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3300 Hyland Avenue
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APR 11 2008

Re: Docket No. 2004P-0557/CP1

Dear Dr. Lamon and Dr. Kricorian:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA) by Valeant Pharmaceuticals International (Valeant) on December 21, 2004 (Petition). The petition requests that FDA refrain from approving any abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) for a generic version of Efudex (fluorouracil) Cream, unless the application contains data from an adequately designed comparative clinical study conducted in patients with superficial basal cell carcinoma.[1]

Valeant submitted additional correspondence to the docket on October 21, 2005, April 3, 2006, and July 13, 2006. On November 7, 2006, Hogan & Hartson LLP submitted supplemental information on behalf of Valeant. The law firm of Rothwell, Figg, Ernst and Manbeck, P.C., submitted comments to the docket in opposition to the petition on September 16, 2005, January 3, 2006, and May 5, 2006.

We have carefully considered the issues raised in your petition, your additional correspondence, and the comments submitted to the docket. For the reasons stated below, your petition is denied.[2]

I. BACKGROUND

A. Efudex Cream

In 1970, Efudex (fluorouracil) Cream, 5%, and Solution, 2% and 5%, (NDA 16-831) were approved for the topical treatment of multiple actinic (or solar) keratoses (AK). AKs are precancerous growths in the epidermis and may protrude into the upper dermis. Rarely, AKs may progress to squamous cell carcinoma.

[1] As noted in your petition, your request also applies to any new drug application (NDA) submitted under section 505(b)(2) of the Act that references Efudex Cream for its currently approved uses. Because there are many possibilities and variations for 505(b)(2) applications that might rely on our findings of safety or effectiveness for Efudex Cream, we are unable to anticipate what we would require for each of these types of applications. Therefore, we deny the 505(b)(2) aspect of your request and we do not address it further in this response.

[2] Today, we are approving an ANDA for a generic fluorouracil cream, 5%, consistent with the analysis described in this petition response.

In 1976, we also approved Efudex Cream, 5%, and Solution, 5%, for the treatment of superficial basal cell carcinomas (sBCC) when conventional methods are impractical, such as with multiple lesions or difficult treatment sites. Like AK, basal cell carcinoma occurs in the epidermis and may protrude into the dermis. Product labeling for the sBCC indication states that "[t]he diagnosis should be established prior to treatment, since this method has not been proven effective in other types of basal cell carcinomas. With isolated, easily accessible basal cell carcinomas, surgery is preferred since success with such lesions is almost 100 [percent]. The success rate with Efudex Cream and Solution is approximately 93 [percent], based on 113 lesions in 54 patients. Twenty-five lesions treated with the solution produced 1 failure and 88 lesions treated with the cream produced 7 failures."

The importance of patient follow-up after completing treatment is emphasized under *Dosage and Administration*:

> Actinic or Solar Keratosis: "Complete healing of the lesions may not be evident for 1 to 2 months following cessation of Efudex therapy."
>
> Superficial Basal Cell Carcinomas: "As in any neoplastic condition, the patient should be followed for a reasonable period of time to determine if a cure has been obtained."

B. Statutory and Regulatory Basis for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD[3] is safe and effective. Under the Hatch-Waxman Amendments, to rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its generic[4] drug is bioequivalent to the RLD.[5] In addition, a drug product described in an

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[3] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book."

[4] For purposes of this response, the term *generic drug* refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[5] See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring "information to show that the new drug is bioequivalent to the listed drug referred to in clause (i) [i.e., listed drug]..."); 21 CFR 314.3 (defining *reference listed drug*); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug upon which the applicant relies); 21 CFR 314.127(a)(6)(i)(providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is

ANDA generally must contain the same active ingredient,[6] conditions of use,[7] route of administration, dosage form, strength,[8] and (with certain permissible differences) labeling[9] as the RLD, unless a petition for certain changes is approved by the Secretary[10] (sections 505(j)(2)(A), (j)(2)(C), and (j)(4) of the Act). Drug products that meet the approval requirements under section 505(j) and are both bioequivalent and pharmaceutically equivalent[11] to the RLD are considered by FDA to be therapeutically equivalent to the RLD. Therapeutically equivalent drugs generally may be substituted for each other with the expectation that the substituted product will produce the same clinical effect and safety profile when used according to the labeling.[12]

To obtain approval of a generic drug, an ANDA applicant must demonstrate that its proposed drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the Act). Section 505(j)(8)(B)(i) of the Act states that a generic drug is bioequivalent to the RLD if:

> . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . .[13]

In 21 CFR 320.1(e), FDA defines bioequivalence (in part) as:

> . . . the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action

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bioequivalent to the listed drug referred to in the ANDA); and the Orange Book at ix (defining *reference listed drug*).

[6] See, e.g., 21 CFR 314.94(a)(5).

[7] See, e.g., 21 CFR 314.94(a)(4).

[8] See, e.g., 21 CFR 314.94(a)(6).

[9] See, e.g., 21 CFR 314.94(a)(8).

[10] An applicant may submit an ANDA for a drug that has a different active ingredient, route of administration, dosage form, or strength from the RLD if the applicant has submitted a petition to the Agency (known as a *suitability petition*) requesting permission to file such an application and has received the Agency's approval (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).

[11] Pharmaceutically equivalent drug products have identical dosage forms that contain identical amounts of the identical active drug ingredient and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. They do not necessarily contain the same inactive ingredients and may also differ in characteristics such as shape, scoring, release mechanism, and, within certain limits, labeling (see 21 CFR 320.1 and the Orange Book, Introduction at p. vii).

[12] See Orange Book, Introduction at p.viii.

[13] See also 21 CFR 320.1(e) and 320.23(b).

> when administered at the same molar dose under similar conditions in an appropriately designed study.

Because a generic drug must contain the same active ingredient as the RLD, a showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and extent that is not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to behave the same way in the body as the RLD. One purpose of bioequivalence testing is to determine whether differences in formulation (i.e., inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action.

The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption (i.e., two solid oral dosage forms) generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single or multiple doses of each drug product to healthy volunteers. When this methodology is not appropriate, for example, because a drug product is locally acting, FDA may, as described in provisions of the Act and 21 CFR part 320, rely on other in vivo and in vitro methods to assess bioequivalence. FDA regulations describe these methods in descending order of accuracy, sensitivity, and reproducibility, including (1) in vivo pharmacodynamic effect studies, (2) clinical trials, (3) in vivo animal studies, and (4) in vitro studies.[14]

FDA generally has relied on in vivo pharmacodynamic or clinical studies to assess bioequivalence of drug products that do not produce measurable concentrations of drug or metabolite in an accessible biologic fluid. For example, for many years, FDA has used pharmacodynamic effect studies to approve generic topical corticosteroid drug products. Studies evaluating blanching or vasoconstriction of the skin microvasculature provide evidence for the amount of drug entering the skin and thus serve as the basis for comparing drug delivery from two potentially equivalent topical corticosteroid formulations.[15] With few exceptions, these products are indicated for the treatment of a broad range of conditions, i.e., for inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Some of the more responsive conditions include atopic dermatitis, seborrheic dermatitis, and lichen simplex chronicus, conditions that are characterized by epidermal and dermal involvement.[16] For these products, FDA has determined that it is not necessary to test for bioequivalence in every clinical indication.

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[14] 21 CFR 320.24.

[15] See the guidance for industry on *Topical Dermatologic Corticosteroids: In vivo bioequivalence*, available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[16] Walter F. Lever and Gundula Schaumburg-Lever (eds.). Histopathology of the Skin, 7th Edition, JB Lippincott Company, Philadelphia, 1990. Chapter 7, Noninfectious Vesicular and Bullous Diseases.

In the case of locally acting topical fluorouracil (5-FU) products, there are no pharmacodynamic endpoints that can be readily measured; hence, decisions regarding the bioequivalence of two potentially equivalent 5-FU formulations are to be based on evidence of comparative efficacy and safety in clinical trials. However, even when clinical trials are needed, it has not been the Agency's policy to require that bioequivalence be shown in every indication if drug release from the dosage form and appearance at the site or sites of activity has been demonstrated.[17] The choice of which study design to use is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug. The courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence requirements.[18]

II. DISCUSSION

Your petition makes several arguments in support of your request that FDA refrain from approving any ANDA submitted under section 505(j) of the Act for a generic version of Efudex (fluorouracil) Cream, unless the application contains data from an adequately designed comparative clinical study conducted in patients with superficial basal cell carcinoma. These arguments, and the Agency's responses, are discussed in this section of the response.

A. Comparative Clinical Studies To Demonstrate the Bioequivalence of 5-FU Products

You state that FDA "has yet to define a validated methodology by which sponsors may establish the bioequivalence of topical dermatological products [other than corticosteroids] through the use of pharmacokinetic measures." In the absence of suitable pharmacokinetic or pharmacodynamic endpoints, you argue that the sponsor of a generic topical 5-FU product must conduct at least one comparative clinical study to establish bioequivalence of its product to the RLD.[19]

The Act does not require comparative clinical studies to demonstrate bioequivalence; in fact, it gives FDA the authority to "establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect" (section 505(j)(8)(C)). Although clinical bioequivalence studies are not necessarily required for locally acting topical formulations, in the absence of pharmacodynamic endpoints, it has generally been FDA's policy to use clinical studies to evaluate bioequivalence (except for solutions). After considering the specific characteristics of Efudex, including the indications for which it is approved, we agree

[17] See, e.g., Citizen Petition Response 2003P-0140/CP1 (November 7, 2003) at 3 and Footnote 6.

[18] See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

[19] Petition at 7-8.

that a sponsor of a generic topical 5-FU cream must conduct at least one comparative clinical study to establish bioequivalence to Efudex Cream.

B. Demonstrating Bioequivalence of 5-FU Products

You cite to FDA's regulations stating that "for drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." You state that AK and sBCC are different conditions that occur in different sites within the epidermis: AK is a precancerous condition that occurs in the stratum spinosum, while sBCC is a malignancy that occurs in the deeper stratum basale. In addition, you argue that sBCCs may grow downward into the dermis and are encased in a fibrovascular stroma; together, these features may further decrease the absorption and penetration of topical 5-FU into sBCC lesions.[20]

You argue that sponsors should either conduct separate comparative clinical bioequivalence studies for each site of drug action, or they should conduct a single study for that site from which it is reasonable to extrapolate equivalence for the remaining sites. In your view, if one study is conducted, it should be in patients with sBCC because (1) the site of action is deeper within the epidermis than the squamous sublayer, and (2) a comparative clinical trial that shows equivalence with respect to the basal sublayer may be sufficient to demonstrate, by implication, equivalence to the squamous sublayer. You further argue that, because generic drugs are required to carry the same labeling as their RLDs, a generic drug sponsor may not omit the sBCC indication from the labeling of its product to avoid having to conduct a comparative clinical study in sBCC patients.[21]

a. Site of Action

We have conducted a thorough review of the medical literature related to AK and sBCC. The relevant scientific evidence supports the conclusion that AK and sBCC are characterized by an abnormal proliferation of cells within the epidermis, which may be involved either in part or in its entirety.[22] In addition, both conditions may protrude minimally into the upper dermis while

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[20] Petition at 8-9.

[21] Petition at 10-11.

[22] See, e.g., Lever and Schaumburg-Lever (eds.). Chapter 26, Tumors and Cysts of the Epidermis; CJ Cockerell. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). *J Am Acad Dermatol* January 2000; 42: S11-17. Publication submitted by Valeant on October 21, 2005; Lever and Schaumburg-Lever (eds.). Chapter 27, Tumors of the Epidermal Appendages; MT Bastiaens, JJ Hoefnagel, JA Bruijn, RGJ Westendorp, BJ Vermeer, and JN Bouwes Bavinck. Differences in age, site distribution, and sex between nodular and superficial basal cell carcinomas indicate different types of tumors. *J Invest Dermatol* 1998; 110:880-884; U Bertheim, PA Hofer, A Engstrom-Laurent, and S Hellstrom. The stromal reaction in basal cell carcinomas. A prerequisite for tumour progression and treatment strategy. Brit Assoc Plastic Surgeons 2004; 57:429-439.

maintaining continuity with the epidermis.[23] Therefore, the site of action for a topical product to treat each of these conditions is the epidermis and the upper dermis. We disagree with your claims that, because AK and sBCC occur in different layers of the epidermis (stratum spinosum versus stratum basale), the site of action is different. We note that the epidermis is only 0.06 to 0.8 millimeters thick and, as explained below, there is no reason to conclude that if the formulation provides the active ingredient to the stratum spinosum, it would not also provide the active ingredient to the stratum basale.

b. Topical Delivery of 5-FU

There is general consensus that the stratum corneum is the predominant barrier to topical drug delivery. In many skin disorders, including tumors, the stratum corneum is compromised, and barrier resistance decreased. As treatment progresses, the condition improves, and the barrier function of the tissue is restored, thereby decreasing drug delivery.[24] In contrast to other skin disorders, in AK, the stratum corneum is often thickened.[25]

Regarding the cutaneous penetration of topical 5-FU, the view has been expressed that "despite decades of experience with products such as fluorouracil cream, we still lack data on the amount of active ingredient actually delivered to AK or sBCC action sites."[26] A review of the published literature uncovered limited data regarding delivery of topical 5-FU in AK patients. Perhaps more important was the lack of information regarding what minimum amount of active drug would need to be delivered to result in effective treatment.

According to the literature, systemic absorption of topical 5-FU varied widely, presumably as a function of the underlying skin disease, integrity of the dermal barrier, and extent and location of the involved skin. In vitro characterizations of the availability of active drug to the different layers of the epidermis and dermis are limited by the use of nondiseased skin and must be interpreted with caution, but they offer guidance. An in vitro study of the permeation of Efudex cream, 5%, through human cadaver skin demonstrated that the product was delivered to the epidermis and dermis, and that only 54 percent of the product was retained in the skin after 24

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[23] Conditions that involve abnormal proliferations of cells embedded within the dermis (e.g., squamous cell carcinoma or nodular BCC) are not relevant to this petition and are conditions for which topical 5-FU is not indicated.

[24] Adrian Williams. Transdermal and Topical Drug Delivery, The Pharmaceutical Press, London, 2003. Chapter 1, Structure and Function of Human Skin. Reference submitted by Valeant on December 21, 2004.

[25] Vinkay Kumar, Abul K. Abbas, and Nelson Fausto (eds.). Robbins and Cotran Pathologic Basis of Disease, 7th Edition, Elsevier Saunders, Philadelphia, 2005. Chapter 25, The Skin: Premalignant and Malignant Epidermal Tumors.

[26] Declaration of Howard I. Maibach, MD, in support of the Citizen Petition of Valeant Pharmaceuticals International, submitted to the docket on October 21, 2005.

hours, suggesting the potential for systemic absorption.[27] In an in vivo study of AK patients, following topical administration of Efudex cream, 5%, plasma fluorouracil concentrations were measurable in 9 of 12 of the patients.[28] In these two studies, a greater percentage of Efudex cream, 5%, appeared to be absorbed in the systemic circulation as compared to a differently formulated 0.5% fluorouracil cream. Despite this finding, a multicenter study showed that the 0.5% cream was as effective as the higher concentration formulation, suggesting that either the 0.5% formulation was better at targeting the skin, *or that higher doses were not needed* to effectively treat AK.[29]

Both the reference Efudex (fluorouracil) Cream, 5%, and Efudex Solution, 5%, have been approved for the treatment of AK and sBCC. These products have combined labeling, which provides no restrictions on the use of one 5% formulation or the other to treat these conditions. Thus, the presumption is that they may be used interchangeably to treat either condition. This argues against some critical formulation issue that could meaningfully affect the ability of these topical 5-FU products to deliver drug to the site of action for the approved uses.

We conclude that if a topical 5-FU formulation penetrates the skin to treat AK, which often involves a thickened stratum corneum, then that formulation would also penetrate the skin to treat sBCC, which usually involves a compromised stratum corneum.[30] The Agency's review of the relevant scientific studies suggests that the thickened stratum corneum in AK could provide a greater barrier to cutaneous penetration of topical 5-FU than the compromised stratum corneum in sBCC. Therefore, if a study demonstrated efficacy for a topical 5-FU formulation to treat AK, this would provide assurance that the formulation would penetrate the skin sufficiently to treat sBCC.

c. Required Clinical Study

Based upon the Agency's thorough review of the record and the available scientific data related to AK and sBCC, we conclude that a single clinical study in AK would be sufficient to demonstrate that a generic topical 5-FU product is bioequivalent to Efudex Cream for both the AK and sBCC indications. As noted above, the published literature supports the contention that the extent of skin involvement, and thereby the sites of action, for AK and sBCC are the same

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[27] S Levy, K Furst, and W Chern. A comparison of the skin permeation of three topical 0.5% fluorouracil formulations with that of a 5% formulation. *Clin Ther* 2001; 23:901-907.

[28] S Levy, K Furst, and W Chern. A pharmacokinetic evalution of 0.5% and 5% fluorouracil topical cream in patients with actinic keratosis. *Clin Ther* 2001; 23:908-920.

[29] K Loven, L Stein, K Furst, et al. Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratosis. *Clin Ther* 2002; 24:990-1000.

[30] Similarly, we do not believe that the actual location of the skin involved (face versus chest, back, and arms) is relevant in this case to determining differences in formulation. We believe that a demonstration of equivalent efficacy in treating AK will ensure bioequivalence of the formulations.

(i.e., the epidermis and the upper dermis), and the stratum corneum is the predominant barrier to topical drug delivery for the sites of action especially for AK. In addition, erosion or compromise of the skin in sBCC can result in greater drug exposure than in AK.

In light of these factors, and in the absence of scientific evidence to the contrary, the Agency concludes an AK bioequivalence study is sufficient to establish that the generic topical 5-FU formulation will be available in the epidermis and the upper dermis to act on both AK and sBCC lesions to an extent that is comparable to Efudex Cream.[31] In addition, we agree that a generic drug sponsor may not omit the sBCC indication from the labeling of its product, absent a listed patent or exclusivity for the RLD that protects the use of the drug to treat sBCC.

C. Relevance of the Most Difficult-to-Treat Condition in Bioequivalence of 5-FU Cream Products

You argue that a proposed generic version of Efudex Cream must be shown to be equivalent in the most difficult-to-treat condition for which the drug is approved. In support of your argument, you cite to a citizen petition response, which stated that "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."[32] For topical products with multiple indications, you argue that bioequivalence may be established by extrapolating from the most difficult condition to all other related conditions. You reason that use of the most difficult-to-treat condition is intended to challenge the proposed generic drug and to prevent a poorly performing product from appearing to be equivalent in a simple-to-treat condition. With simple-to-treat conditions, virtually all patients will experience high cure rates, regardless of the tested products. You claim that the use of the most difficult-to-treat condition is intended to ensure that the studies that are conducted are able to discriminate differences in the reference and generic formulations.

The statement from the citizen petition response cited in your letter was taken out of context and is not relevant to the bioequivalence evaluation of 5-FU cream. The citizen petition response referenced an earlier response in FDA Docket Number 88P-0369/CP regarding bioequivalence requirements for mebendazole, an anthelminthic. In that response, it was stated that pinworm (enterobius) infestation would not be an acceptable bioequivalence test "because the dose of 100 mg mebendazole twice a day for 3 days would eradicate a pinworm infestation, even for relatively bioinequivalent products." That is, a condition with a lower cure rate would be more sensitive in detecting efficacy differences between formulations. However, a study in a condition for which the cure rate is very low would also lack sensitivity to detect formulation differences, because even a product that is relatively non-equivalent would likely show an equally low cure rate.

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[31] We note that this conclusion is based on the specific characteristics of this topical product and the indications at issue. Factors involved in the assessment of other topical products may warrant a different result.

[32] Citizen Petition 1995P-0379 at 4.

The ideal clinical endpoint bioequivalence study should be conducted in the indication which will be the most sensitive in discriminating formulation differences. The optimal indication is generally one with the least variability in the disease state and expected course of disease and for which the recommended duration of treatment is the same for all patients. This is often, but not necessarily, the most difficult-to-treat condition. Furthermore, the shortest duration of treatment for which a significant treatment effect is expected is likely to be the most discriminatory, since extending the duration of therapy may result in a higher probability of success for all study groups and less ability to differentiate between products.

The sBCC indication may not be the indication that is the most sensitive in discriminating formulation differences between 5-FU products According to the Efudex product label, the recommended treatment duration for AK is 2 to 4 weeks, although complete healing may not be evident for 1 to 2 months following cessation of therapy. For sBCC, the recommended treatment duration is at least 3 to 6 weeks, but treatment may be required for as long as 10 to 12 weeks. Therefore, a comparative study in the treatment of sBCC is likely to be less discriminatory in detecting a difference between products. Furthermore, although management of sBCC is more complicated from a clinical practice perspective, the reported cure rate of sBCC with 5-FU treatment is actually higher than that of AK. The success rate for sBCC is 93 percent, compared with the 84 percent success rate reported in clinical studies of AK. The sBCC success rate is based on 113 lesions in 54 patients, pooling together those treated with 5-FU solution and those treated with 5-FU cream. This finding strongly suggests that the formulation of 5-FU was not considered especially significant in evaluating the efficacy of 5-FU in the treatment of sBCC, and is another reason why sBCC may not be a particularly sensitive condition in which to evaluate the bioequivalence of 5-FU formulations.

Although certain sites involved with sBCC may be more difficult to treat and would not be amenable to treatment with either the reference or a generic topical 5-FU product, the success of treatment (i.e., complete clearance rate) with the reference 5-FU product when *used as indicated in appropriately selected patients* is excellent for both AK and sBCC. If "difficult to treat" is gauged by the likelihood of treatment success with topical 5-FU, then neither condition is "difficult to treat." Therefore, the Agency concludes an AK bioequivalence study is sufficient to establish that the generic topical 5-FU formulation will be available in the epidermis and the upper dermis to act on both AK and sBCC lesions to an extent that is comparable to Efudex Cream.

D. The Design of Comparative Clinical Studies

You argue that the design of a comparative clinical bioequivalence sBCC study must reflect the Agency's current standards for the conduct of a well-controlled study in this patient population. You offer as an example the two double-blind, vehicle-controlled clinical studies conducted in support of Aldara Cream, in which 364 patients with primary sBCC were treated with Aldara Cream or vehicle five times a week for six weeks. FDA agrees that if a comparative clinical

sBCC study were to be conducted to demonstrate bioequivalence of a generic topical 5-FU cream, its design should reflect current clinical dermatology management of the disease. However, as discussed above, the Agency has concluded that one comparative clinical AK study is sufficient to establish bioequivalence to Efudex Cream. We note that the sponsor of the generic topical 5-FU cream we are approving conducted a clinical trial to demonstrate bioequivalence between the generic drug and Efudex Cream in the complete clearance of AKs. The study also demonstrated the superiority of both formulations to vehicle and showed that the safety profiles of the two 5-FU formulations were similar and considered acceptable.

III. CONCLUSION

For the reasons discussed above, FDA will not require that ANDAs for a generic version of Efudex Cream contain data from comparative clinical studies conducted in patients with sBCC. Therefore, your petition is denied.

Sincerely,

Janet Woodcock
Director
Center for Drug Evaluation and Research