1035 pg*h/ml for formulations A, B, C and CR, respectively) with t_{max} estimates being 0.5, 0.33, 0.3 and 0.27 h respectively, for formulations A, B, C, and CR. C_{max} of formulation A, even after lung dose normalization,

was significantly smaller than those of the others. Compartmental analysis suggested that the concentration time profiles could be best described by a three-compartment body model for FP with two first-order input rates k_{aC} and k_{aP} from the central and peripheral lung respectively. The first-order rate constants, k_{aC} and k_{aP}, differed for all formulations by a factor of approximately 10 (Table 2). For formulation A (with the largest MMAD), a greater fraction of the deposited dose was absorbed more slowly, as indicated by a modeling-derived central/peripheral deposition (c/p) ratio of 2.32 (the best estimate for the ratio of the fraction of the lung deposited dose that was absorbed more slowly). This value compared to c/p ratios of about 0.6 for formulations B and C (Table 2). In agreement with the results from dissolution experiments, absorption rate constants of formulation A for both the fast and slow absorption processes were smaller than those determined for the other two formulations (Table 2). Physiologically based pharmacokinetic (PBPK) simulations indicated that differences in the FP's k_{aC} and K_{aP} are related to permeability differences between the peripheral and central lung. Because of the distinct differences between k_{aC} and k_{aP}, two FP products that differ in their c/p ratios are likely to differ in C_{max}.

Table 2.

Pulmonary model parameters derived from the popPK analysis.

Formulation	c/p	k_{aC} h^{-1}	k_{aP} h^{-1}
A	2.32	0.177	2.48
B	0.60	0.216	5.37
C	0.51	0.193	5.25

k_{aC}: absorption rate constant-slow (presumably from central lung); k_{aP}: absorption rate constant- fast (presumably from peripheral lung) c/p: central to peripheral deposition ratio (amount of drug absorbed slow divided by amount of drug absorbed fast)

CONCLUSIONS

The pharmacokinetics of three fluticasone propionate dry powder formulations for oral inhalation, differing only in the composition of the lactose/lactose fines used as carriers for the same batch of FP, showed differences in the amount of FP available to the lung (AUC_{0-inf}), mirroring the differences in the NGI-based FPM <3µm estimates *in vitro*. In addition, the ability to detect differences in the values of t_{max} and the lung dose-adjusted C_{max} across the formulations indicated that PK has a great potential to identify differences in the pulmonary residence time of FP.

Compartmental analysis suggested biphasic absorption of FP, presumably related to slow absorption from the more central and faster uptake of FP from the peripheral lung, as hypothesized above. This behavior may logically be driven by differences in the membrane permeabilities of the central and peripheral lung combined with the effects on FP's regional dissolution kinetics (dissolution under sink or non-sink conditions; see Figures 1 and 2). The ability of PK to provide information on how much FP was absorbed via slow or fast absorption kinetics indicated that PK may not only provide information on the pulmonary available dose (AUC) and pulmonary residence time (C_{max}, t_{max}) but also whether T and R formulations would be equivalent with respect to their regional deposition, with PBPK based simulations, suggesting that C_{max} would also capture these differences in regional deposition.

The results from compartmental PK analysis (differences in k_{aC} and k_{aP}, Table 2) and dissolution tests (mean dissolution times, MDT) both underscored the importance of adjuvant composition in modulating FP's pulmonary fate. One reason for batch to batch differences in PK might therefore be related to batch to batch differences in carrier or adjuvant characteristics, an observation that might be helpful during development of generic FP OIDPs. Strong correlations between *in vitro* aerodynamic size distribution test results and PK parameters, taken with the ability to relate these differences to formulation-dependent differences in lung dose, regional permeability differences and dissolution suggested that differences between PK and PD results in some previous studies (see Table 1) are most likely related to FP's flat dose response relationships and the inability of PD studies to identify differences between products.

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