

October 21, 2005

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004P-0557/CP1

**Reply Comment of
Valeant Pharmaceuticals International**

On behalf of Valeant, we are writing in response to the comment submitted September 16, 2005, by Rothwell, Figg, Ernst & Manbeck ("Comment") to the above-referenced citizen petition ("Petition").

The Petition requests that any application for a generic version of Efudex® (fluorouracil) Cream contain data from a comparative clinical study in patients with superficial basal cell carcinoma ("sBCC"). The Comment argues that a study in patients with actinic keratosis ("AK") would be sufficient. According to Rothwell, Figg, a demonstration of bioequivalence in AK would constitute "scientific evidence" of bioequivalence in sBCC. Comment at 8. For the reasons discussed below, and as shown in the attached declaration of Howard I. Maibach, M.D. (attached at Tab A), the Comment is without merit.

Simply put, 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. The conditions are categorically different, with different sites of action, different growth patterns, and different recommended treatment regimens. As discussed by Dr. Maibach, comparable performance of two products in the treatment of AK does not predict – with *any* degree of scientific certainty – comparable performance in the treatment of sBCC.

Despite having had nine months to consider the issue, Rothwell, Figg was unable to locate any substantive scientific evidence to the contrary. Without

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such evidence, the authors of the Comment are simply guessing. Scientific evidence, and not guesswork, should determine the outcome of this proceeding, however. Accordingly, we urge FDA to grant the Petition as expeditiously as possible.

I. Any Generic Version of Efudex® Cream Will Be Approved for the Treatment of Both sBCC and AK

Efudex® Cream is approved for the treatment of two distinct conditions – sBCC and AK. As the Petition explains, because sBCC occurs at a different, more difficult to reach site of action, and is decidedly more difficult to treat than AK, the equivalence of a generic product must at a minimum be shown by a comparative study in patients with sBCC.

In arguing otherwise, Rothwell, Figg first states that a comparative clinical study in sBCC is unnecessary because, according to IMS data, only approximately 1% of Efudex® Cream prescriptions are for the treatment of sBCC. Comment at 1-2. The IMS data, which may or may not reflect actual patient usage, is completely irrelevant, however. Under the FDCA, a generic product must be approved for the same conditions of use, and with the same labeling, as the reference listed drug, except in cases not applicable here. 21 USC 355(j)(2)(A); *see* 21 CFR 314.94(a)(8)(iv). Accordingly, any generic version of Efudex® Cream will be labeled for the treatment of sBCC, and so must be bioequivalent in the treatment of that condition.

The implication of Rothwell, Figg's argument is that, because Efudex® Cream is prescribed far more often for the treatment of AK than sBCC, it is not important that a generic product be equally effective as the reference listed drug in treating that condition. In fact, many sBCC patients *are* prescribed Efudex® Cream to treat this form of cancer; for these patients, the safety and effectiveness of a generic product is critically important.

II. The Bioequivalence of a Generic Product Must Be Established for Each Site of Drug Action

The Comment states that generic drug applicants are not required to submit bioequivalence studies on an indication-by-indication basis. Comment at 2, 3-4. This is a true statement and – contrary to Rothwell, Figg's characterization of the Petition – Valeant does not argue otherwise. The Comment also states that FDA has discretion to determine the types of evidence that may be used to establish bioequivalence. *Id.* Again, we agree. The issue on which we disagree, however, is much more focused. Namely, where comparative clinical studies are required to

establish bioequivalence, what are the appropriate patient populations for those studies?¹

As discussed in the Petition, a generic drug applicant must show that its proposed product is “bioequivalent” to an approved “listed drug.” 21 USC 355(j)(2)(A)(iv); *see* Petition at 5-6. Bioequivalence generally means that there is no significant difference in the “bioavailability” of one product when compared with another. 21 USC 355(j)(8)(B). Bioavailability, in turn, means “the rate and extent to which the active ingredient . . . is absorbed from a drug and becomes available at the site of drug action.” *Id.* at 355(j)(8)(A)(i).

Thus, a generic drug application must contain information showing that the active ingredient in the proposed product becomes available “at the site of drug action” at the same rate and to the same extent as the reference listed drug. For a product approved for use at more than one site of action, the demonstration of bioequivalence is, potentially, more involved than for a product approved for use at a single site of action.

For systemically absorbed drugs, bioequivalence typically is assessed through valid surrogates, such as the amount of a drug measured in the blood or plasma, before it has reached any site of action. Thus, a single bioequivalence study generally is sufficient, even for products approved for use at multiple sites of action; once bioequivalence is demonstrated through the surrogate, all “downstream” effects of the drug are presumed to be the same, regardless of the specific site of action. *See* Petition at 5-6.

For non-systemically absorbed drugs, however, measurement of the amount of drug in the blood or plasma is not a valid surrogate. Rather, equivalence typically is assessed through a clinical study comparing the rate and extent to which the active ingredient becomes available at a specific site of action. *See* 21 USC 355(j)(8)(A)(ii); 21 CFR 320.24(b)(4). Thus, for a product such as Efudex® Cream, approved for use at multiple sites of action, FDA must determine whether a single study is sufficient and, if so, at which site of action and in which condition the study should be conducted.

¹ Rothwell, Figg quotes extensively from FDA’s citizen petition response to Westwood Squibb Pharmaceuticals for the proposition that a generic drug applicant is not required to submit bioequivalence studies for each of a reference listed drug’s indications. Comment at 4. The Comment ignores, however, the agency’s discussion in that same response about conducting a single bioequivalence study in the most difficult to treat condition for which a topical product is approved. *See* Petition at 11-13; *see also infra* at Section IV.

With regard to Efudex® Cream, as shown in the Petition and below, if bioequivalence is to be demonstrated through a single comparative clinical study, that study must be conducted in patients with sBCC. See Petition at 8-10. While it may be appropriate to extrapolate the results of a study in sBCC to the more superficial AK, for purposes of establishing bioequivalence, the reverse is certainly not true.

III. AK and sBCC Occur at Different Sites of Drug Action

AK and sBCC occur at different sites of drug action within the skin. Rothwell, Figg takes exception to this fact, asserting instead that “both AK and BCC are located in the epidermis” and that they should be considered to occur at the same site. Comment at 2. Rothwell, Figg also disputes Valeant’s explanation of the growth pattern of sBCC, claiming that *superficial* basal cell carcinoma grows upward into the squamous layer of the epidermis (*i.e.*, to where AK occurs), not downward into the dermis. *Id.* at 6. On both counts, the Comment is simply wrong as to the science.

As discussed in the Petition, AK is a pre-cancerous condition that occurs in the stratum spinosum, an intermediate level of the epidermis. sBCC, by contrast, is an actual malignancy that continually grows and is capable of invading local tissues. This form of cancer begins in the stratum basale, a level of the epidermis deeper than the stratum spinosum, nearer to the papillary dermis. Petition at 3-4, 9.

And sBCC routinely grows downward into the papillary dermis, not upward. See *id.* at 9-10. Valeant submitted with the Petition several chapters of the recently published textbook, *Cancer of the Skin* (2005). In the chapter on basal cell carcinoma, P.G. Lang and J.C. Maize, Sr., describe superficial BCC as follows:

Histologically, these tumors show horizontally arranged lobules of atypical basal cells in the papillary dermis that have broad-based connections with the epidermis (Fig. 9.23). All islands of basal cells contact the epidermis. Therefore, there is no downward extension into the middle or deep dermis but rather only superficial centrifugal growth typically seen. The lobules of basal cells show palisading of the peripheral basal cells as do other types of BCC. A thin fibrovascular stroma, often

with a host response of lymphocytes and histiocytes,
underlies the tumor nests.

Petition, Tab B at 109-110 (emphasis added). As noted, the chapter provides a magnified image of an sBCC tumor, showing islands of cancer cells *in the papillary dermis*. *Id.* at 110.

Even a source relied upon by Rothwell, Figg clearly acknowledges the differences between AK and sBCC. An American Academy of Dermatology article, "Actinic Keratosis and Non-Melanoma Skin Cancer" (Attachment 4 to the Comment), describes AK as characterized by "large keratinocytes with atypical nuclei *in the lower portion of the epidermis*" and sBCC as 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*" (emphases added). Dr. Maibach's declaration further supports this description of sBCC as occurring at a different site, and exhibiting a different growth pattern, than AK. Declaration at ¶ 23.

IV. sBCC is a More Difficult Condition Than AK to Treat

Recognizing that AK and sBCC occur at different sites of action within the skin, it is within FDA's discretion to develop an appropriate bioequivalence methodology. But sound science – and the FDCA – require that any methodology be capable of establishing the bioequivalence of products at both sites of action, and in the treatment of both conditions. In the event that a single study is used to make such a demonstration, FDA already has resolved that the study should be conducted in the most difficult to treat condition for which Efudex® Cream is approved. *See* Petition at 11-12.

The reason for such a requirement is that a single study must have the sensitivity to detect a significant difference in the relative performance of the tested products. Products that produce similar cure rates when tested in a less difficult to treat condition (and which would therefore appear bioequivalent) might perform very differently when tested in a more difficult to treat condition. A study in the most difficult to treat condition thus provides a greater likelihood of showing "separation" between the products. *See id.*; *see also* 21 USC 355(j)(8)(C) (any method that purports to show the bioequivalence of non-systemic drugs must be able to detect a significant difference in safety and therapeutic effect).²

² In his declaration, Dr. Maibach provides several reasons why two fluorouracil cream products containing the same active and inactive ingredients in the same quantities may nonetheless

Rothwell, Figg disputes none of this, but rather makes the remarkable argument that AK is the most difficult to treat condition for which Efudex® Cream is approved. The Comment quotes the product's labeling, approval documents, and a recent article to support the claim that while 93% of sBCC tumors may be treated successfully with Efudex® Cream, only 84% to 89% of AK lesions may be cured with the product. This, the Comment asserts, demonstrates that AK is the more difficult to treat condition. Comment at 2, 7.

Here, too, however, the Comment is wrong as a matter of science. sBCC is a cancer that grows into the papillary dermis and is capable of invading other local tissues, while AK is a pre-cancerous condition that may resolve on its own. Moreover, the approved labeling for Efudex® Cream recommends that AK be treated for only two to four weeks, while sBCC should be treated for up to 10 to 12 weeks, if not longer. Plainly, sBCC is significantly more difficult than AK to treat. See Petition at 12-13; Petition, Tab B at 122 (describing the difficulties in treating sBCC with fluorouracil cream products); Declaration at ¶23; see also R. Marks, *et al.*, *Spontaneous Remission of Solar Keratoses: The Case for Conservative Management*, *Br. J. Dermatol.* 115: 649-55, 1986 (attached at Tab B).

Additionally, as Dr. Maibach discusses in his declaration, the precise success rates cited in the Comment cannot bear the weight that Rothwell, Figg places upon them. Declaration at ¶¶ 25-31. As Dr. Maibach explains, AK studies depend upon investigators' visual diagnoses and counting of lesions, a methodology that suffers from very high inter-observer variability. In one study, for example, the minimum and maximum numbers of AK lesions found on the *same* patient by different physicians were 30 and 105, respectively. Because of this variability, the success rates in AK studies must be viewed with "extreme skepticism." *Id.* at ¶ 30. Although such studies may be sufficient for demonstrating efficacy, the success rates are not precise enough to permit a meaningful comparison of the difficulty of treating AK and sBCC.

Ultimately, because sBCC is the most difficult to treat condition for which Efudex® Cream is approved, any single, comparative clinical study to establish the bioequivalence of a generic fluorouracil cream product must be conducted in patients with that condition. In contrast, a study conducted in

perform very differently in the treatment of AK and sBCC. For example, permissible differences in the quantity, quality, purity, or source of the ingredients, or in the manufacturing process, may affect the penetration of the active ingredient to different disease sites within the skin. Declaration at ¶¶ 16-24.

patients with AK may not reveal significant differences between the tested products in treating sBCC, a different condition at a different site of action.

V. Conclusion

Because AK and sBCC occur at different sites of action within the skin, the bioequivalence of Efudex® Cream and any proposed generic version must be established for each site of action. Although a single comparative clinical study may be sufficient to meet that standard, it cannot be a study in patients with AK. Any application for a generic version of Efudex® Cream must at a minimum contain data from a comparative clinical study in patients with sBCC. Only such a study can provide assurance that the tested products will perform the same in the treatment of that condition.

Respectfully submitted,



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