Letter to the Editors

Systemic bioavailability of hydrofluoroalkane formulations containing fluticasone propionate and salmeterol

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We read with interest the recent article on the systemic bioavailability of hydrofluoroalkane (HFA) formulations containing fluticasone propionate and salmeterol by Clearie *et al.* [1]. The authors concluded that the generic and innovator products were clinically interchangeable despite an incomplete evaluation of the *in vitro* data and a failure to demonstrate bioequivalence for all the primary PK/PD endpoints.

One of the main findings was a lack of correlation between *in vitro* fine particle dose data and *in vivo* PK/PD outcomes [1]. However, it is not clear whether this observation was confounded by the methodology used. Although not mentioned by the authors, this lack of *in vivo/in vitro* correlation has been reported previously for a study comparing two combination dry powder inhalers containing fluticasone propionate (FP) and salmeterol (SM) [2] and discussed extensively [3–5]. Although interesting, in both cases the lack of *in vivo/in vitro* correlation is not a justification for less stringent criteria for *in vivo* equivalence.

The authors gave no details of the generic formulation and device being tested and insufficient details of the *in vitro* testing. In reporting the *in vitro* data the authors describe the test (T) and reference (R) products as having similar overall fine particle dose (FPD) (particles <4.7 µm). However in Tables 1 and 2 fine particle mass is reported. Were these terms being used interchangeably or do the tables represent an alternative size grouping? The grouped stage data in Tables 1 and 2 suggest the FPD for test and reference are similar, but stages 6–7 show appreciable differences. The T : R ratios for SM and FP for the pMDI alone were 6.2 and 1.7, respectively, and similar with the spacer (5.2 and 1.8 for SM and FP, respectively). The testing flow rate is omitted. However if a typical flow rate of 28 l min⁻¹ is assumed [6] then stages 6–7 would represent material with an aerodynamic particle size range of 0.4–1.1 µm [7]. Therefore, although the Andersen Cascade impactor is essentially a quality control tool and not predictive of

pulmonary deposition, the test product does appear to have more finer particles, which might lead to greater peripheral lung delivery and account for the higher systemic exposure for SM reported. This difference might be related to the observed differences in stages 6–7 or be indicative of differences in distribution within the stage 3–5 grouping (1.1–4.7 µm [7]). This could be better evaluated by assessment of individual stage data.

In describing clinical study 1, no details were given of the charcoal block procedure or its validation. The higher systemic exposure for SM for the generic inhaler could be interpreted as either greater lung deposition and/or altered lung deposition favouring peripheral deposition and increased systemic absorption. However, the impact of this on topical efficacy was not investigated. The design of clinical study 2 was not complimentary to study 1 as a spacer was used to administer the doses. Stopping PK sampling after 2 h was inadequate for FP, a drug with an 8 h half-life. For both drugs the impact on the primary endpoints of multiple inhalations (2–4 times the clinical dose) being given via a spacer was ignored. The time taken to administer the doses could have influenced the $C_{\max}$ and $t_{\max}$ values observed. In the case of FP it is not clear if actual $C_{\max}$ was achieved as the median value (2 h) was the last sampling point for all treatments. The reported $C_{\max}$ and $t_{\max}$ values were therefore likely a function of the sampling schedule and time taken to administer the multiple inhalations via a spacer thereby limiting the ability to detect differences between the two inhalers.

Systemic PK data are considered useful to evaluate the safety profiles of test and reference products [8], but there is doubt about their relevance as a surrogate of topical efficacy in the airways [9]. The PK data collected in these studies [1] were incomplete and the pharmacodynamic endpoints insufficiently sensitive to detect differences between the two products after a single dose. Overall, the products cannot be regarded as bioequivalent as the SM component of the test product gave higher systemic exposure. The

authors' comment that 'pharmacokinetic analysis of plasma FP concentrations may not adequately account for the overall bioavailability of the drug, especially if the drug being examined partitions preferably into fat...' is not a relevant argument, since the test and reference products contain the same active drug moiety. Hence tissue partitioning will be the same for both products and have no influence on the outcome. On the other hand, pharmacodynamic endpoints such as overnight urinary cortisol are variable, lack sensitivity due to their non-linear relationship with drug exposure and are not sufficiently quantitative.

The authors' conclusions, that despite the PK differences, the results 'demonstrate that generic and innovator HFA formulations of FP/SM are clinically interchangeable' are not robust since no efficacy or safety data were presented to support their claim. There were also differences in heart rate and potassium related to the higher SM exposure from the Neolab inhaler. Therefore, in the light of the lack of PK bioequivalence for SM it cannot be argued that these differences are not clinically relevant since they are only biomarkers of systemic exposure and do not constitute an adequate assessment of the risk benefit ratio for the generic inhaler. The authors' final conclusion that 'a product which does not demonstrate bioequivalence in pharmacokinetic studies may still be acceptable to patients and clinicians...' is not in keeping with the accepted bioequivalence criteria. If two products are not PK equivalent then at the very least they do not have the same rate and extent of drug availability at the site of action or potentially the same systemic safety profile and therefore there is no justification for claiming bioequivalence irrespective of the route of administration or site of action.

Competing Interests

The authors are employees of GlaxoSmithKline.

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RECEIVED

22 December 2010

ACCEPTED

19 February 2011

ACCEPTED ARTICLE

31 March 2011

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