Expert Opinion

Establishing bioequivalence for orally inhaled drug products

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Dear Editor,

Daley-Yates and Parkins reviewed the methodologies used to investigate bioequivalence for orally inhaled products (OIPs) [1]. I would like to clarify that, thanks to the Committee for Human Medicinal Products guideline [2], the demonstration of equivalence for OIPs in the EU is based on a multi-step process and the requirements are a flexible weight-of-evidence approach to be applied on a case-by-case basis as the authors claim. Generally, it is essential to combine *in vitro* and *in vivo* evidence; however, it is necessary to consider the possibility of demonstrating bioequivalence with *in vitro* data alone for cases with only minor differences (e.g., variations of an innovator not affecting the release/inhalation procedure or a generic OIP considered as a minor variation such as a suspension for nebulization with identical composition). It would be unwise to believe that generic OIPs are approved frequently with *in vitro* data alone.

It is incorrect that systemically-acting generics have the same excipients and show equivalence *in vitro* and pharmacokinetically. On the contrary, *in vitro* data are enough in certain cases (e.g., Biopharmaceutical Classification System biowaivers, solutions for injection), although usually *in vivo* studies are required and sufficient even if *in vitro* differences exist [3]. This error should not be an excuse to require *in vitro* similarity in addition to *in vivo* similarity for OIPs as some *in vitro* differences are clinically irrelevant.

Although the text indicates three cases where clinical differences were not detected by pharmacokinetic studies, this only occurs in the first case of Table 1. In this case, the difference was detected in only one out of eight group comparisons due to a multiplicity problem. The second, eighth and ninth cases do not show any disagreement. The third case shows that pharmacokinetic data are very sensitive and all strengths should be investigated, although these results might be caused by the wide specifications of any OIP, which do not ensure pharmacokinetic bioequivalence within specification limits. The fifth case shows that healthy volunteers are more sensitive than patients to detect differences. All other cases illustrate the superior sensitivity of pharmacokinetics.

The claim that the plasma concentrations and concentrations at the site of action are not in equilibrium and consequently pharmacokinetic data are not a valid surrogate of efficacy is a misinterpretation of a paper that only shows that the plasma levels are not responsible for the efficacy [4]. This is simply a matter of distribution and not of equilibrium. After oral administration, fluticasone distributes to fatty tissues and not to the lungs [5].

The views expressed in this letter are the personal views of the author and may not be understood or quoted as being made on behalf or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Declaration of interest

A García Arieta is a member of the drafting group to elaborate the CHMP guideline.

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