Regulatory Note

Similarities and Differences of International Guidelines for Bioequivalence: an Update of the Brazilian Requirements

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Received 20 November 2013; accepted 10 January 2014; published online 4 February, 2014

KEY WORDS: bioequivalence; biowaiver; generic drugs; regulatory authority; Brazil.

We would like to comment on an interesting review article on the similarities and differences among international guidelines for determining bioequivalence (BE) of generic drug products (1). Because the legal framework of the Brazilian Health Surveillance Agency (ANVISA) is available only in Portuguese, it might have been difficult to search information properly or to identify updated guidelines. In this context, we would like to clarify some misunderstood definitions. Whatever is not mentioned here is correctly stated in the article.

The first rectification would be the guideline cited in Table I presented by Davit and co-workers (1). It was replaced by the RE n.1170/2006 in 2006, which is currently valid (2). In this guideline, the age range of the subjects is not specified, rather it states only that they should be older than 18 years old. It mentions also that the number of subjects in a BE study should be at least 12, but in the case of unknown within-subject variability, the researcher should opt to use a minimum of 24 subjects. The number of units of test product to be manufactured for the BE study is specified in the IN n.02/2009, which is at least 10% of the commercial batch size or 50,000 units, whichever is greater (3).

Regarding the dose strength used in the *in vivo* studies, a guideline published in 2011 (RDC n.37/2011) concurs with European Medicine Agency (EMA) and Health Canada (HC) guidelines, viz, that the strength to be tested *in vivo* will depend on the type of nonlinearity of the pharmacokinetics (PK) (4). The distinction is that the Brazilian agency usually requests either fast or fed studies, based on how food interacts with the PK (2). Both fast and fed studies are demanded only

for prolonged release dosage forms. A list indicates the study conditions for immediate release oral dosage forms (5).

The RDC n.37/2011 also specifies the conditions under which biowaivers could be granted and it includes a section of biowaiver based on Biopharmaceutical Classification System (BCS) (4). Although the criteria for establishing the high solubility and the high permeability of a substance are similar to those of HC and EMA, Brazilian jurisdiction differs from them in that the biowaiver candidates are determined by the regulatory agency, and a list of those candidates is released and updated periodically. The list is comprised of drugs that exhibit an absorbed fraction of $\geq 85\%$ (based on reliable investigations in human) and an absence of reported bioinequivalence that had not been detected by *in vitro* studies performed under BCS conditions (6). The submitted applications for BCS-based biowaiver should enclose documents that confirm the high solubility of the drug and the similarity of dissolution profiles of the test and reference drug products, which should be rapid or very rapid dissolving (4). The solubility test should be performed by shake-flask or phase diagram methods, at pH values of 1.2, 4.5, and 6.8 at $37 \pm 1^\circ\text{C}$. The dissolution profiles should be obtained in 900 ml of dissolution media at pH 1.2, 4.5, and 6.8 at $37 \pm 1^\circ\text{C}$, using paddle or basket speeds of 50 and 100 rpm, respectively. The use of surfactants is prohibited, and enzymes are allowed for gelatin capsules only. At least 12 units of each product should be tested. The profile comparison should be done by *f2* metric. A dosage form is considered as rapidly or very rapidly dissolving if $\geq 85\%$ is dissolved in 30 and 15 min, respectively (7).

Concerning the formulation composition for biowaiver of oral dosage forms, the test drug product should preferably use the same excipients as the reference drug product, but other excipients that are well established for the dosage form, administration route, and drug substance in usual amounts are

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allowed (4). Excipients known to affect the bioavailability should be qualitatively the same in the test and reference formulations. Parenteral aqueous solutions do not have to be formulated with the same inactive ingredients as their reference formulations. However, in the case of parenteral oily solutions, the type of oil used as a vehicle has to be qualitatively the same.

It is important to highlight that only BE studies conducted by certified contract research organizations (CROs) are accepted to support the registration of a generic drug product. A list of such certified CROs could be found at ANVISA's website. Other regulatory guidances that should be followed for the establishment of BE are the following: RE n.898/2003, which is the guideline for BE statistics (8); RDC n.27/2012, which is the guideline for bioanalytical method validation (9); and RDC n.103/2003, which defines the requirements for the CRO certification (10).

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