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January 3, 2006

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 October 21, 2005 reply comments of Valeant Pharmaceuticals International ("Valeant").

Valeant's citizen petition asks the FDA to require companies filing abbreviated new drug applications ("ANDAs") for generic versions of Efudex® (fluorouracil) Cream to either (1) submit bioequivalency studies in both actinic keratosis ("AK") and superficial basal cell carcinoma ("sBCC"); or (2) submit bioequivalency studies in the more difficult to treat condition, which Valeant argues is sBCC.

In its September 16, 2005 comments, Rothwell Figg asked the FDA to deny Valeant's citizen petition and approve ANDAs for generic versions of Efudex® Cream that include bioequivalency studies in AK because (1) both AK and sBCC occur at the "same site of action;" (2) for every sixty-one Efudex Cream prescriptions written, sixty are for AK and only one is for sBCC; and (3) the FDA has the discretion to determine which indication can be used to show bioequivalence.

In its October 21, 2005 reply comments, Valeant misrepresents the scientific literature and Agency precedent. Valeant's reply comments also rely heavily on the Declaration of Howard I. Maibach, M.D. ("Maibach Declaration"). The more general issues discussed in paragraphs 13-14 and 16-17 of the Maibach Declaration have previously been considered by the Agency at length for other topical drugs and their pertinence to this drug will be evaluated during the routine technical review of ANDAs for generic versions of Efudex® Cream. The formulation-

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specific issues raised in paragraphs 18-22 will likewise be evaluated during the routine technical review process.

The FDA should deny Valeant's citizen petition for the following additional reasons.

First, the efficacy of a topical drug product is a function of the release of the drug product, not the condition being treated. In this case, the same active ingredient is being released at the same site of action; therefore, the same concentration of active ingredient will be available regardless of the condition being treated. This fundamental point is supported by Dr. Thomas Franz, who has extensive experience and knowledge of the behavior of topical drug products in the skin. In Dr. Franz's expert opinion, "if bioequivalence is demonstrated for a disease in the upper epidermis it will have been demonstrated for a disease in the lower epidermis." Dr. Franz's opinion and *curriculum vitae* are attached in Appendix 1. See Section I, below.

Second, both AK and sBCC occur at the same site of action -- the epidermis. Valeant's argument that sBCC grow downward flies in the face of the published scientific literature, which explains that an sBCC that grows downward becomes an invasive BCC and is no longer considered an sBCC. Moreover, Valeant's Efudex® Cream is only approved for sBCC and its label warns: "[d]iagnosis should be established prior to treatment, since this method has not been proven effective in *other* types of basal cell carcinoma." (emphasis added). See Section III, below.

Third, Valeant has not come forward with a scintilla of evidence to support its claim that a generic drug product that is approved based on bioequivalency studies in AK will not be safe and effective in the treatment of sBCC. See Section II, below.

Fourth, bioequivalency studies in the more difficult to treat condition are not *always* required. This decision is made on a case-by-case basis at the discretion of the FDA. This Agency discretion will include consideration of additional important factors, such as the sensitivity and reliability of the study and the difficulty of demonstrating bioequivalency in the study. Dr. Dale Conner, the Director of the Division of Bioequivalence in the Office of Generic Drugs, has stated at public scientific meetings that drugs with very high clinical efficacy do not differentiate between two products as well as drugs with lower efficacy. The success or cure rate is lower for AK (84-88%) than for sBCC (93%). This means that an AK bioequivalency study would be more sensitive and reliable than an sBCC study, and therefore it could be more difficult to demonstrate bioequivalence in an AK study. See Section IV, below.

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I. THE EFFICACY OF A TOPICAL DRUG PRODUCT IS A FUNCTION OF THE RELEASE OF THE DRUG PRODUCT – NOT THE CONDITION BEING TREATED

Valeant argues that “there is no sound scientific basis for concluding that two fluorouracil cream products that perform similarly in patients with AK will perform similarly in the treatment of sBCC.” Valeant reply comments at 1. Dr. Thomas Franz has over 35 years of clinical research experience and has made numerous noteworthy contributions to the study of topical drug release. A copy of Dr. Franz’s opinion and *curriculum vitae* are provided in Appendix 1. In Dr. Franz’s expert opinion based upon principles of percutaneous absorption and the laws of diffusion, if a topical drug product is shown to be bioequivalent to the innovator for one skin disease, it will be bioequivalent for a second skin disease. In other words, the efficacy of two drug products is based on the release of the drug substance from the drug product – not the condition being treated.

When two drug products release the same active ingredient, at the same site of action, at a comparable rate, the same concentration of active ingredient will be available regardless of the particular condition being treated. Therefore, there is *no sound scientific basis to conclude that two fluorouracil cream products will not perform with the same effectiveness in both AK and sBCC.*

First, both AK and sBCC exist in the same site of action – the epidermis. The epidermis is an extremely thin structure (.05 to .15 mm). *Second*, the drug products will be released at comparable rates. As acknowledged in the December 21, 2004 Valeant citizen petition (page 4), the stratum corneum is the primary barrier for penetration by topical drug products. Once the topical drug products penetrate the stratum corneum to the epidermis at the same rate and to the same extent, there will be not be any difference in effect of the two products. *Therefore, the drug will be equally effective in the two conditions once it is within the epidermis, whether in the upper or lower epidermis.* In Dr. Franz’s expert opinion, “if bioequivalence is demonstrated for a disease in the upper epidermis it will have been demonstrated for a disease in the lower epidermis.” (Appendix 1).

II. VALEANT HAS NOT IDENTIFIED ANY EVIDENCE THAT A GENERIC PRODUCT APPROVED BASED UPON AK BIOEQUIVALENCY STUDIES WILL NOT BE SAFE AND EFFECTIVE IN PATIENTS WITH sBCC

Valeant argues that the “safety and efficacy” of a generic version of Efudex® Cream that is prescribed to sBCC patients is “critically important” (Valeant reply comments at 2); however, Valeant fails to identify even one iota of evidence that a generic version of Efudex® Cream approved on the basis of AK bioequivalency studies would not be safe or effective for sBCC.

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Presumably, if Valeant had such evidence it would have included it in its reply comments or asked its expert, Dr. Maibach, to opine about it.

III. AK AND sBCC OCCUR AT THE SAME SITE OF DRUG ACTION – THE EPIDERMIS

Valeant challenges Rothwell Figg's assertion that sBCC grow upward into the same layer of the epidermis in which AK occurs (Rothwell Figg comments at 5-7), arguing that sBCC "routinely grows downward into the papillary dermis, not upward" (Valeant reply comments at 4).

First, Valeant's argument is contradicted by a primary text book of dermatology, which explains that "[t]he peripheral cell layer of the [sBCC] tumor formations often show palisading. In most cases, there is *little* penetration into the dermis." Walter F. Lever, Lever's Histopathology of the Skin 569 (J.B. Lippincott 1983) (emphasis added). In other words, sBCC generally grow upward, not downward into the dermis, as incorrectly stated by Valeant. Thus, Dr. Maibach's statement that "AK tends to be more superficial and occurs within an upper level of the epidermis, while sBCC tends to occur within a deeper area of the skin" (Maibach Dec. ¶23) is also incorrect.

Dr. Maibach's statement that "AK remains in the upper epidermis and does not exhibit this growth pattern" is contradicted by Cockrell (Valeant reply comments, tab 7) – a reference cited by him in paragraph 26 of his declaration. Figure 1 in the Cockrell reference illustrates the presence of AK in the lower epidermis. C.J. Cockrell, "Histopathology of Incipient Intraepidermal Squamous Cell Carcinoma ('Actinic Keratosis')," *J. Am. Acad. Dermatol.* 42:S11-17, 2000 ("Fig. 1. Photomicrograph of solar (actinic) keratosis (KIN II). There is proliferation of atypical keratinocytes involving the *lower* portion of the epidermis.") (emphasis added). Thus, even if the lower and upper epidermis are considered separate sites of action – which they are not -- both AK and sBCC can be found in the lower epidermis and are therefore found at the same site of action.

Second, if Valeant were correct and sBCC grew downward into the dermis, then they would no longer be sBCC (superficial BCC), but would become invasive BCC. Valeant, however, has only received approval for use of its Efudex® Cream for sBCC -- *not* for any other type of BCC, such as invasive BCC. Valeant cannot have it both ways. Either sBCC grow upward into the same layer where AK is found (which means that both conditions occur at the same site) or they grow downward and are no longer sBCC (conditions for which Valeant does not have FDA approval).

Valeant also misrepresents the discussion of pathology in "Actinic Keratosis and Non-Melanoma Skin Cancer" (Appendix 4), incorrectly stating that it supports Valeant's argument that sBCC

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grow downward. Valeant reply comments at 5. Valeant provides a truncated quote from this reference; however, the full quotation pertains to nodular and infiltrative BCC – neither of which is considered a superficial BCC:

Superficial spreading BCC appears as a red, scaly, finely wrinkled plaque that may be confused with dermatitis (Figure 5 and Figure 6). The typical *nodular BCC* is a shiny or pearly, translucent papule with overlying telangiectases and rolled borders (Figure 7). Because the center often outgrows its blood supply, there may be a central, depressed ulcer with or without overlying hemorrhagic crust (Figure 8 and Figure 9). *Infiltrative or morpheaform BCCs* often feel indurated, resemble scars, and possess histologic margins far wider than would be suspected clinically (Figure 10). *Microscopically a basal cell carcinoma is characterized by islands of intensely basophilic keratinocytes with peripheral palisading seen extending from the bottom of the epidermis or freely as islands in the dermis.* In the more infiltrative types of BCC, thin strands of atypical cells are found within scar-like collagen.

(emphasis added). The microscopic description is about nodular and infiltrative BCC, not sBCC. Therefore, this reference does not support Valeant's argument that sBCC grow downward and that AK and sBCC do not occur at the same site.

IV. AN AK BIOEQUIVALENCY STUDY WOULD BE MORE SENSITIVE AND RELIABLE AND THEREFORE IT WOULD BE MORE DIFFICULT TO PROVE BIOEQUIVALENCY IN AN AK STUDY

Valeant's statement that "FDA already has resolved that the study should be conducted in the most difficult to treat condition for which Efudex cream is approved" is misleading. 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). *First*, the FDA has stated that it will "*usually*" require studies in the most difficult indication. The FDA has not stated that such studies are *always* required or that such studies *must* be submitted for approval. *Second*, as defined by Webster's New Collegiate Dictionary, usual is defined as "accordant with usage, custom or habit." "Usually" is not defined

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as “always” or mandatory. Thus, the FDA specifically used the term “usually” to allow appropriate agency discretion for case-by-case evaluation.

Valeant argues that sBCC is more difficult to treat than AK because the former is “a cancer that grows into the papillary dermis and is capable of invading other local tissues” and the latter is “a pre-cancerous condition that may resolve on its own.” Valeant reply comments at 6. These statements are misleading because if the BCC is invasive it is no longer classified as a sBCC, but rather a nodular or invasive BCC. While it is true that “[s]ome superficial basal cell carcinomas after having persisted as such for various lengths of time, become invasive basal cell epitheliomas” (Walter F. Lever, Lever’s Histopathology of the Skin 569), Efudex® Cream is not an approved method of treatment for invasive BCC. For this reason, the approved label for Efudex® Cream states: “[d]iagnosis should be established prior to treatment, since this method has not been proven effective in *other* types of basal cell carcinoma.” (emphasis added).

Valeant also argues that sBCC is more difficult to treat because the Efudex® Cream label recommends treatment for 10 to 12 weeks, as compared to 2 to 4 weeks for AK. Valeant reply comments at 6. Agency discretion reflected in its aforementioned use of the term “usually” lends itself to consideration of additional important factors, such as the sensitivity and reliability of the study and the difficulty of demonstrating bioequivalency in the study.

Dale Conner, Pharm.D., Director, Division of Bioequivalence, Office of Generic Drugs (“OGD”), has stated at public scientific meetings that bioequivalence determinations are more sensitive and reliable when clinical studies are designed to clearly differentiate between two drugs. Dr. Conner has demonstrated this concept using the sigmoidal dose response curve. According to Dr. Conner, drugs with very high clinical efficacy do not differentiate between two products as well as drugs with lower efficacy on the curve. (Appendix 3).

In this case, bioequivalency studies in AK, which has an 84-88% success rate, will be lower on the sigmoidal curve, compared to sBCC, which has a 93% success rate (Nancy A. Melville, “5-FU for BCC: Well Tolerated by Underused,” *Skin and Allergy News*, April 2005, at 12-13). Because the AK bioequivalency study is lower on the sigmoidal curve, an AK study would be more sensitive and reliable and therefore it could be more difficult to demonstrate bioequivalency in an AK study.

Finally, the Agency has the discretion and scientific expertise to determine the appropriate comparative studies to demonstrate bioequivalence based upon the study design and condition being treated. The overwhelming use of Efudex® Cream in AK in comparison to sBCC also supports approval of Efudex® Cream based upon bioequivalency studies in AK. For every *one* patient who uses Efudex® Cream to treat sBCC, *sixty* patients use Efudex® Cream to treat AK. See Rothwell Figg comments at 1-2.

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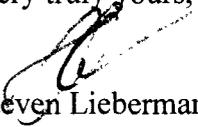
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Valeant, through its retained expert Dr. Maibach, also argues that the success rates for AK “must be viewed with ‘extreme skepticism.’” Valeant reply comments at 6. Dr. Maibach’s opinion is based upon a high inter-observer variability in one investigator’s diagnosis of the number of lesions on each study subject. Maibach Dec. ¶¶25-31. This variability can be easily addressed through clinical design enhancements and adjustments that will be critically assessed by the FDA during the ANDA review process.

V. CONCLUSION

FDA should approve ANDAs for generic versions of Efudex® Cream based upon bioequivalency studies in AK for the following reasons. *First*, both AK and sBCC occur at the same site of action – the epidermis. *Second*, the efficacy of a topical drug product is a function of the release of the drug product, not the condition being treated. *Third*, if bioequivalence is demonstrated for a disease in the upper epidermis, it will have been demonstrated for a disease in the lower epidermis. *Fourth*, sBCC grow upward into the same layer of the epidermis in which AK occurs, not downward as suggested by Valeant. Moreover, if sBCC grow downward, then they are no longer considered sBCC and Valeant’s Efudex® Cream is not approved for treatment of these types of BCC. *Fifth*, while an sBCC usually takes longer to treat than an AK, the sigmoidal dose response curve establishes that an AK bioequivalency study represents a more sensitive and reliable study than an sBCC study, and therefore it would be more difficult to demonstrate bioequivalence in an AK study.

Very truly yours,



Steven Lieberman

Enclosures

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