Bioequivalence of Topical Dermatological Dosage Forms—Methods of Evaluation of Bioequivalence


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The three-day AAPS/FDA workshop on “Bioequivalence of Topical Dermatological Dosage Forms—Methods for Evaluating Bioequivalence,” held on September 4–6, 1996 in Bethesda MD was attended by 260 scientists from industry, academia and regulatory authorities. The goals and objectives of the workshop were to:

1. Discuss scientific issues and approaches for bioequivalence (BE) evaluation of topical drug products;
2. Explore principles of dermopharmacokinetics (DPK) in BE evaluation;
3. Discuss DPK and statistical evaluation for BE of dermatological products; and
4. Review other methodologies applicable to BE demonstrations for topical drug products.

INTRODUCTION

With the exception of topical corticosteroids, the only means an US generic company has to demonstrate bioequivalence of a topical dermatological product to an innovator’s product is through comparative clinical trials with a bioequivalence endpoint. An innovator company wishing to replace an already approved post-1962 topical dermatological product with a new formulation exhibiting appreciable compositional changes is also faced with the need to demonstrate bioequivalence using clinical studies, again with the exception of topical corticosteroids. In the specific instance of topical corticosteroids, the demonstrations of BE of two physically alike (e.g., cream versus cream) formulations may now be done using a vasoconstriction protocol, as outlined in FDA Guidance (Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, June 2, 1995), irrespective of whether the product is for an Abbreviated New Drug Application or for updating an existing New Drug Application.

Clinical efficacy trials aimed at showing the bioequivalence of topical dermatological products are relatively insensitive, time-consuming, and costly. To gain adequate statistical power required to make a clear BE determination, they may require as many as 500 patients. A problem in the topical dermatological area is that no recognized surrogate measures are currently available that might be used in replace of clinical efficacy studies. For drugs where effect is related to concentration in the systemic circulation, the concentrations of a drug and/or active metabolite in blood and/or urine have been viewed as surrogate measures of clinical safety and efficacy. For many years, FDA has thus relied on blood and/or urine concentration time curves as a measure of BE. A key assumption in this approach is that concentrations of a drug in blood are also in equilibrium with concentrations in the target organ/tissue. This workshop explored the possibility that a dermopharmacokinetic characterization might provide an alternative approach to clinical trials for the determination of BE of topical dermatological products, analogously to the use of concentration-time curves for systemically administered drugs. If accepted, this approach might allow dermopharmacokinetic studies to

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replace comparative clinical trials as a means of documenting bioequivalence of selected topical drug products.

The DPK approach includes any measure of drug concentration in the skin, whether directly or indirectly related to the drug's therapeutic action, which can be determined continuously or at least intermittently for a period of time. This may include measurement of either drug concentrations in stratum corneum (SC) over time and/or drug concentrations in serial biopsy samples. To be a useful DPK measure, the time-integrated DPK response must reflect both local safety and efficacy of the topical drug product. One assumption in the DPK approach is that excipients are pharmacologically inactive. In some instances, however, an excipient may exert a direct or an indirect effect, by enhancing or inhibiting drug penetration into the skin. Such effect should be accounted for by DPK methodology through implementation of proper experimental controls (i.e., placebo formulations).

DPK methods should be validated and verifiable. Validation should include all aspects of sampling, e.g., SC stripping and measurement of drug concentration in the SC, or any other analysis. At every critical step in the method development, accuracy, precision, sensitivity, specificity, and other standard aspects of validating an assay methodology should be established. Beyond these obvious checks and balances, all measurements must stand up to rigorous scientific scrutiny.

Before a DPK method is adopted as a basis for BE, it must be shown that differences in DPK capture or reflect significant clinical important differences in formulations. Delivery of a drug into the stratum corneum may not be the only factor in therapeutic efficacy. Other formulation factors may contribute to a topical product's therapeutic efficacy. Therefore, a multi-tiered approach to BE assessment may be a prudent strategy. For instance, one might determine that DPK, e.g., SC concentration-time profiles, are the same in the test and reference product which have qualitatively same composition (Q1), similar physicochemical properties such as pH, viscosity, consistency, residues upon drying, and comparable in vitro release rates.

The most promising DPK method involves assessment of drug concentrations in SC through skin stripping (SS). The SC is the rate limiting barrier for most topically applied drug products. The SC also lies in a direct path to the viable tissues of the skin where many diseases of the skin manifest themselves, making either the SC and/or the viable tissues below the site where most drugs must be delivered. Therefore, the concentration of a topically applied drug in the SC for therapeutic efficacy may theoretically be expected to be related to its concentrations in viable tissues such as the epidermis and dermis. Because dermatological products deliver the drug locally and close to the intended site of action in the skin, DPK measurement may provide a means of assessing BE of two dermatological drug products. Two formulations that produce comparable SC drug concentration-time curves may be bioequivalent just as two oral formulations are judged bioequivalent if they produce comparable plasma concentration-time curves. The successful application of DPK thus rests on the assumption that SC concentration-time curves are directly related to concentration-time curves of the active drug substance in the epidermis and dermis.

The results of preliminary investigations indicate that SS allows assessments of both drug uptake into and clearance from the SC. Assessments based on common pharmacokinetic metrics, such as area under the curve (AUC), maximum concentration (Cmax), and time to maximum concentration (Tmax) in SC, have been demonstrated. It should be pointed out that although the DPK metrics are similar to those obtained from plasma based traditional BE studies, (AUC, Cmax, Tmax), the interpretation of DPK is different. SC parameters reflect the driving concentrations that deliver the drug to the epidermis or dermis (site of action). Although these results are useful, actual methodological details for a DPK study involving SS would necessarily be product specific. Because the formulation is removed prior to determining a drug's concentration from the SC, the Cmax obtained by this procedure is not functionally equivalent to Cmax of a drug following oral administration. Subjects employed in a DPK study would ordinarily be individuals exhibiting normal skin, similar to the use of normal healthy subjects in BE determination of oral drug products. Employing patients with diseased skin may introduce additional variability in drug penetration into SC, although it might suggest a subject by formulation interaction. Neither in vitro diffusion cell studies with human skin sections nor in vivo work performed on animals would be acceptable as the sole criteria for BE assessment of topical products. Both cadaver skin and animal skin are known to differ significantly in their physiological properties from normal human skin, and thus both are inappropriate for BE assessment. For this reason, DPK measurements obtained by harvesting SC from cadaver, animal, or ex-vivo human skin (the latter by surgical harvesting) will deviate in important ways from those obtained from live human skin. An important asset of the stripping DPK procedure is that the test and reference formulations can usually be applied to a given subject at the same time, allowing each subject to become his or her own control. Adequate sampling from a sufficient number of stripping sites would be required to characterize drug uptake into and clearance from the SC. Based on preliminary investigations, all the conditions important in the application of the DPK approach in assessing BE seemed manageable.

SPECIFIC CONSIDERATIONS/CONCERNS WITH THE SKIN STRIPPING METHOD

Skin is known to be a highly variable organ in its chemical and physical properties. It exhibits appreciable site-specific inter-intra subject permeability differences in its barrier function properties. Therefore, considerable thought and attention must be given to validation of the SS method and experimental design when conducting a BE study based on measurements of drug concentration in SC. These considerations are discussed in the following paragraphs.

Skin stripping is a technique sensitive operation. Each technician's ability to remove, reproducibly and carefully, the SC should be demonstrated. Appropriate tape or tape discs used for the purpose of SS should be demonstrated to have uniform adhesive properties and to have reproducible properties relative to SC removal. Validation in this regard can be achieved in terms of reproducible amount of skin (weights) or protein contents recovered from test sites. Within subject variability in SS recoveries may be minimized during the experiment through randomization of the product applications to specific sites.