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Short communication

Using the BCS-based biowaiver approach to exempt *in vivo* bioequivalence studies

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Introduction

Bioequivalence (BE) for immediate-release solid oral dosage forms with systemic action is largely established via clinical pharmacokinetic BE studies, in order to prove therapeutic equivalence between generic drug products and their respective comparator products.

However, ever since the first EMA *Note for guidance on the investigation of bioavailability and bioequivalence* guideline, the concepts underlying the Biopharmaceutics Classification System (BCS) were mentioned in order to justify a possible request for exemption from in vivo BE studies (EMA, 2011).

The final version of the ICH M9 *Biopharmaceutics classification system-based biowaivers* guideline was adopted in November 2019, providing detailed recommendations to support the biopharmaceutics classification of drug substances and the BCS-based biowaiver of bioequivalence studies for drug products (ICH, 2019).

Application of the ICH M9 guideline: proprietary experience

Background

Following the general principles outlined in ICH M9, a proprietary development program was evaluated to assess the applicability of the BCS-based biowaiver approach in a real-world regulatory context.

A bioequivalence study for the highly-soluble drug product in question had previously been conducted; however, the same was deemed not fully compliant with current industry guidelines by the Regulatory Authority during a national registration procedure, necessitating an alternative strategy to support equivalence. The applicant considered two possible mitigation scenarios: conducting a new BE study, or providing a justification based on a BCS-biowaiver approach, of which a BCS-based biowaiver application was selected.

Biopharmaceutics classification of the drug substance

BCS-based biowaivers are applicable to drug products where the drug substance(s) exhibit high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III).

1. Solubility: a solubility study was conducted in a horizontal shaking water bath, in 200 ml 0.01M HCl, buffer pH 1.2, 4.5, 6.2 and 6.8, during a 24-hour period, at 37°C. The results showed pH-dependent solubility of the drug substance, with very high solubility in the acidic mediums and decreased solubility under neutral and near-neutral conditions. All values were above the threshold for high solubility (0.04 mg/ml), and adequate stability of the substance was proven across all pH media (degradation levels remaining below the 10% threshold).

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2. Permeability: a literature investigation was conducted, covering all available references. After a thorough search, four literature references were used for discussion: three papers describing permeability assays employing cultured Caco-2 epithelial cell monolayers (proving >80% recovery compared to the high-permeability standard metoprolol); and one paper that used a pharmacokinetic simulation model (proving high predicted permeability). In addition, the SmPC of the drug product in question stated that ≥85% of the administered dose is recovered in urine and feces as oxidative and conjugative metabolites.

Based on the above, the drug substance in question satisfied the criteria for a BCS class I classification.

Eligibility of the drug product for a BCS-based biowaiver

The drug product in question satisfied the basic eligibility criteria: the drug substance in the test and the reference product was identical; the test product was an immediate-release oral dosage form with systemic action; the test product was in the same dosage form and strength as the reference product; and the test product was not considered as a narrow therapeutic drug.

1. Excipients: the components of the formulation complied with those permitted under ICH M9, and the excipients in the composition did not adversely affect the permeability or solubility of the active substance. Qualitative composition sameness was proven between the test and the reference product, with quantitative differences being within the permitted limits.

2. *In vitro* dissolution: a comparative dissolution study was presented according to the guideline recommendations.

2.1 Apparatus and conditions: USP apparatus 2 (paddle); 900 ml media; 37°C; 50 rpm; 12 units of each drug product were used for each dissolution profile determination.

2.2 Media: buffers pH 1.2, 4.5 and 6.8, and 0.01M HCl.

2.3 Comparison of the dissolution profiles: a model-independent approach using the similarity factor (f2) (four time points – 10, 15, 30 and 45 minutes (zero excluded)) was implemented; RSD of the mean time point data was below 20% at 10 minutes, and below 10% at all the later time points.

2.4 f2 factor values: all values were above 50 (buffer pH 6.8: f2 = 59.91, buffer pH 4.5: f2 = 58.70, buffer pH 1.2: f2 = 60.21, and 0.01M HCl: f2 = 55.25), indicating similarity between the dissolution profiles of the test and reference product.

Both the test and the reference product showed rapid (≥85% for the mean percent dissolved in ≤ 30 minutes) *in vitro* dissolution.

Conclusion

Based on the results of the solubility testing, permeability investigation and *in vitro* dissolution, as well as the suitability of the excipients, Alkaloid's product fully complied with the requirements of ICH M9 for a BCS-based biowaiver class I. The BCS-based biowaiver application was indeed accepted by the Regulatory Authority, thus exempting an additional in vivo bioequivalence study.

References

Committee for proprietary medicinal products (CPMP), EMA, 2001. Note for guidance on the investigation of bioavailability and bioequivalence. CPMP/EWP/QWP/1401/98.

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