

Exhibit 16

**Johnson & Johnson**  
CONSUMER PRODUCTS WORLDWIDE  
SKILLMAN, NJ 08558-9418

*Citizen Keaton  
8/17/98  
Dr. Williams*

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**AUG 17 1998**

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville  
Maryland 20852

**Re: Docket No. 98D-0388; Draft Guidance for Industry,  
Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability,  
Bioequivalence, In Vitro Release, and Associated Studies; Response to Request for  
Comments.**

Dear Sir/Madam:

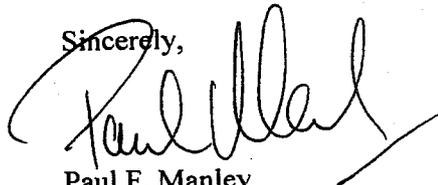
The purpose of this correspondence is to provide, on behalf of Johnson & Johnson, comments on the above Draft Guidance published in the Federal Register dated June 18, 1998 (63FR 33375).

Johnson & Johnson supports the Food and Drug Administration initiative to determine viable approaches to establishing bioequivalence for topical dermatological drug products, and applauds the efforts put into preparing this draft guidance. However, we also believe it to be imperative that all interested parties view any proposed methodology as scientifically valid and robust. At this time, we respectfully feel that the guidance has serious limitations, many of which have been raised previously by practicing dermatologists, the academic, industrial and government scientific community.

To that end, we have put forward a detailed response, with data where appropriate, for your review and consideration. Three copies of this response, with supporting data, are enclosed, including 2 desk copies for Drs Vinod Shah and Roger Williams. We would also like to request the option to present data at any forthcoming Advisory Committee or other meeting on this subject.

Should you have any questions regarding this document, or require further copies, please do not hesitate to contact me on (908) 874 1239, or our number dedicated for FDA use, (908) 874 1700.

Sincerely,



Paul F. Manley  
Director  
Regulatory Affairs

cc: Vinod P. Shah, PhD, FDA, CDER, (HFD-350)  
Roger L. Williams, MD, FDA, CDER, (HFD-003)

98D-0388

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Johnson & Johnson  
Skillman, NJ 08558

**Docket 98-D-0388**

**Johnson & Johnson  
Comments on the Draft Guidance for Industry**

**Topical Dermatological Drug Product NDAs and ANDAs - In Vivo  
Bioavailability, Bioequivalence, In Vitro Release,  
and Associated Studies**

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Docket 98-D-0388

Comments on the Draft Guidance for Industry

Topical Dermatological Drug Product NDAs and ANDAs – In Vivo Bioavailability  
Bioequivalence, In Vitro Release, and Associated Studies

1. INTRODUCTION

The above entitled Guidance contains recommendations for the establishment of bioequivalence (BE) by the use of dermatopharmacokinetics (DPK or tape stripping) for all topical products, including antifungals, corticosteroids, antiacne (retinoids) and vaginally applied products. This issue has been the subject of several Workshops and recently was presented to the FDA Advisory Committee for Pharmaceutical Science (PS) and the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) at public meetings. Although we agree that DPK is conceptually a good methodology for supplementing data to determine topical bioequivalence, serious limitations in implementation have been raised by practicing dermatologists, and the academic, industrial, and government scientific community, which we feel have not been adequately addressed by the available data.

2. HISTORY

The main feature of the Guidance is the use of dermatopharmacokinetics (DPK), i.e., the measurement of stratum corneum drug concentrations in tape stripped skin, as a measure of bioequivalence. This technique was considered by academic, government and industry scientists at several workshops sponsored by the FDA and the American Association of Pharmaceutical Scientists (AAPS). In the report from the *AAPS/FDA Workshop on in vivo Percutaneous Penetration/Absorption* held May 1-3, 1989, the advantages/disadvantages of this technique were outlined and the following issues were identified:

*"The correlation between the amount of drug in the stratum corneum and total drug absorption has only been established for some drugs and formulations. Since different body sites of skin have different drug penetration properties, the site of application has to be specified for predicting drug absorption like for any other method. This method does not sample the epidermis or the dermis (i.e. the normal 'targets' of topical drug products). The cleaning and preparation of the skin for stripping is a critical determinant of drug recovery".*

These issues, and others identified in subsequent Workshops and Advisory Committee meetings, have not been addressed in the proposed Guideline.

The possibilities of utilizing skin stripping methodology (DPK) were examined in September, 1996 at the *AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms – Methods for Evaluation of Bioequivalence*. As part of this workshop, a protocol outline for a skin stripping BE study was presented. Although this protocol made attempts to address some of the issues mentioned above, either no data, or preliminary, unvalidated information was presented to justify many of the procedures used, i.e, site of application, which tape to use, the number and size of the sites, cleaning and preparation of skin, validation of sample analytical techniques, appropriate statistical measures, etc. The protocol described in the Workshop report, however, remains the basis of the current Guidance.

The use of DPK as a measure of BE was also the subject of a December 11, 1997 meeting of the Advisory Committee for Pharmaceutical Science. One of the Committee's conclusions was that *"I think that we agree that perhaps, if there are specific targets to the lower follicle, perhaps DPK may not be appropriate."* (Transcript, pg. 108).

Another conclusion from one of the presenters, Dr. Hans Schaefer, was that *"If ever you have an influence on the properties of the horny layer itself, on its barrier and reservoir function, it doesn't hold anymore."*, and in response to the question from Dr. Lamborn, *"You're saying that this substitute assay would not pick-up whether or not it's bioequivalent if in fact the vehicles were different?"*, Dr. Schaefer replied, *"Yes. I would say you would find a difference anyway."* (Transcript, pg. 103). As is discussed later in this response, tretinoin formulations induce changes in the stratum corneum (Effendy, et al). We therefore agree with these conclusions, and present herein the additional reasons that for certain compounds and indications, DPK methodology is not appropriate as a method for establishment of BE.

This current guidance was also presented at the 49<sup>th</sup> Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) on *Bioequivalence of Topical Dermatological Drug Products* on March 19, 1998. This committee cited lack of validation of the skin stripping technique and variability of the method. Lynn Drake, M.D., Member of the Advisory Committee, stated regarding DPK that, *".... I am unwilling as one member....to accept this test as a replacement for what we actually do in patients and see in patients,.....and this test as far as I am concerned is still way far away from me being able to accept it as the best way to evaluate or accept judgement on equivalent drug..."* (Transcripts, pg 139).

Another committee member, O. Fred Miller, III, M.D., stated that *"I think that (DPK).....might become the surrogate for antifungals, but not for retinoids and not for corticosteroids. But I think in this infancy stage and with all the variables that we have and that have been discussed, that there certainly has to be clinical correlation with what we are seeing with the DPK, and can we consistently say the DPK showed this, and this is what the clinical correlation was, and then maybe we can go forward with it."* (Transcript, pg. 140).

The Guidance also contains recommendations for using in vitro release (IVR) technology as a measure of bioequivalence for lower strengths of topical products (Section D of this response). The recommendation that a waiver of BE studies for lower strengths by the use of IVR was specifically addressed at the *AAPS Workshop on Assessment of Value and Applications of In-Vitro Testing of Topical Dermatological Drug Products* (September, 1997) in which the consensus of the scientific community, as published in the Workshop report, stated that this technique was not appropriate as a measure of bioequivalence. This opinion was seconded at the recent (March 19, 1998) DODAC meeting by Jonathan Wilkins, M.D., Director, Division of Dermatological and Dental Drug Products (DDDDP). Despite these recommendations, the use of IVR as a substitute for in vivo bioequivalence studies of lower strengths of certain NDA and ANDA products is being recommended in the Guidance.

The Guidance also proposes the use of IVR as a routine Quality Control test for topical products (see Section V of the guidance). This recommendation was previously, specifically removed from the *Guidance for Industry, Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation*, based on a consensus of industry, academia and government scientists. To our knowledge, there has been no additional data made available to support a change in policy on this issue.

## 1. SPECIFIC COMMENTS ON THE DRAFT GUIDANCE

We have the following comments on specific items in the Guidance which are presented in the order they appear in the document.

### Section II. BACKGROUND

We agree with the statement that "*For topical dermatological drug products, PK measurements in blood, plasma, and/or urine are usually not feasible to document BE because topical dermatologic products generally do not produce measurable concentrations in extra-cutaneous biological fluids. The BA/BE determination for these products is thus often based on PD or clinical studies.*" However, in view of the comments which will follow in this correspondence, we feel it necessary to emphasize that the subsequent statement within the draft guidance, "*An additional approach considered in this guidance is to document BA/BE through reliance on measurement of the active moiety(ies) in the stratum corneum. This approach is termed dermatopharmacokinetics (DPK)*" should be interpreted in such a fashion that data could only be considered as potentially supportive in complementing efficacy data from at least one adequate and controlled clinical trial comparing the ANDA product to both placebo and the reference listed drug (RLD). As our response outlines, DPK data has not been proven thus far to be a reliable and reproducible marker for BE of all topical drug products, and as such cannot be regarded as a valid methodology to be utilized on its own for such determinations.

### Section III. INACTIVE INGREDIENTS

We are in agreement with the statement confirming that an ANDA may not be approved in circumstances where preclinical or clinical studies are needed to demonstrate the safety of inactive ingredient(s). In particular, there has been at least one circumstance where an applicant has filed ANDAs for formulations which included novel excipients not included previously in pharmaceuticals. In that case, the presence of the novel excipient prompted Agency requests for the applicant to file a modified NDA (a 505(b)2 application), which included at least one adequate and controlled clinical trial against placebo and the RFL. This allowed the approved product to ultimately be rated AB bioequivalent. Therefore we strongly support the need for such products to be supported by data from nonclinical studies as well as clinical safety information.

### Section IV. BIOAVAILABILITY AND BIOEQUIVALENCE

#### A. Clinical Trials Approaches

We agree that clinical trials for topical bioequivalence are hard to perform, highly variable and insensitive. However, we also agree with the comment from S. James Kilpatrick, Jr., Ph.D. during the DODAC Advisory Committee meeting of March 19, 1998 that *"I am suggesting, like other members of the committee, that we should look for more information on the conformability or coherence between clinical results and DPK results...I feel we need more information before we can let DPK fly on its own."* (Transcript, pg 146).

#### B. Dermatopharmacokinetic Approaches

Currently there is little or no data to support the DPK approach for establishing bioequivalence. The DPK methodology makes a number of assumptions based on the way bioequivalence is established for orally administered drugs. One such assumption is that the stratum corneum is an appropriate dose surrogate for target site tissues in the skin. Another assumption is that we can compare the amount of drug in the tape strips vs. time data to perform pharmacokinetic analysis of SC concentrations, as is routinely done with plasma concentrations after oral administration. However, many years of study have shown that the use of blood concentrations as a surrogate for target site concentrations for establishing oral BE is an acceptable approach, presumably due to the fact that the concentration of drug in the plasma is in equilibrium with the organs that are the site of activity. For topical drug products, no such equilibrium has been shown to exist. We challenge these assumptions based on the results of studies conducted by Johnson & Johnson which will be discussed below and for which full reports of the experiments are given in the attached Appendices.

In light of the lack of available data, one of the main questions that has been consistently raised about the use of DPK for determination of topical bioequivalence has been whether stratum corneum drug concentrations can be correlated with clinical efficacy. To date, no such clinical studies are available. If the amount of drug in the tape strips is expected to predict clinical outcome, then two key questions arise: First, is drug content in the tape strips indicative of drug content in the stratum corneum? Secondly, are stratum corneum concentrations correlated with the concentration of the tissue at the target site? The ultimate answers to these questions would require one to conduct a clinical pharmacokinetic study in which skin sections were collected, drug (and active metabolites) content for stratum corneum and target tissue (i.e. epidermis, dermis, sebaceous gland, and/or hair follicles) was determined, and the data analyzed to see whether they correlated in any acceptable fashion. Such a study is difficult to conduct because of the need for biopsies, as well as the low concentrations of drug at the target sites, which often require the use of radioactive tracers (Jamouille and Schaefer, 1993).

Therefore, in order to provide some scientific rationale for the DPK approach, several different types of studies have been cited in the Draft Guidance. In one study, a correlation was found between the amount of compound in the stratum corneum of hairless rats 30 minutes after dosing with the amount of drug *predicted* to be *absorbed* in these animals (Rougier and Lotte, 1993). This correlation was shown under the ideal conditions of the study, i.e., for **hydrophilic**, permeable compounds in simple vehicles of maximum solubility.

It has been noted that "....it (DPK) has not yet been accepted or recommended by the regulatory agencies in bioequivalence determination, possibly because of its apparent limitations in the area of very lipophilic drugs (e.g., retinoids or antifungals such as ketoconazole), where the quantity measured is too low". (Jamouille and Schaefer, 1993). Even for the model compounds used in the aforementioned study, (caffeine, benzoic acid, acetylsalicylic acid) *in vivo* human studies indicate that under ideal conditions the correlation between amount of drug in the stratum corneum and "predicted" percutaneous absorption is low ( $r=0.7$ ) (Rougier and Lotte, 1993). It should also be noted that the DPK method as used above was a surrogate for **systemic** absorption, and not for the concentration of drug (and/or active metabolites) at the possible target sites in the skin. As stated on page 3 of the current Draft Guidance "Although measurement of the active moiety(ies) in blood or urine is *not* (emphasis added) regarded as an acceptable measurement of BA/BE for dermatological products, it may be used to measure systemic exposure." Thus, while the work of Rougier cited in the Guidance may support the use of DPK as a surrogate for absorption (for the compounds and conditions studied), it does not provide any information on whether a correlation exists between stratum corneum concentrations and those in the epidermis, dermis, pilosebaceous glands, hair follicle or any other skin appendage that may be a site of action for dermatological products.

In order to address the issue of whether stratum corneum tissue concentrations, as assessed by the amount recovered from tape strips, is an appropriate surrogate for dermal and epidermal tissues, an investigation was conducted with human skin in vitro. This commonly used model was used in lieu of a clinical study due to the technical/ethical issues such as use of a radiolabelled tracer or the need for biopsies as discussed previously. A full report of the results of these studies, which were presented at the September, 1996 *AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms - Methods for Evaluation of Bioequivalence* are presented in **Appendix A**. This work also examined the effect of minor formulation and manufacturing changes on the profile of retinoid concentrations in the various tissue layers. The results of these studies clearly showed that there is no linear correlation between the amount of compound in the stratum corneum tissue and the amount in the epidermis, dermis, or combined dermal and epidermal tissue ( $r= 0.02-0.66$ ) at the time points investigated. In addition, minor changes in manufacturing and/or the formulation were found to alter concentrations in the different skin compartments, but the changes seen in the tape strippings were not correlated with changes found in other tissues. These studies concluded that one cannot, therefore, use the stratum corneum concentrations to predict what is in the epidermis or dermis (the target site for many dermatological products).

The Guidance does recognize that antifungals are the only topical product for which the stratum corneum may be a site of action and for which DPK methodology may be considered to be an appropriate way to sample target site tissue. This was acknowledged by both Advisory Committees and the Draft Guidance states: "*For antiacne drug products, target sites are the hair follicles and sebaceous glands. In this setting, the drug diffuses through the stratum corneum, epidermis, and dermis to reach the site of action. The drug may also follow follicular pathways to reach the sites of action.*" Despite this, the Draft Guidance continues to support the use of stratum corneum drug concentrations in lieu of target site tissue, and states "...*the DPK approach is still expected to be applicable because studies indicate a positive correlation between stratum corneum concentrations and follicular concentrations.*" No details or references are given to demonstrate this important correlation. It is not known therefore whether this correlation was shown in animals or humans, in vivo or in vitro, and whether it may be applied, as is suggested in this Guidance, universally to all dermatological compounds. We question the validity of such a statement without adequate and substantial supportive scientific data.

In addition, no experimental evidence is referenced that would validate this guideline for vaginally administered products. The Draft Guidance states that, "...*DPK principles should be generally applicable to all topical dermatological drug products including antifungal, antiviral,..... and vaginally applied drug products*". The guidance goes on to say that, "*A DPK approach is not generally applicable .....3) for ophthalmic preparations because the cornea is structurally different from the stratum corneum*".

The following presents evidence that the DPK approach cannot be utilized for vaginally applied drugs for similar reasons.

- (i) Skin is quite different from vaginal mucosa, both structurally and biologically (Table I, Osborne et al, 1990; Burgos et al, 1978), most notably because of the absence of stratum corneum. As opposed to skin, where stratum corneum presents a barrier to penetration of drug and a drug reservoir, vaginal mucosa is a hormone-sensitive, vascular, highly absorptive structure. Because of these differences, it would, of course, be inappropriate to predict the delivery of a topically acting drug to vaginal mucosa, based on its delivery to stratum corneum. Determining equivalence through stratum corneum stripping may not be sufficiently sensitive to discriminate two products which could possess different absorption profiles from the vaginal mucosa. This could represent a safety issue in that a product determined to be equivalent by stratum corneum stripping could be absorbed much more readily from the vagina, compared to its "equivalent" comparator, resulting in unsafe systemic levels of drug. Stripping the vaginal mucosa in the same fashion as stratum corneum is not likely to be predictive of equivalence and would be fraught with difficulty and considerable pain. Thus, for the same reasons that ophthalmic preparations are excluded from this guidance, vaginally applied drugs should also be excluded.

Table 1. COMPARISON OF SKIN STRUCTURE vs. VAGINAL MUCOSA

SKIN			VAGINAL MUCOSA ( no stratum corneum)		
Layer	Structure	Function	Layer	Structure	Function
Stratum corneum	Non-viable keratin-filled cells (squames) with bilayer-structured lipids fill between the intercellular space.	Provide a barrier against the permeation of most substances	Superficial zone: Superficial layer and Transitional layer	The superficial zone contains squamous cells which reach maximal thickness at ovulation	Forms the outer layer of the vaginal mucosa
Viable epidermis	Lie below the stratum corneum and consists of stratified keratinizing epithelial cells; does not contain blood vessels; rely on nourishment by cell fluid from the deeper dermis layer	Produce stratum corneum	Intermediate layer	Round or irregular shape; increase in volume toward the ovulation time when the intermediate layer becomes the thickest layer of the epithelium.	Produce superficial zone
Dermis	Consists of dense, irregularly arranged connective tissue; nourished directly by blood vessels.	Provide cell fluid to the viable epidermis	Parabasal layer	Has several layers of polyhedral cells with distinct nuclei.	Proliferative compartment
			Basal layer	Has a single row of cuboidal cells overlying the basement membrane.	Proliferative compartment; contact with blood vessels

- (ii) Vaginal fluid and mucosa are significantly different chemically, compared to stratum corneum (Osborne et al, 1990; Burgos et al, 1978; Benziger et al 1983; Park et al, 1979). The suggested method for bioequivalence testing may not be sensitive enough to detect important differences in vaginal formulations. For drugs applied to the skin, the stratum corneum is the rate limiting barrier. The partitioning of the drug from the formula into the stratum corneum, as expressed by the ratio of the drug solubility in the formula and stratum corneum is the key to optimizing a formulation. For vaginally applied drugs the partitioning of drug from the formula into vaginal fluid and then from vaginal fluid into vaginal mucosa are key to optimizing delivery (Benziger et al, 1983; Park et al, 1979). Thus the chemical properties and volume of vaginal fluid, as well as the chemical properties of vaginal mucosa are important.
- (iii) There is currently no validated method to determine bioequivalence through proxy vaginal measures. Investigators have utilized vaginal swabs, or vaginal scrapings in an attempt to determine levels of drug in vaginal tissue (Odds and McDonald, 1981). However, the body of work needed to correlate these values to clinical cure has not been performed and there is a great deal of variability in the results.
- (iv) Since efficacy of locally acting drugs (such as antifungal treatments for vulvo-vaginal candidiasis) is a combination of microbiological cure and improvement or elimination of signs and symptoms, the delivery of drug to the diseased tissue is only part of the equation. The concomitant application of an emollient formulation to the inflamed tissue, can have an impact on elimination of symptoms. Thus the overall cure rate will be affected by the type of formulation (e.g., emollient cream, emollient suppository or solid insert, with or without vulvar cream). Again, a dermatologic model may not be sufficiently sensitive to discriminate between two different vaginal formulations.
- (v) Utilizing systemic bioavailability data to predict cure of locally acting drugs suffers from other limitations. The ideal vaginal formulation would deliver high local levels of drug with minimal systemic absorption. No data correlate systemic levels with local effect. Additionally, there has recently been a question of whether vaginal administration of drug results in high levels of drug at the uterus, compared to systemic administration.

#### 1. Performance and Validation of the Skin Stripping Technique

We agree with the guidance statement that, "*DPK studies should include validation of both analytical methods and the technique of skin stripping.*", and support many of the recommendations made in this section regarding "*....considerations for performing the skin stripping technique.*" However in addition to some of the considerations outlined, we have demonstrated that there are numerous other issues that need to be addressed in the validation of the tape stripping procedure. The results of these studies were originally presented at the *AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms - Methods for Evaluation of Bioequivalence* (September, 1996) and at the March 19, 1998 DODAC Public meeting.

In brief, these studies examined some of the parameters that may be important in the validation of the tape stripping assay, and determined how methodological issues in this technique may affect the pharmacokinetic analysis. These investigations revealed that even under rigorously controlled conditions, the process of applying and removing the tape strips leads to wide inter-subject and intra-subject variability in the amount of stratum corneum that is recovered. This variability is due to several factors: inherent variability in individual skin type and variability in stratum corneum thickness at different anatomical sites of a given individual, inherent variability in the application and removal of the tape by different "operators", and variability related to the tape selected and environmental conditions. It is clear that such variability would only be increased in skin stripping studies conducted in a multi-center fashion.

This variability in tissue recovery has important implications in the pharmacokinetic analysis of the data obtained using this method. Unlike concentrations in the blood stream, drug content in the stratum corneum is not homogeneous, but rather forms a gradient through the skin. When a standard number of tapes are removed, one does not know what percentage of the stratum corneum tissue (and drug) has been recovered in the tapes. For some individuals it may be 25%, while for others it may be 2 or 3 times that amount. In order to do pharmacokinetic analysis, the amount of drug would have to be standardized or normalized in order to construct a meaningful concentration vs. time plot. Expressing the data in amount of drug per mg of stratum corneum tissue, as is suggested in the draft guidance, would not take into account the varying percentage of drug that is recovered from the site. For example, if 25% of the total drug amount in the tissue is recovered in 3000 ug of tissue from one site, we cannot assume that 50% is recovered in 6000 ug of tissue from another site because of the lack of homogeneity in the stratum corneum sample. The effect of the unknown recovery on the concentration vs. time plot is to distort the shape of the plot. Without an accurate measure of drug concentration, no meaningful information on the rate and extent of absorption can be obtained from the pharmacokinetic plot.

The results of this study are consistent with the results of work presented by Dr. S. P. Shrivastava entitled "Validation of DPK Methods and Standardization of Bioequivalence Protocol." at the aforementioned *AAPS Workshop on Bioequivalence of Topical Dermatological Dosage Forms - Methods for Evaluation of Bioequivalence* (September, 1996). In this study, conducted with multiple concentrations of tretinoin products (0.025 - 1.0%), inter-subject and inter-site variation in amount of tretinoin recovered was high. For example, there was a 7 fold (650%) difference in drug recovered in one subject from one site on the forearm to another (exact site not specified). The importance of a single person or "operator" doing the application and removal of the tape was highlighted by the finding that the profiles attained with a dose of 0.05% by one technician were similar to that obtained by another technician with the 0.025% dose. Based on this data obtained with topical tretinoin formulations, it was concluded that the following were "critical considerations in the standardization of a bioequivalence protocol":

- *Stability of drug under testing and sample storage conditions should be determined.*
- *Number of tape strips required to remove excess drug should be determined.*
- *Number of tape strips required to remove over 85% of drug from stratum corneum should be determined.*
- *Drug application, excess drug removal, and drug desorption procedures should be validated.*
- *Drug amount-time profiles should be plotted. A standardized unit, e.g. ug/sq cm should be adopted.*
- *DPK parameters including LAUCs, LCmax (ss), Tmax (ss), T-half, etc should be calculated.*

As suggested above, one answer to the variability in drug recovery noted above may be to strip the entire stratum corneum, thereby assuring 100% removal of the drug, or at least 85% as recommended at the 1996 Workshop. In this scenario the amount of skin recovered would not be relevant. However the tape stripping process is a mildly invasive one and the amount of discomfort increases as one penetrates deeper into the stratum corneum. As presented at the March 19, 1998 DODAC Advisory Committee meeting by Dr. Latriano of Johnson & Johnson, a photograph (see **Appendix B** of this response) of sites of the forearm from several subjects shows that after the skin is stripped, there may be some redness in the area, which, after a period of time becomes hyperpigmented; in some subjects this hyperpigmentation can last for weeks or months. This further limits the feasibility of DPK methodology.

### Pilot Study

The recommendations in the pilot protocol as to number of subjects, sites, timepoints, etc. have not been shown to address the above considerations. The pilot protocol also suggests the establishment of a dose-response relationship using a "simple drug solution" to show the method is validated for use with the drug product. Due to the very different types of release that may be expected with a solution vs. a more complicated drug formulation, Section III B of the Guidance indicates that a "*topical solution drug product should be considered independently.*" This is supported by published results indicating "*However, use of the dilution methods to create a dose-response has the inherent danger of altering the physicochemical parameters of that drug in the vehicle, which may alter drug release from the vehicle, drug uptake into the stratum corneum, and the drug activity in the skin (Pershing, et al, 1994).*" We agree that these two types of products have different characteristics and feel it is inappropriate to suggest that the results obtained with a drug in solution should be presumed valid for a semisolid preparation.

## 2. DPK Bioequivalence Protocol

### a. Protocol and Subject Selection

The protocol calls for using healthy volunteers. It has been amply demonstrated that topical drug absorption and distribution is different in healthy vs. diseased skin (Wester and Maibach, 1992). Although using healthy subjects might be appropriate for oral BE studies, where the factors that determine rate and extent of absorption may not be affected by the diseased state, this is not true for percutaneous absorption. The stratum corneum is a major barrier for absorption of many topical products and whether the stratum corneum is impaired will have a major effect on the rate and extent of absorption of topical dermatological products that may not be captured using healthy skin. Also to be considered in subject selection is the age, gender, and skin type of the subjects. These and other variables have been shown to affect the amount of stratum corneum removed during the tape stripping process (Reed, Ghadially and Elias, 1995; Kompaore et al, 1993).

b. Application and Removal of Test and Reference Products

We agree that an SOP must be developed and validated on the application and removal of test product, as this procedure has a large influence on the reproducibility of the study (**Appendix B**). The recommendation calls for removal of "certain oily preparations such as ointments" by "washing with a mild soap". It has been shown for a lipophilic pesticide (alachlor) that the addition of soap reverses the partitioning of this compound into the stratum corneum (Wester and Maibach, 1992). Any procedure involved in the removal of test product needs to be validated to show that only excess drug at the stratum corneum surface is being removed and that the procedure does not affect drug concentrations in the stratum corneum.

c. Sites and Duration of Application

The recommendations in this section do not address the intra- and inter-subject variation in the amount of skin removed during the tape stripping process. Based on the data shown in **Appendix B**, the intra-subject variability, whether from one site to another, or from one arm to the contralateral arm, may be considerable and cannot be predicted. Also, from the data presented in **Appendix B**, the variability in the amount of skin collected (and therefore in drug concentration) is not due to biological variation, but from variation in the recovery of the drug from the skin. This variation in tissue recovery affects the reproducibility and accuracy of the measurement of drug concentration, and cannot be eliminated by randomization of the sample sites.

d. Collection of Sample  
and

e. Procedure for Skin Stripping

No information supporting the validation of the skin stripping procedure and the sample collection scheme has been presented. No data has been shown that supports the premise that all excess drug is removed in the first one or two strips. The data presented in **Appendix B** indicated that with 10-12 tape strips only a small fraction of stratum corneum tissue is removed. This data also show that the amount of stratum corneum removed with 10-12 strips can vary tremendously from person-to-person and site-to-site. The data in the attached study is consistent with published data where it was shown that after stripping with ten strips of 3M Tape the amount of stratum corneum removed can range from approximately <5% - 30% (Van Der Valk and Maibach, 1990). In order to recover >85% of the stratum corneum tissue (as recommended at the 1996 DPK workshop), one needs to reach the point of barrier disruption, which can require 30-67 tape strips, depending on the subject's skin type (Reed, Ghadially and Elias, 1995). In addition, the vehicle affects the stripping properties of the skin and it has been concluded that "the effect of vehicle treatment on stripping properties precludes one from determining drug and vehicle concentration gradients in the stratum corneum at different treatment times by direct comparison of corresponding strips." (Tsai, et al, 1991).

The important question of normalization of the amount of skin obtained has not been addressed. The Draft Guidance calls for expressing the data in amounts/area. As a standardized area is being used, the denominator of area falls out of the equation, so this approach does not address this issue. We concur with the recommendations made by Dr. Shrivastava that at least 85% of the drug should be recovered. As indicated above, this would require >24 strips as used in the validation study presented in Appendix B. Removing that amount of stratum corneum produces a post-inflammatory response, which may be followed by hyperpigmentation of the area as shown in the photograph in Appendix B. We therefore question the statements that this technique is "minimally invasive".

### 3. Metrics And Statistical Analyses

No data has been presented that shows which are the appropriate metrics upon which to base a BE determination for topical products. No discussion around the criteria for BE has been made to determine whether the statistical criteria put forward has a relevance to clinical outcome, or in our ability to determine a formulation that may be predicted to be bioequivalent, but which fails in the clinic.

#### C. Pharmacodynamic Approaches

The Draft Guidance suggests a pharmacodynamic approach to establish bioequivalence may be acceptable. Specifically the guidance states that "*Topically applied retinoid produces transepidermal water loss that may be used as a pharmacodynamic measure to assess BA/BE.*"

This approach to establishing BE for retinoids, in particular for tretinoin, was addressed at a FDA Advisory Committee on September 13, 1994. At this meeting Gary Grove, Ph.D, presented to the Committee the results of a study conducted at the K.G.L. Skin Study Center that demonstrated that transepidermal water loss (TEWL) is an accepted measure of irritancy potential, but that irritation was not a reliable predictor of efficacy. This conclusion was based on a facial tolerance study that compared 0.1% RETIN-A<sup>®</sup> Cream to an experimental 0.1% aqueous gel formulation. In this study a bilateral, paired comparison between left and right side of the face in 25 volunteers, selected for sensitive skin, was made after 14 days of treatment. At the end of the treatment period, the TEWL value for the subjects treated with 0.1% RETIN-A cream was 30.8 g/m<sup>2</sup> compared to 22.0 g/m<sup>2</sup> for the subjects treated with the experimental 0.1% aqueous gel. This is in contrast to the placebo-controlled clinical studies with these two formulations (conducted separately), in which there was a similar percentage of subjects improved (reduction in overall lesion count) relative to the placebo.

Transepidermal water loss measurements were also used by Penederm to compare their tretinoin formulation (Avita<sup>™</sup>) to RETIN-A (Penederm Summary Basis of Approval - Page 39-40 of Biopharmaceutics Review for NDA 20-404). In these studies, Penederm compared their product to RETIN-A at the same strengths in the same type of formulation (i.e. cream and gel products). Although the two different Penederm formulations gave identical TEWL values when compared head-to-head to their Retin-A counterpart, in a clinical bioequivalence study of these Penederm products vs. RETIN-A, it was demonstrated that only the Penederm cream product was bioequivalent to the innovator. These results clearly indicate the inability of TEWL measurements to distinguish between two formulations that had different clinical outcomes.

These findings are consistent with others that support the inability of TEWL measurements to distinguish between compounds as well as formulations. In a study entitled "Functional Changes in Human Stratum Corneum Induced by Topical Glycolic Acid: Comparison with All-trans Retinoic Acid" (Effendy, et al, 1995), it was found that the plot of TEWL values over the eleven days of treatment with 12% glycolic acid in water was superimposable over the plot of obtained with 0.1% retinoic acid in ethanol. From this data one can conclude that these two compounds have a similar ability to alter the stratum corneum and that TEWL, as a measure of stratum corneum integrity, was unable to distinguish between them.

#### **D. In Vitro Release Approaches (Lower Strength)**

This current Draft Guidance ignores the following points of consensus which were reached in the *Workshop on the Assessment of Value and Applications Of In-Vitro Testing of Topical Dermatological Drug Products* (September, 1997):

- "The release test is not a surrogate test for bioavailability nor bioequivalence and should only be used as supportive evidence in such evaluations."
- "The in vitro release test is of no use for comparing fundamentally different formulations (ointments vs: creams, etc.)."
- "In vitro release is formulation dependent and therefore should not even be used in comparisons of similar formulations made by different manufacturers. Rather, the meaningful use of the release test is for showing that the fundamental properties of a formulation of given content and manufacturing method have essentially been maintained following a SUPAC-SS-defined level 1 or level 2 change in the formulation."
- "There is no universal release testing procedure and no universal test conditions which are applicable to all dosage forms. Rather, the release test must be tailored to individual drug delivery formulations."

Again, since that meeting, where a clear consensus was reached, we are unaware of any new, valid, substantial scientifically accepted data generated to refute these issues.

Within the proposed Draft Guidance it is stated that it is possible that the release rates from the test formulations are slower or faster than those of the reference formulations. The only criteria that the formulations are expected to meet is that the ratios of their release rates are similar at a given concentration. The Draft Guidance also assumes that the physical form of the drug remains constant at varying concentrations. However, it is also possible that drug in a test formulation may exist as suspended solid and in a saturated solution at higher strength, while at the lower strength, the drug may exist only in solution. The theoretical basis for release kinetics would be different and a valid comparison could not be made between high and low strength versions.

Given the possibility that the physical form of the active ingredient may differ from one strength to another, and may exhibit different release profiles, then the current Draft Guidance is inconsistent with the SUPAC-SS Guidance due to the possible effect an excipient may have on release rate. The SUPAC-SS Guidance states that if there is a change in the amount of any excipient >10% (of that present in the marketed product), then this Level 3 change would require a bioequivalence study to be conducted. The current Draft Guideline would allow a company who had demonstrated bioequivalence with a 0.1% formulation to obtain a waiver for a 0.05% or 0.025% product. This would mean a change in the active ingredient of 200-300% would be essentially deemed equivalent to a Level 1 and Level 2 SUPAC change (no bioequivalence study required). As indicated in the consensus statement above, this was not an intended use for in vitro release.

As indicated in the current Draft Guidance there is also no expectation that the innovator and generic will have similar release profiles. The only criteria would be to show similar ratios at different strengths. This criteria can result in the following clinical outcomes: If the generic formulation releases at a lower rate (the example cited in the Draft Guidance) than although it may have shown bioequivalence at the highest strength, it may fail to be clinically effective at the low strength. This is because the lower release may result in drug concentrations too low to be considered clinically effective. If the DPK test alone were sufficient to establish BE; in the instance where the generic has a faster release rate than the innovator, and efficacy was demonstrated at the high dose, the higher drug concentrations that may be produced by the generic may produce a safety problem that was not observed with the innovator. Since classic in vivo clinical BE testing would no longer be performed, the Agency would not be able to monitor adverse events in a clinical setting and may therefore fail to identify a product that has a significantly different safety profile.

#### Section V. IN VITRO RELEASE: EXTENSION OF THE METHODOLOGY

This section includes a statement that "*With suitable validation, in vitro release may be used to assess batch-to-batch quality...*" This statement does not agree with the consensus reached at the aforementioned September 8-10, 1997 AAPS/FDA Workshop which states "*Though it provides an indication of the sameness, or lack thereof, of different batches of a given semisolid product, the release test does not appear to be sufficiently discriminating to function as the sole measure or even the principal measure of batch-to batch product consonance.*"

Furthermore, for semisolids where the drug is completely in solution, the Workshop concluded, "*While the theoretical principles associated with release testing of semisolid suspensions (drugs in suspension) are well established, more work is needed to reach the same level of understanding of semisolids which have their drugs completely in solution.*"

With these comments in mind, it is hard to envision, without substantial new supportive data, extending the applicability of In Vitro Release methodology.

## Section VI. SYSTEMIC EXPOSURE STUDIES

The DPK approach proposes only to measure target site concentrations indirectly by assessing stratum corneum concentrations. This approach does not take into account systemic exposure, which, for topical products, is an assessment of a product's safety. The importance of the safety assessment for formulations of existing products that are not equivalent in terms of Q<sub>1</sub> and Q<sub>2</sub> is demonstrated by routine expectation from the Division of Dermatological and Dental Drug Products (DDDDP) that percutaneous absorption studies would be conducted to support NDA approval. We feel that without an assessment of the safety of a new formulation there can be no true "risk/benefit" assessment for generic comparator drugs. Therefore, it is appropriate to expect generic formulations to meet similar criteria in this regard.

### 4. CONCLUSION

Johnson & Johnson supports the Food and Drug Administration initiative to determine viable approaches to establishing bioequivalence for topical dermatological drug products, and applauds the efforts put into preparing this draft guidance. However, we also believe it to be imperative that all interested parties view any proposed methodology as scientifically valid and robust.

Although we agree that DPK is conceptually a good methodology for supplementing data to determine topical bioequivalence, serious limitations in implementation have been raised by practicing dermatologists, and the academic, industrial, and government scientific community, which we feel have not been adequately addressed by the available data.

Similarly, despite numerous recent workshops in which In Vitro release methodology has been shown by consensus to be applicable, both as a research tool and as a means of assuring product sameness within SUPAC-SS, this draft guidance elevates its usefulness to other applications that are not supported scientifically.

At this time therefore, we respectfully feel that the guidance, although a good initial step, has flaws which would make it invalid for adoption. We are anxious and willing to partner with FDA and other relevant scientific bodies to investigate these and other alternate methodologies further, to achieve a final document that can be acceptable to all concerned.

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