Expert Opinion

Establishing bioequivalence for orally inhaled drug products

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We thank Dr García Arieta for his interest and comments on our article.

The use of *in vitro* data alone is a feature of the European guidance [1]. Dr García Arieta's comment that this route of approval is unlikely to be a common occurrence appears to be in-line with our conclusion that unless there is a high degree of pharmaceutical equivalence between the test and reference products, consideration of a combination of preclinical and clinical data may be preferable to abridged approaches relying on *in vitro* data alone.

We did not address the bioequivalence of systemically acting drugs but mentioned it to contrast the simplicity compared to inhaled drugs [2]. Dr García Arieta wrote that *in vitro* differences may be considered clinically irrelevant, but that is usually in the context of some understanding of the *in vivo–in vitro* correlation. However, such a correlation for inhaled drugs is generally lacking.

Dr García Arieta did not agree with our conclusions on the value of pharmacokinetic data for some of the bioequivalence examples we cited [2] but rather advocates pharmacokinetic data for its superior sensitivity. Although pharmacokinetic data may well be sensitive, for example, to a change in the particle size profile, dissolution rate or altered regional lung deposition, these parameters may not exhibit the same relevance for efficacy. There are few well-documented examples with robust data for *in vitro* profiling, pharmacokinetics, lung deposition and clinical efficacy testing and, therefore, insufficient data to allow a general conclusion at this time.

The assumption that systemic pharmacokinetic data are a valid surrogate of topical efficacy in the lung has been questioned [2,3]. Dr García Arieta suggests this is a misinterpretation of the supporting data we cited [4], arguing that it is simply a matter of tissue distribution and that after oral administration fluticasone propionate distributes to fatty tissues and not to the lungs. The volume of distribution of fluticasone propionate, and indeed of any drug, is a primary pharmacokinetic parameter and independent of its route of administration [5]. Therefore at steady-state, fluticasone propionate's volume of distribution and its rate and extent of tissue partitioning should be the same for oral and inhaled administration. After single dose administration the rate of tissue distribution may well be relevant, but in the cited study [4], 6 weeks dosing was used and steady-state equilibrium should have been achieved between plasma and tissues compartments. However, despite the higher systemic concentration of fluticasone propionate achieved after oral compared to inhaled dosing, only the inhaled regimens were efficacious, suggesting a lack of equilibrium between the site of action in the lung and the drug concentrations in plasma.

Declaration of interest

Both authors are employees of GlaxoSmithKline, who develop and manufacture inhaled drug products.

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Bibliography

1. Committee for Human Medicinal Products (CHMP) EMA. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents. 2009
2. Daley-Yates PT, Parkins DA. Establishing bioequivalence for inhaled drugs; weighing the evidence. Expert Opin Drug Deliv 24 June 2011. [Epub ahead of print]
3. Daley-Yates PT. The clinical utility of pharmacokinetics: theoretical consideration across drug classes. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM. editors. Respiratory Drug Delivery. ISBN: Book 1, 1-933722-41-X. David Healthcare International Publishing; Orlando Florida, River Grove IL: 2010. p. 273-84
4. Lawrence M, Wolfe J, Webb DR, et al. Efficacy of inhaled fluticasone propionate in asthma results from topical and not from systemic activity. Am J Respir Crit Care Med 1997;156(3 Pt 1):744-51
5. Rowland M, Tozer TN. Clinical pharmacokinetics concepts and applications. 4th edition. Williams & Wilkins; Lippincott: 2011. p. 561-602

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