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VIA HAND DELIVERY

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Re: Citizen Petition Requesting FDA Not to Approve any ANDA for a Generic Version of Efudex® that Does Not Include Data from a Comparative Clinical Study Conducted in Patients with Superficial Basal Cell Carcinoma
Docket No. 2004P-0557/CP1

Rothwell, Figg, Ernst & Manbeck ("Rothwell Figg") submits this response to the April 3, 2006 Reply Comment of Valeant Pharmaceuticals International ("Valeant").

I. RESPONSE TO PATHOLOGY DISCUSSION IN VALEANT'S REPLY COMMENT

Valeant disagrees with Dr. Franz's assertion that "if bioequivalence is demonstrated for a disease in the upper epidermis it will have been demonstrated for a disease in the lower epidermis" because "Dr. Franz's position rests upon the mistaken premise that such products are necessarily 'virtually identical in composition.'" Valeant Reply Comment at 4. According to Valeant, "two fluorouracil products, formulated to be Q1/Q2 equivalent, may nonetheless have differences in particle size and distribution that may cause the products to release different amounts of active ingredient at different rates and to different extents." Valeant Reply Comment at 4. Valeant ignores the fact that if there were differences in product composition, particle size, or distribution, then the movement through the stratum corneum would be expected to be different. As Valeant correctly points out, "the stratum corneum is considered the predominant barrier to topical drug delivery." December 21, 2004 Valeant Petition. Therefore, if there were significant differences between products, then products would not be bioequivalent based on measurements taken in the mid epidermis, *i.e.*, the squamous layer of the epidermis. Thus, if the reference product and the ANDA product have already been found to be bioequivalent based on measurements in the upper and mid epidermis, then they will also be bioequivalent in the lower epidermis. An AK study in the mid dermis would not be bioequivalent if differences in penetration existed. Once an AK study does show bioequivalence in the upper and mid dermis

2004P-0557

C3

Division of Dockets Management
Food and Drug Administration
May 5, 2006
Page 2

which is the squamous layer (stratum spinosum), it will also be bioequivalent in the lower epidermis. This argument is supported by Dr. Franz:

If bioequivalence is demonstrated for a dermal disease, it will also have been demonstrated for an epidermal disease, and vice versa. Likewise, if bioequivalence is demonstrated for a disease in the upper epidermis it will have been demonstrated for a disease in the lower epidermis.

Drug movement through the skin is driven by that gradient, as governed by the laws of diffusion.

Valeant in its December 21, 2004 Citizen Petition on page 1 states that "sBCC occurs in the stratum basale, the deepest sublayer of the epidermis. AK, by contrast, occurs in the more superficial stratum spinosum." We submit that the epidermis is one pharmacologic site of action as dictated by Fick's Laws of Diffusion. In addition, any sBCC which extends into the dermis would be treated by drugs which are bioequivalent in the epidermis, as explained above by Dr. Franz.

Valeant submitted the declaration of Dr. Khanh P. Tran, M.D. in support of its argument that actinic keratosis ("AK") and superficial basal cell carcinoma ("sBCC") occur at different sites of drug action. Valeant Reply Comment at 3. The debate as to the extent to which sBCC infiltrates into the dermis is not important because if the drug is bioequivalent in the mid epidermis, it will be bioequivalent in the lower epidermis and dermis because of Fick's Laws of Diffusion. A discussion of the laws of diffusion in the epidermis and dermis is described in Section II, below.

II. THE LAWS OF DIFFUSION IN THE EPIDERMIS AND DERMIS

Formulation differences between two products only affect their movement through the stratum corneum. However, once the products are in the epidermis, the molecules continue to diffuse into the lower epidermis and dermis according to Fick's Laws of Diffusion. In "Strategies for Skin Penetration Enhancement," Rolf Daniels explains the laws of diffusion and how they relate to the skin:

Considering that the skin is such a heterogeneous membrane, it is surprising that simple diffusion laws can be used to describe the transport through the skin.

For steady-state conditions, this can be described with Fick's first law of diffusion:

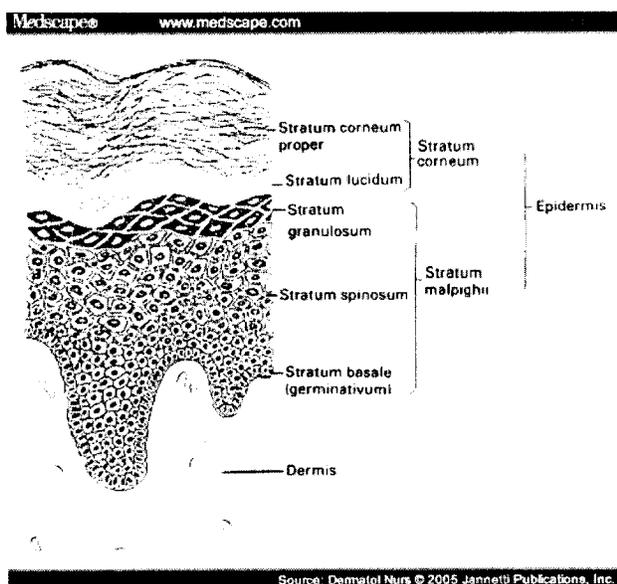
$$J = \frac{KD}{h}(c_0 - c_i)$$

Where J is the flux per unit area, K is the stratum corneum-formulation partition coefficient of the active, and D is its diffusion coefficient in the stratum corneum of the thickness h; c_0 is the concentration of active substance applied to the skin surface, and c_i is its concentration inside the skin.

A copy of the Daniels article from the Skin Forum Society for Dermopharmacy is provided in Appendix 1. Therefore, a product that is bioequivalent for AK in the upper or mid epidermis, will also be bioequivalent for sBCC in the lower epidermis or upper dermis according to Fick's Laws of Diffusion.

III. PATHOLOGY OF THE SKIN: KERATINOCYTES FROM THE BASAL LAYER OF THE EPIDERMIS BECOME KERATINOCYTES IN THE SQUAMOUS LAYER OF THE EPIDERMIS

The keratinocytes of the squamous cell layer are actually the same cell type as the keratinocytes in the basal cell layer. The stratum corneum, epidermis, and dermis are illustrated below:



Division of Dockets Management
Food and Drug Administration
May 5, 2006
Page 4

The keratinocytes from the basal cell layer move up through the epidermis into the squamous cell layer gradually changing shape but not changing cell type. W.M. Sams and P. Lynch, Principles and Practice of Dermatology 5 (Churchill Livingstone 1990) ("A daughter cell from the basal layer moves upward through the squamous cell layer as an individual"). A copy of an excerpt from this text is provided in Appendix 2. Even though these layers have different names, it is important to recognize that they are composed of the same cell type. This means that there is a continuum of the same cell type from the mid to the lower epidermis. Therefore, because Fick's laws of diffusion apply, if bioequivalence is demonstrated in the mid or upper epidermis, then it has also been demonstrated in the lower epidermis.

IV. THE FDA DOES NOT REQUIRE THAT THE APPLICANT DEMONSTRATE BIOEQUIVALENCE IN THE MOST DIFFICULT TO TREAT CONDITION AND DOES NOT REQUIRE THE APPLICANT TO DEMONSTRATE BIOEQUIVALENCE IN EACH INDICATION

Valeant argues that an ANDA for a generic version of Efudex® must be supported by a comparative clinical study in patients with sBCC. Valeant Reply Comment at 1. The Agency has the discretion to decide whether a bioequivalence study in AK is most appropriate, or whether it is instead appropriate to study bioequivalence in either AK or sBCC, provided that the protocol is reviewed and approved by the Agency. In the alternative, the Agency can decide to recommend that a study be performed in the condition in which the drug product is most commonly used by patients when use is overwhelming in one condition over the other.

V. SUMMARY OF ROTHWELL FIGG'S ARGUMENTS IN SUPPORT OF DENIAL OF VALEANT'S CITIZEN PETITION

Rothwell Figg has demonstrated that the Valeant petition requesting that the FDA require ANDAs for generic versions of Efudex® to perform comparative clinical endpoint studies in patients with sBCC as a condition for approval should be denied for at least the following reasons:

- Valeant has not come forward with any evidence to support its claim that a generic drug product that is approved based on bioequivalence studies in AK, will not be safe and effective in the treatment of sBCC. Rothwell Figg January 3, 2006 Response at 3-4. Its submissions contain nothing more than speculation on this point.
- Neither the FDA statute nor its implementing regulations require an applicant to submit studies for each indication. The statute merely requires that applicants demonstrate bioequivalence, but it does not prescribe the precise methodology or standards to be used by FDA to assure bioequivalence. The FDA has the discretion to determine the

appropriate bioequivalence standards based on the characteristics and approved uses of the product. Rothwell Figg September 16, 2005 Comments at 3-4.

- As previously demonstrated, there is no evidence that sBCC is truly the more difficult to treat condition. See discussion in Rothwell Figg September 16, 2005 Comments at 7.
- Moreover, the Agency does not always require bioequivalency studies in the most difficult to treat condition. Quite to the contrary, the FDA exercises its scientific discretion on a case-by-case basis. In its May, 22, 2002 response to a petition filed with regard to ammonium lactate, the FDA explained:

Generally, bioequivalence testing for topical products using clinical studies with clinical endpoints relies on a single study in one indication, usually the one that is most difficult to treat. If the generic drug product is shown to be bioequivalent for one indication, it is expected to be bioequivalent for all related indications with the same site of action.

(emphasis added). Thus, the Agency has stated that it will usually require such studies, not that it will always require such studies. Rothwell Figg January 3, 2006 Response at 5-6. The FDA has therefore made clear in prior cases that it will exercise its scientific judgment on a case-by-case basis to determine the disease states that are to be the subject of such studies.

- Agency discretion includes consideration of factors such as the sensitivity and reliability of the study and the difficulty of demonstrating bioequivalence in the study. In this case, an AK bioequivalency study would be more sensitive and reliable than a sBCC study, and therefore it could be more difficult to demonstrate bioequivalence in an AK study. Rothwell Figg January 3, 2006 Response at 5-7.
- The site of action is a moot point because once bioequivalence is demonstrated in the upper and mid epidermis in an AK study, then pursuant to Fick's Laws of Diffusion it will also be proven for sBCC in the lower epidermis or upper dermis. May 5, 2006 Rothwell Figg Response at 1-3.
- The cells in the squamous and basal layers are of the same cell type, so there is a continuum of the same cell type as one transitions from the mid to the lower epidermis. This provides further support for the conclusion that if bioequivalence is proven in the upper or mid epidermis, then it will also have been proven in the lower epidermis. May 5, 2006 Rothwell Figg Response at 3-4.

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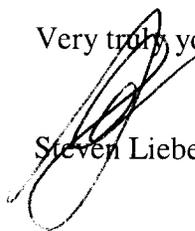
Food and Drug Administration

May 5, 2006

Page 6

- For every one patient who uses Efudex® to treat sBCC, sixty patients use Efudex® to treat AK. Rothwell Figg September 16, 2005 Comments at 1.

Very truly yours,



Steven Lieberman

Enclosures