

Regulatory Note

An Update of the Brazilian Regulatory Bioequivalence Recommendations for Approval of Generic Topical Dermatological Drug Products

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Abstract. This note aims to clarify the Brazilian regulatory bioequivalence recommendations for approval of generic topical dermatological drug products, since the legal framework of the “Brazilian Health Surveillance Agency” (ANVISA) is only available in Portuguese. According to Resolutions RE n. 1170 (December 19th 2006) and RDC n. 37 (August 3rd 2011) in Brazil, only *in vitro* studies are required for registration of generic topical dermatological drug products. Current Regulatory Agenda of ANVISA, which contains possible future resolutions to be revised over 2015–2016, includes a discussion on biowaiver requirements and on possible *in vitro* and *in vivo* comparability tests for these products.

KEY WORDS: bioequivalence; generic; topic.

In this note, we would like to comment a recently published review article on the similarities and differences among some international jurisdictions in accepting bioequivalence approaches for generic topical dermatological drug products [1]. The aims are to clarify the current requirements of the *Brazilian Health Surveillance Agency* (ANVISA) for registration of these products and to present the updated guidelines. Some language misinterpretations may have occurred, since the legal framework of the *Brazilian Health Surveillance Agency* (ANVISA) is only available in Portuguese.

The Brazilian guide cited in Table I of Braddy and co-workers' paper, relative to bioavailability/bioequivalence tests for dermatological topical drug products [1], has been replaced by the Resolution RE n. 1170 (December 19th 2006), which is still the currently valid document [2]. The current guideline describes how pharmacokinetics tests should be performed for those medicines requiring a demonstration of blood level bioequivalence and, in cases where it is not possible to precisely and accurately quantify the drug in circulation, when pharmacodynamic measurements may be accepted. Resolution RE n. 1170 does not provide guidance on how to conduct pharmacodynamic studies for topical formulations.

In spite of the mention of such pharmacodynamic tests, they are not required for topical dermatological drug product approval, as suggested in Tables II and III of the aforementioned review. Actually, bioequivalence studies with

pharmacodynamic endpoints are not required for any topical dosage form. According to the Resolution RDC n. 37 (August 3rd 2011), topical medicines, *i.e.*, those not intended for systemic effects, are granted a biowaiver if the generic product contains the same active ingredient, in the same concentration as that of the reference product (pharmaceutical equivalents), and the generic product contains excipients that the same function as those of the reference formulation [3]. Therefore, only *in vitro* studies are required for registration of all generic topical dermatological drug products, including those containing corticosteroids. Such *in vitro* tests are described in either the *Brazilian Pharmacopeia* or in other official compendia acknowledged by ANVISA. Consideration for equivalence includes formulation general aspect, pH, viscosity, density, drug active concentration assay, and microbiological tests results [4].

Current Regulatory Agenda of ANVISA, which contains possible future resolutions to be revised over 2015–2016, includes a discussion on biowaiver requirements and on possible *in vitro* and *in vivo* comparability tests for these products [5]. Nonetheless, only the post-approval guidance RDC48, of October 6th 2009, has mentioned the need to assess the drug permeability of topical dermatological products, although this guidance has not specified the experimental procedures to be followed [6].

In revision process of Resolution 1170, ANVISA is considering the need to require additional tests as supportive evidences for safety and efficacy of these products. Bioequivalence approaches such as *in vitro* release tests, *in vitro* skin permeation tests, dermatopharmacokinetic studies, and *in vivo* pharmacodynamic studies for corticosteroids, which are the most common therapeutic class of topical dermatological drug products in Brazil [7], may be included as requirements in the future.

In the continuous process of revising and updating regulatory recommendations, it is essential that international regulatory

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authorities and organizations share their experiences. Successful approaches implemented internationally could lead to a global alignment in regulatory requirements and would improve the efficacy of topically administered generic formulations.

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