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Food and Drug Administration
Department of Health and Human Services
Room 1-23
Document Management Branch
12421 Parklawn Drive
Rockville, MD 20857

Citizen Petition

The undersigned, on behalf of Pharmacia & Upjohn, submits this petition to request that the Commissioner of Food and Drugs not approve any ANDA for a topical dermatological drug product based upon a purported showing of bioequivalence consistent with the principles outlined in the draft guidance for industry entitled *Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies*. This guidance was announced in the June 18, 1998 Federal Register.

A. Action Requested

The petitioner requests that the FDA not approve ANDAs for topical drug products on the basis of dermatopharmacokinetic (DPK) studies that purportedly establish bioequivalence with a reference listed drug product based on the principles outlined in the draft guidance.

B. Statement of Grounds

1. DPK is scientifically unjustified as a surrogate for clinical evaluation of efficacy and/or safety of dermatological drug products. The arguments supporting this contention are summarized in the comments provided by the Pharmaceutical Research and Manufacturers of America organization on September 22, 1998 (Docket No. 98D-0388). This is particularly a concern when the test and reference products are not qualitatively *identical* (Q1) and quantitatively similar (+/- 5%) since the clinical efficacy and safety of topical skin products are composites of drug and vehicle effects.

2. Expert panels convened by the FDA for the specific intent of discussing the application of DPK to establish bioequivalence did not support implementation of the

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guidance. Two joint meetings of the Pharmaceutical Sciences and Dermatologic and Ophthalmic Drugs Advisory Committees were held to discuss the guidance: March 19, 1998 and October 23, 1998. At each meeting, DPK was found unacceptable due to the lack of validation assuring the clinical relevance of DPK assessments. In point of fact, the Chairman of the joint Advisory Committee, in remarks made in summarizing committee discussions on October 23, 1998, specifically noted that "much work remained to be done" before DPK could be furthered considered as a basis for bioequivalence. Since this meeting, no additional data supportive of the guidance has been put forth by the FDA for public review and comment.

3. Dissension exists within the FDA itself on the use of DPK to assess bioequivalence of dermatological drug products. The Director of Dermatologic and Dental Drug Products, Dr. Jonathon Wilkin, openly declared at the October 23, 1998 joint Advisory Committee that he did not support implementation of the guidance due to the lack of consistent, validated evidence demonstrating that DPK is an appropriate surrogate measure of clinical effect. Major issues he noted were that levels of drug in the stratum corneum are not necessarily reflective of that reaching the target site; DPK ignores transport across follicular and sebaceous glands; stratum corneum is not a well-mixed compartment (as is the blood); and healthy stratum corneum, identified in the guidance as the target site for DPK assessment, is absent in diseased skin, lip and vaginal mucosa. These criticisms were commonly shared among the members of the joint Advisory Committee members.

Dissension within the FDA on the implementation of this guidance is notable for 2 reasons:

a. It reflects the lack of consistent, validated data to support the key assumptions underlying the governing principles of the guidance.
b. It indicates that a dual standard of FDA approval may apply depending on whether or not the Office of Generic Drugs or the Division of Dermatologic and Dental Drug Products is responsible for establishing the equivalence of dermatological drug products. For example, changes in Q1 and/or Q2 for innovators' products may require additional safety studies (i.e., photobiology, photocarcinogenicity) that are not addressed in the draft guidance.

The use of DPK as an assessment tool in establishing bioavailability/bioequivalence of dermatological drug products is not supported by a consistent, validated scientific database; is not supported by the recommendation of expert panels convened by the FDA; and is not uniformly and consistently supported by the reviewing divisions and offices within the Center for Drug Evaluation and Research. Consequently, the FDA should not approve any generic product based upon a determination of bioequivalence consistent with the principles outlined in the draft document. Therefore, the draft guidance should be withdrawn.

C. Environmental Impact

Preparation of an environmental impact statement is exempted under 21 CFR§25.31(g), since this action relates to bioequivalence requirements for a human drug product.

D. Economic Impact

Information regarding economic impact will be submitted if requested by the Commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

Pharmacia & Upjohn

Robert A. Paarlberg
Senior Director, Global Regulatory Affairs

cc: Janet Woodcock, MD