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October 30, 1999

Janet Woodcock, M.D.
Director
Center for Drug Evaluation
FDA
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Woodcock,

I am writing to support DPK as the method for assessing bioequivalence of topical drug products and the approval of the FDA Guidance, entitled "Topical Dermatological Drug Product NDAs and ANDAs--In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies".

I have been involved in the research, development and critical evaluation of the dermatopharmacokinetic (DPK) as a method for establishing bioequivalence both with the FDA under contract for 8 years (1987- 1994) and more recently with evaluation of the method with actual drug products for industry. I therefore qualify as an expert in the field.

I am also writing to contest statements made in the Citizens Petition submitted to the FDA by Glaxo Wellcome, in which the latter objects to approval of any ANDA for a topical dermatological drug product based upon bioequivalence assesment using the Draft guidance for industry issued by the Agency June 18, 1999.

1. The citizens petition argues that there is "...preponderance of expert opinion that DPK methodology requires correlation with clinically important differences in formulations".

It is unclear in the petition what are "clinically important differences". They might include the ability of the DPK methodology to differentiate between drug concentration, vehicle type or vehicle composition. Many examples (topical corticosteroids, retinoids, antifungals) have, in fact, addressed the

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above issues at the Pharmaceutical Sciences (March 19, 1998) and Dermatological Board Meetings (October 23, 1998), in which changing the drug concentration, or the vehicle (ointment, creams) or composition of the vehicle statistically alters the drug content in the skin using the DPK methodology.

The examples presented at these Board Meetings therefore all confirm and document that the DPK methodology is able to "capture and reflect significant clinically important differences in drug products".

Further, it is a prudent reminder that bioequivalence issues are assessed for the oral solid dosage forms by PHARMACOKINETIC METHODS, in HEALTHY subjects, WITHOUT Clinical Efficacy studies. Therefore the application of DPK to bioequivalence assessment for topical drug products is consistent and appropriate with existing regulatory practice (see point 2 and 3).

2. Consistency and Uniformity of Approving Topical Drug Products by NDA vs ANDA approaches

The petition expresses concern about approval of a topical drug product using DPK methodology in the ANDA vs NDA processes. It is my understanding, that the ANDA process approves topical drug products based on already established clinical indications with that product. Thus, a generic product that is Q1 (qualitatively) and optimally Q2 (quantitatively) similar to an existing drug product with an established clinical application, would apply for an ANDA. The innovator company may want to use this ANDA route, however, for establishing changes of bioavailability of the drug in a new vehicle formulation of the original drug product for the same clinical indication.

In contrast, the NDA process approves a topical drug product for a new clinical indication, in which the sponsor provides "proof of concept" or positive new drug activity against the stated clinical disease state for approval of this new clinical indication of an existing drug product. DPK methodology for a new drug product would be desirable, but not sufficient in and of itself to

prove the drug product's use for a new clinical indication. The guidance should be clarified in regard to this issue.

3. Consistency and Uniformity of Bioequivalence Assessment Among All Drug Products (solid-oral semi-solid dermatological products) using a pharmacokinetic method.

A point eluded to, but not discuss thoroughly in this petition, is the uniformity and consistency in methods for review of topical drug products for bioequivalence assessment. The majority of other drug products (solid oral dosage forms) are currently assessed for bioequivalence using pharmacokinetic methods. These studies are also performed in healthy subjects.

Similar to the fact that drugs in a solid oral dosage form must produce similar blood concentrations for bioequivalence, so must two semi-solid topical dosage forms produce similar stratum corneum concentrations of drug. If the drug does not leave the topical vehicle and partition into the rate-limiting barrier of the skin and the systemic circulation stratum corneum, the rate-limiting barrier of the skin and the systemic circulation, there will be NO pharmacological activity.

Important to the review process by all departments in the FDA is uniformity and consistency in the methods used to assess bioequivalence and approval of all drug products. Where technology (analytical instrumentation, adhesive systems, DPK) is now available to discriminate between topical drug products using pharmacokinetic methods, with adequate sensitivity and reproducibility, it is only appropriate that these methods be used for bioequivalence assessment of topical drug products in the skin.

DPK methodology is exquisitely sensitive to changes in the vehicle formulation, drug particle size and vehicle composition. Data was presented at the October 23, 1998 Dermatological Advisory Board, in which two miconazole nitrate creams, 2% demonstrated statistically different DPK parameters (C_{max} , AUC_{0-t}) values, but no difference in clinical efficacy. The basis for the discrepancy was shown to be due to the fact that more drug is actually delivered to the skin with both drug products than required to

maximally inhibit the target organism. Thus, a 2 fold increase in an already maximal skin concentration of the drug will not demonstrate any difference in clinical efficacy, nor in vitro specific bioassay.

These data clearly demonstrate that while DPK methods differentiated between the above products, the clinical study endpoints did not.

These data support DPK methodology as the most discriminating and sensitive method and therefore preferred method for bioequivalence assessment of topical drug products. The sensitivity of DPK methodology to discriminate between products offers the consumer added confidence that generic topical drug products are indeed bioequivalent to their otherwise more expensive listed drug products.

In conclusion, DPK methodology 1) is scientifically sound, 2) is sensitive and discriminating, 3) can be scientifically validated, 4) meets existing FDA bioanalytical method requirements

It is most useful in assessing two drug products that are Q1 (qualitative vehicle composition similarity) and to the best ability, Q2 (quantitative vehicle composition similarity) in vehicle composition.

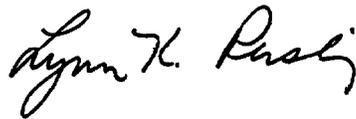
In contrast, clinical studies rarely address the issue of intra-subject variability, the reproducibility of end point parameters or reproducibility of investigator scoring. These are difficult, with many times poor end points, investigator bias, and are expensive to perform. Failed clinical efficacy studies are generally explained away by stating that the drug wasn't delivered effectively into the skin. Why not use a method that will provide a mechanistic basis for those failed clinical efficacy studies?

Recent research in my laboratory has convinced me that DPK is the ultimate performance evaluation test for two topical drug products that are Q1 similar. Deviation from qualitatively similar vehicle composition, or manufacturing processes, will result in failed bioequivalence by DPK methodology, yet many demonstrate equivalent clinical efficacy.

As a consumer and scientist, I want the most sensitive, scientifically quantifiable and validated method by which to assess the bioequivalence of generic drug products. This information will assure me that when I purchase a prescription drug, I have received the best product at the best price for my health care needs.

I strongly encourage you to approve the DPK methodology guidance for bioequivalence assessment of dermatological drug products. It is a sound, well-researched, and validated step ahead to the future.

Respectfully yours,

A handwritten signature in black ink, reading "Lynn K. Pershing". The signature is written in a cursive style with a large initial "L".

Lynn K. Pershing, Ph.D.