VALEANT
Pharmaceuticals International

International Headquarters
3300 Hyland Avenue Costa Mesa, CA 92626
714.545.0100 FAX 714.556.0131
www.valeant.com

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BY HAND DELIVERY

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

CITIZEN PETITION

On behalf of Valeant Pharmaceuticals International ("Valeant"), the undersigned submit this petition under section 505 of the Food, Drug, and Cosmetic Act ("FDCA") and 21 CFR 10.30, among other provisions of law, to ensure that any abbreviated new drug application ("ANDA") for a generic version of Efudex® (fluorouracil) Cream includes data from a comparative clinical study conducted in patients with superficial basal cell carcinoma ("sBCC").

Efudex® Cream is approved for use in the treatment of sBCC when conventional methods of treatment are impractical, and in the treatment of multiple actinic keratoses ("AK"). sBCC occurs in the stratum basale, the deepest sublayer of the epidermis. AK, by contrast, occurs in the more superficial stratum spinosum, a different site of drug action within the skin.

Under the FDCA, the bioavailability of topical drug products may be assessed "by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient . . . becomes available at *the site of drug action.*" 21 USC 355(j)(8)(A)(ii) (emphasis added). For a product such as Efudex® Cream, which is approved for use at two different sites of action, bioequivalence must be established for each applicable site. As demonstrated below, an ANDA for a generic version of Efudex® Cream, based solely on a comparative clinical study conducted in patients with AK, would not meet the statutory standard for approval. *See* 21 USC 355(j)(4)(F).

In addition, the Food and Drug Administration ("FDA") has determined that the bioequivalence of topical products approved for multiple uses must generally be established in the most difficult to treat condition. *See* Citizen

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Petition Response, Docket No. 1995P-0379 (May 22, 2002). Here, as well, a bioequivalence study conducted in patients with AK would not meet the agency's standard. sBCC requires a longer period of treatment, is prone to recur, and is generally regarded as a more difficult condition than AK to treat. A study in the more challenging sBCC population is needed to provide the sensitivity to detect differences between the proposed generic product and the listed drug.

For this reason we submit the following petition.

I. ACTION REQUESTED

The undersigned hereby request that the Commissioner of Food and Drugs refrain from approving any ANDA submitted under section 505(j) of the FDCA for a generic version of Efudex® Cream, unless the application contains data from an adequately designed comparative clinical study conducted in patients with sBCC. *See* 21 USC 355(j). This request also applies to any new drug application ("NDA") submitted under section 505(b)(2) of the FDCA that references Efudex® Cream for its currently approved uses. *See id.* at 355(b)(2).

II. STATEMENT OF GROUNDS

A. Factual and Scientific Background

1. Efudex® Cream and Related Products

Efudex® is approved for use in the topical treatment of multiple actinic or solar keratoses, pre-cancerous growths within the stratum spinosum caused by overexposure to the sun. The product is available in 2% and 5% topical solutions and as a 5% cream. *See* Efudex® Labeling (2004) (attached at Tab A).

The 5% topical solution and cream are also approved for use in the treatment of patients with superficial basal cell carcinoma when conventional methods of treatment are impractical, such as with multiple lesions or difficult treatment sites. *See id.* Basal cell carcinoma is the most common form of cancer in humans. Like AK, it occurs in areas of chronic sun exposure. Unlike AK, however, it originates in the stratum basale, the deepest sublayer of the epidermis. sBCC tumors are also known to grow downward into the dermis and typically are encased in an additional layer of cells. *See* P.G. Lang and J.C. Maize, Sr., *Basal Cell Carcinoma*, in Cancer of the Skin at 101, 109-10 (D.S. Rigel *et al.*, eds. 2005) ("Basal Cell Carcinoma") (attached at Tab B).

Two other fluorouracil ("5-FU") products are approved for use in the topical treatment of AK:

- Fluoroplex® (fluorouracil) Cream, 1.0%, is approved for twice daily use in the treatment of multiple actinic (solar) keratoses. *See* Flouroplex® Labeling (2003).

- Carac™ (fluorouracil) Cream, 0.5%, is approved for once daily use in the treatment of multiple actinic or solar keratoses of the face and anterior scalp. *See* Carac™ Labeling (2003).

Neither of these products, however, is approved for use in the treatment of sBCC. A third product, Aldara™ (imiquimod) Cream, 5.0%, was previously approved for use in the treatment of clinically typical AK on the face or scalp in immuno-competent adults. Only recently, on the basis of additional clinical studies, was Aldara™'s sponsor able to gain approval for its use in the treatment of certain cases of biopsy-confirmed, primary sBCC. *See* Aldara™ Labeling (2004).[1]

2. Human Skin Physiology

The human skin is a complex organ that performs several vital functions. It serves as a protective barrier that regulates body temperature and fluid loss, detects sensation and, most importantly, shields the body and internal organs from external harmful agents. This protective effect exists on a variety of levels, because human skin is composed of multiple layers and sublayers, with each site acting as a protective barrier for deeper layers and, ultimately, for the internal organs. The three main sections of the skin, from outermost to innermost, are the epidermis, the dermis, and the hypodermis. *See* A. Williams, *Transdermal and Topical Drug Delivery – From Theory to Clinical Practice* at 2 (2003) ("Topical Drug Delivery") (attached at Tab C).[2]

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[1] Aldara™ Cream is also approved for use in the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above. *See* Aldara™ Labeling.

[2] The dermis is composed primarily of collagen, elastin fibers, capillaries, lymph nodes, sebaceous glands, sweat glands, and hair follicles. *See* Topical Drug Delivery at 2-5. Relative to the epidermis, permeation of the dermis is generally not as challenging even though the dermis is the thickest layer of the skin. The hypodermis is the deepest layer of the skin and is composed primarily of fat cells that insulate the body and absorb physical shock. *See id.* at 2.

The epidermis ranges from 0.06 mm to 0.8 mm in thickness, depending on its location on the body. It is the thinnest of the three layers in the skin, but is considered the most difficult barrier for drugs to permeate. The epidermis itself contains four distinct sites, or sublayers, consisting of cells at different stages of differentiation – the regenerative process by which skin cells mature, die, and are eventually shed:

- The stratum corneum, or the horny sublayer, is the uppermost sublayer of the epidermis. This site consists of flattened, dead keratinocyte cells that have hardened into proteins (keratins);

- Below this is the stratum granulosum, also known as the granular sublayer, where cellular shape flattens, enzymes degrade cell nuclei, and lipids begin to form between cells;

- Below this is the stratum spinosum, or the squamous sublayer, which is composed of several layers of irregularly-shaped cells; and

- Finally, the stratum basale, or the basal sublayer, is the deepest layer of the epidermis, where living cells known as keratinocytes continuously generate new cells through division.

See id. at 5-13. These four sublayers are illustrated in the figure below:

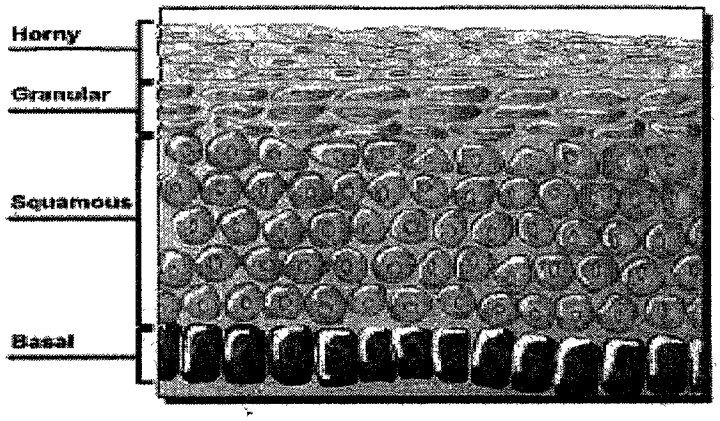

Figure 1. Diagram of the Epidermis

The effective delivery of topical drugs requires drug molecules to permeate these different layers and sublayers of the skin to the target site of action. The rate and extent to which drugs "diffuse" through human skin is therefore critical. "Diffusion" describes the movement of drug molecules along a concentration gradient – from higher concentrations of drug (in the formulation) to lower concentrations (across skin layers and sublayers). In other words, diffusion refers to the active ingredient's permeation through the different layers and sublayers of the skin to the site of action.

The intricate structure of human skin – particularly the resistant nature of the epidermis – can complicate drug uptake. The affinity of cell membranes to the lipid bilayers occupying the intercellular space in the horny sublayer creates a tightly stacked and cohesive "brick-and-mortar" formation. For this reason, the stratum corneum is considered the predominant barrier to topical drug delivery. *See id.* at 5, 9-10. It is, however, not the exclusive barrier. Drug molecules must also permeate or navigate around the cells below the stratum corneum to reach the deeper sublayers and sites of action within the epidermis.

B. Statutory and Regulatory Background

Under the FDCA, a sponsor seeking approval of a generic drug must demonstrate that the proposed product is "the same as" a reference listed drug ("RLD") with respect to active ingredient, dosage form, route of administration, strength, and labeling. 21 USC 355(j)(2)(A). A generic drug also must be shown to be "bioequivalent" to the RLD. *Id.* at 355(j)(2)(A)(iv); 21 CFR 314.94(a)(7).

Generally, a proposed generic drug is considered bioequivalent to the RLD if the rate and extent of absorption of the generic drug do not show a significant difference from the rate and extent of absorption of the RLD when administered under similar experimental conditions. *See* 21 USC 355(j)(8)(B)(i).

Because most drugs are intended to be absorbed into the systemic circulation, bioequivalence typically is demonstrated by pharmacokinetic measures, such as the rate and extent to which the active ingredient is absorbed into the bloodstream. Such measures assess bioequivalence *before* the active ingredient reaches any site of action. For this reason, pharmacokinetic measures act as surrogates for the rate and extent to which the drug becomes available at the site of action. *See generally Approved Drug Products with Therapeutic Equivalence Evaluations* (2004) at Preface 1.3. For a systemically absorbed drug with multiple

sites of action, one pharmacokinetic study is generally considered sufficient to establish bioequivalence.

The Medicare Prescription Drug, Improvement, and Modernization Act ("MMA") amended the FDCA to address the issue of bioequivalence for drugs that are not intended to be absorbed into the bloodstream. *See* Pub. L. No. 108-173, 117 Stat. 2066 (2003). As amended, the FDCA allows FDA to establish "alternative, scientifically valid methods" to demonstrate the bioequivalence of such drugs, if those methods are expected to detect a significant difference in safety and therapeutic effect. 21 USC 355(j)(8)(C).

The MMA also amended the FDCA to provide that FDA may assess the bioavailability of non-systemically absorbed drugs "by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at *the site of drug action*." *Id.* at 355(j)(8)(A)(ii) (emphasis added); *see also* 21 CFR 320.1 (defining "bioavailability" and "bioequivalence" based on the rate and extent to which an active ingredient becomes available at the site of drug action).

In contrast to systemically absorbed drugs, the bioequivalence of non-systemic drugs generally cannot be assessed through pharmacokinetic measures. The agency therefore generally requires appropriately designed comparative clinical studies to demonstrate the bioequivalence of such drugs, including topical products. *See* 21 CFR 320.24(b)(4). Unlike pharmacokinetic measures, clinical endpoints assess bioequivalence *after* the drug has reached the site of action and produced a therapeutic effect. As such, a clinical endpoint acts as a surrogate only for the rate and extent to which the drug becomes available at the particular site of action studied.

This fundamental difference in the bioequivalence testing of oral and topical drug products was illustrated in a slide presentation by Dale P. Conner, Pharm.D., Director of the Division of Bioequivalence of the Office of Generic Drugs, on March 12, 2003. *See* Advisory Committee for Pharmaceutical Science ("ACPS") Transcript at 173-78; *compare* Slide 7 *with* Slide 8 (slide presentation attached at Tab D). In short, for a non-systemic drug with more than one "site of drug action," more than one set of "scientifically valid measurements" may be needed to satisfy the statutory standard.

III. ARGUMENT

A. Comparative Clinical Studies Are Needed To Demonstrate The Bioequivalence Of 5-FU Cream Products

The agency has yet to define a validated methodology by which sponsors may establish the bioequivalence of topical products through the use of pharmacokinetic measures. *See* 21 CFR 320.24(b)(1). In a 1993 publication, Vinod P. Shah, Ph.D., and other current and former agency officials examined the deficiencies of bioequivalence methods for topical products. *See* V.P. Shah *et al.*, *Bioequivalence of Topical Dermatological Products*, in Topical Drug Bioavailability, Bioequivalence, and Penetration at 393-412 (V.P. Shah & H.I. Maibach eds.) ("Topical Dermatological Products") (attached at Tab E).

The authors observed that, for topical dermatological products other than corticosteroids, suitable pharmacokinetic or pharmacodynamic measures are not available to allow the development of an alternate methodology to assess bioavailability and bioequivalence. *See id.* at 411. For that reason, "comparative clinical studies between the generic and pioneer [topical] products are now required by the FDA to document bioequivalence." *Id.* Similarly, the former director of FDA's Office of Generic Drugs stated in 1998 that "[t]he real important thing [for topical products] is equivalent safety and efficacy which really should be shown in comparative clinical trials." ACPS Transcript (Oct. 23, 1998) (statement of Roger L. Williams, M.D.).

More than a decade after Dr. Shah's article, FDA still has not developed an adequate bioequivalence methodology using pharmacokinetic measures for topical products. As another FDA official stated, "[w]e have struggled for the last 12 years trying to develop a method for assessing the bioequivalence to drugs applied to the skin and we have not been successful in trying to move the decision forward in a consensus way." ACPS Transcript (Mar. 12, 2003) (statement of Ajaz S. Hussain, Ph.D.).[3] And, earlier this year, an Office of Generic Drugs

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[3] FDA previously issued a Draft Guidance for Industry: *Topical Dermatological Drug Product NDAs and ANDAs – In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies* (June 1998). This document attempted to define an objective method, known as dermatopharmacokinetics ("DPK"), to establish the bioequivalence of topical products through measurement of the active moiety in the stratum corneum. The guidance was withdrawn in 2002 after questions were raised regarding the reproducibility of the methodology and its applicability to products used to treat diseases in different sites in the skin. *See* 67 FR 35122 (May 17, 2002).

official confirmed that "[t]he current state of topical bioequivalence is that . . . for almost all locally acting dermatological products clinical trials are necessary to demonstrate bioequivalence." ACPS Transcript (Apr. 14, 2004) (statement of Robert A. Lionberger, Ph.D.).

Thus, FDA's position could not be clearer: For locally acting topical drug products, comparative clinical studies, with clinical endpoints, remain the norm. *See* 21 CFR 320.24(b)(4).[4] As applied here, the sponsor of a generic topical 5-FU product must conduct at least one comparative clinical study to establish the bioequivalence of its product to the listed drug.

B. The Bioequivalence Of 5-FU Products Must Be Demonstrated For Each Site Of Drug Action

The FDCA provides FDA with authority to assess the bioavailability of topical drug products "by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient . . . becomes available at *the site of drug action.*" 21 USC 355(j)(8)(A)(ii) (emphasis added). FDA's regulations likewise require that sponsors demonstrate the bioavailability of topical products for the site of action:

> 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.*

21 CFR 320.1(a) (emphasis added); *see id.* at 320.1(e) (defining bioequivalence).

This focus on the site of drug action is scientifically and medically appropriate because a single topical product may be intended for use in different sites of action. As discussed above, while the bioequivalence of systemically absorbed drug products may be assessed before the active ingredient reaches any site (or sites) of action, the bioequivalence of topical products is assessed only *after*

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[4] In limited circumstances, FDA may waive its requirement for *in vivo* bioequivalence documentation where equivalence is considered "self-evident." For example, the agency may waive the requirement for products in solution, including topical solutions, provided the products contains no inactive ingredients or other changes in formulation that may significantly affect the absorption of the active ingredients. *See* 21 CFR 320.22(b)(3). On November 5, 2003, FDA approved ANDA 76-526 for a generic version of Efudex® 2% and 5% topical solution on the basis of such a waiver. The issues presented by that approval are not the subject of this petition.

the active ingredient has reached a specific site of action. *See supra* at section II.B. To the extent that FDA is required to assess bioequivalence at the site of action, products with multiple sites of action may require multiple demonstrations of equivalence.

In this case, AK and sBCC are different conditions that occur in different sites within the skin. AK is a pre-cancerous condition that occurs in the stratum spinosum. By contrast, sBCC is an actual malignancy that continually grows, is capable of invading local tissues, and in rare instances may metastasize to other parts of the body. It occurs in the stratum basale, a sublayer deeper within the epidermis, close to the dermis. *See id; see also* Basal Cell Carcinoma at 101. Thus, the treatment of sBCC requires the penetration of 5-FU to the basal sublayer of the epidermis, rather than simply to the more superficial squamous sublayer, as with the treatment of AK.[5]

The agency itself has recognized that the stratum corneum and other sublayers of the skin function as different sites of action. *See, e.g.*, ACPS Transcript (Apr. 14, 2004) (statement of Ajaz S. Hussain, Ph.D.) ("Now, if the site of action is the stratum corneum or the dermis or the follicles, and so forth, clearly that is important from an efficacy perspective."); *see also id.* (statement of Robert A. Lionberger, Ph.D.). One of the reasons FDA's DPK guidance document was withdrawn was the concern that the method could not effectively "assess the bioequivalence of topical dermatological drug products because the products are used to treat a variety of diseases in *different parts of the skin*, not just the *stratum corneum* . . . ." 67 FR at 35123 (first emphasis added).[6]

In addition, the cell of origin is not only deeper in sBCC than in AK, but the growth pattern of sBCC is such that the tumors actually grow *downward* into the papillary dermis, to a much deeper level than where AK is found. *See*

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[5] These two conditions also occur on different parts of the body. AK is commonly found on the face. sBCC more commonly occurs on the chest, back, and arms. The absorption of drugs through the skin is known to differ among different regions of the body. Generally, skin on the head and neck is more permeable than skin on the trunk (*i.e.*, the torso), which is more permeable than skin on the arms and legs. *See* Topical Drug Delivery at 16.

[6] *See also* Topical Dermatological Products at 401 ("Because a topical dermatological product will generally be applied to diseased skin, formulation/excipient factors may play a much larger role in how the drug moves to *the primary site of action within the epidermis or dermis* than in the case of a solid oral dosage form, for which drug-excipient interactions after absorption are generally thought not to occur.") (emphasis added).

Basal Cell Carcinoma at 109-110. The islands of tumor cells also demonstrate "palisading" on their periphery, meaning that the outer layer of each nest of cells aligns in a parallel array approximately one to three cells thick. These islands are then encased in a thickened dermis (called the fibrovascular stroma) that consists of fibroblasts and mucin, as well as inflammatory cells such as lymphocytes and histiocytes. *See id.* Together, these features may further decrease the absorption and penetration of 5-FU into sBCC tumors. AK remains in the upper epidermis and does not exhibit a growth pattern that creates these additional impediments to absorption.

Because AK and sBCC occur at two different sublayers within the skin, under the FDCA, bioequivalence must be demonstrated for each site of action. It is within the agency's discretion, however, to determine the manner in which the sponsor of a product with multiple indications may demonstrate equivalence at each site of action. *See* Citizen Petition Response, Docket No. 2003P-0140 (Nov. 7, 2002) at 3 ("The number of [bioequivalence] studies necessary for approval will depend on the specific product."). Sponsors should either conduct separate comparative clinical bioequivalence studies for each site of action, or they should conduct a single study for that site from which it is reasonable to extrapolate equivalence for the remaining sites.

With respect to a generic version of Efudex® Cream, a sponsor must conduct a comparative clinical study in patients with sBCC in either case. If FDA determines that a study at one site of action is sufficient, that site must be the stratum basale, and not the stratum spinosum. The basal sublayer is deeper within the epidermis than the squamous sublayer. *See supra* at section II.A. For an active ingredient to become available in the basal cells, it must pass around or through the squamous cells, including both healthy and diseased tissue. A comparative clinical study that shows equivalence with respect to the basal sublayer may be sufficient to demonstrate, by implication, equivalence in the squamous sublayer. This is the case because the drug must have passed through the squamous sublayer to reach the basal cells. Simply put, the same cannot be said for a study conducted only in a disease that occurs in the squamous sublayer.[7]

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[7] The agency recently demonstrated its recognition that a drug approved as safe and effective in treating AK is not necessarily safe and effective in treating sBCC. In July 2004, FDA approved Metvixia™ (methyl aminolevulinate) Cream, in combination with a proprietary light source, for use in the treatment of AK. On or about December 3, 2004, however, FDA refused to approve Metvixia™ for use in the treatment of sBCC. *See* Photocure Press Release (Dec. 3, 2004) at cws.huginonline.com/P/131151/PR/200412/971251_5.html.

Moreover, a generic 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. Such a study is required for the sponsor to meet its burden of demonstrating bioequivalence to Efudex® Cream. Generic products are also required to carry the same labeling as their RLDs, except in certain limited circumstances. *See* 21 USC 355(j)(2)(A)(v); 21 CFR 314.94(a)(8)(iv). A "labeling carve out" based on a sponsor's refusal to demonstrate bioequivalence in all approved indications is not a recognized basis for omitting an indication. *See id.*

C. The Bioequivalence Of 5-FU Cream Products Must Be Demonstrated In The Most Difficult To Treat Condition

In addition to the need to establish equivalence for each site of drug action, a proposed generic version of Efudex® Cream must also be shown to be equivalent in the most difficult to treat condition for which the drug is approved. For topical products with multiple indications, bioequivalence may be established by extrapolating from the most difficult condition to all other related conditions. To proceed in the opposite direction, from a showing in the most accessible and easiest to treat condition to the most difficult, would defy sound scientific principles.

1. Prevailing Agency Precedent

The agency has, in fact, already explored and resolved this issue. In a citizen petition response regarding generic ammonium lactate lotion, FDA stated:

> 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.

Citizen Petition Response, Docket No. 1995P-0379 at 4 (emphasis added).

The agency explained its focus on the most difficult to treat condition in an earlier petition response involving products approved to treat both roundworm and pinworm infections. There, FDA determined that generic sponsors seeking to demonstrate equivalence through a single study would need to conduct that study in the more difficult infection (roundworm). The agency ruled out pinworm as the

test infection because the approved treatment regimen "would eradicate a pinworm infestation, even for relatively bio*in*equivalent products." Citizen Petition Response, Docket No. 1988P-0369 (July 1, 1994) at 3 (emphasis added). Use of the most difficult to treat condition is intended to challenge the proposed generic product, to prevent a poorly performing product from appearing to be equivalent in a simple to treat condition.

Underlying FDA's determination that sponsors should conduct topical bioequivalence studies in the most difficult to treat conditions is the need to ensure the sensitivity of those studies. The nature of studies with clinical endpoints is such that, with high doses or relatively simple conditions, virtually all patients will experience high cure rates, regardless of the equivalence of the tested products. *See generally* ACPS Transcript (Mar. 12, 2003) (statement of Dale P. Conner, Pharm.D.). Such a study is incapable of showing any "separation" between the test and reference products. With a more difficult to treat condition, there is a greater likelihood that differences in the bioavailability of the products will yield differences in cure rates. *See id.* (statement of Dena R. Hixon, M.D.) (describing the selection of the study population and endpoints as among the most significant challenges in conducting topical bioequivalence studies).[8]

2. sBCC is More Difficult to Treat

According to Efudex® Cream's labeling, sBCC is significantly more difficult than AK to treat. For AK, the product is to be applied twice daily in an amount sufficient to cover the patient's lesions. Treatment is simply continued until the patient's inflammatory response reaches the erosion stage, at which time use of the product is stopped. The usual duration of such therapy is only two to four weeks – during which time the condition simply may self-resolve. *See* Efudex® Labeling; J.P. Callen, *Possible Precursors to Keratinocytic Epidermal Malignancies*, in Cancer of the Skin at 96 (attached at Tab F).

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[8] One advantage to conducting bioequivalence studies of systemically absorbed drugs in blood is that the dose-response curves are usually linear. Such studies are sensitive to differences in the bioavailability of the tested products – small changes in dose yield differences in response. Comparative clinical studies, however, "generally have a sigmoidal dose-response curve." ACPS Transcript (Mar. 12, 2003) (statement of Dale P. Conner, Pharm.D.); *see also id.* (statement of Dena R. Hixon, M.D.) (discussing a drug product for which there has been difficulty selecting the appropriate study population and endpoints). That means the sponsors must be much more selective in choosing the dose or the patient population to ensure a sufficiently sensitive comparative clinical study.

For sBCC, any diagnosis must be confirmed through a biopsy before treatment may begin, because topical 5-FU has not been proven to be effective against other types of cancer. Treatment with the 5% solution or cream must then be applied twice daily for at least three to six weeks, and may be required for *10 to 12 weeks* before the patient's lesions are obliterated. Furthermore, as in any neoplastic condition, the patient must be followed for a reasonable period of time after treatment to determine whether the cancer has been cured or has recurred. *See* Efudex® Labeling; *see also* R.I. Ceilley and J.Q. Del Rosso, *Topical Chemotherapy for the Treatment of Skin Cancer*, in Cancer of the Skin at 620 ("Inadequate treatment may resolve only the superficial component and make the diagnosis of recurrence difficult.") ("Topical Chemotherapy") (attached at Tab G).

In addition, only sBCC can provide the dose-response sensitivity needed for sponsors to conduct adequate bioequivalence studies. A comparative clinical study conducted in patients with AK would not be sensitive enough to detect differences in the bioavailability of the test and reference products. *See* 21 USC 355(j)(8)(C) (providing FDA with authority to establish "scientifically valid methods" to show bioequivalence only if the methods are expected to detect a significant difference in safety and therapeutic effect).

As noted above, Efudex® is approved for use in the treatment of AK in a 2% topical solution. Two other topical 5-FU products, Carac™ Cream, 0.5% and Fluoroplex® Cream, 1.0%, are also approved to treat AK. These three products demonstrate that the use of 5% 5-FU, twice a day for two to four weeks, exposes a typical patient to *five to 10 times* the amount of drug necessary to cure the patient's AK. In a bioequivalence study conducted in AK patients, such a comparatively high dose could well produce high cure rates, even for relatively bioinequivalent products. *See* Topical Chemotherapy at 619 (describing the comparable efficacy in AK of various strengths of 5-FU). Only a study in patients with sBCC would provide the greater sensitivity necessary to detect differences in the bioavailability of the tested products, as the statute requires. *See* 21 USC 355(j)(8).

D. The Design Of Any Comparative Clinical sBCC Study Must Reflect The Current State Of The Art

As discussed above, whether FDA concludes that sponsors of generic 5-FU cream products must conduct one or two comparative clinical bioequivalence studies, at least one study must be conducted in patients with sBCC. *See supra* at section III.B. Further, the design of any such clinical study must reflect the

agency's current standards for the conduct of a well-controlled study in this patient population. *See* 21 CFR 320.24(b)(4).

One recent example of studies deemed adequate by FDA are those that were conducted in support of Aldara™ Cream. In July 2004, FDA approved Aldara™ Cream for use in the treatment of biopsy-confirmed, primary sBCC. This approval was based on two double-blind, vehicle-controlled clinical trials, in which 364 patients with primary sBCC were treated with Aldara™ Cream or vehicle five times per week for six weeks. Patients with one biopsy-confirmed sBCC tumor were randomized in a 1:1 ratio to active treatment or vehicle (placebo). Twelve weeks after the last scheduled application of the product, the entire target tumor area was clinically assessed, excised, and examined histologically. The primary efficacy endpoint for the studies was the complete response rate, defined as the proportion of patients with clinical (visual) and histological clearance of the sBCC lesion at 12 weeks post-treatment. *See* Aldara™ Labeling.

This represents a valid study design for proposed generic sponsors seeking to show bioequivalence through comparative clinical study. For example, because 5-FU, imiquimod, and other topical agents have only been proven safe and effective in the treatment of sBCC, diagnosis must be confirmed by biopsy before treatment begins. Treatment with 5-FU must then continue for at least three to six week, preferably for 10 to 12 weeks. Finally, because sBCC may recur after treatment, patients' clinical responses must be determined histologically, at least 12 weeks after treatment has stopped. *See, e.g.,* Efudex® Labeling.

IV. CONCLUSION

The inadequate treatment of sBCC can lead to serious complications for patients, including the growth of their cancer. In that light, and based on the discussion above, it is critical that FDA not make assumptions about whether a proposed generic product will be safe and effective in treating sBCC, based on a showing of comparable efficacy in patients with AK. These two conditions occur at different sites of drug action and exhibit different growth patterns. Comparable absorption of a drug to one site of action does not demonstrate comparable absorption to another, more difficult to reach site of action. Similarly, comparable efficacy in an easier to treat condition does not demonstrate comparable efficacy in a more difficult to treat condition.

For these reasons, FDA must not allow onto the market generic versions of Efudex® Cream until a demonstration of bioequivalence has been made, at a minimum, in patients with sBCC.

V. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 CFR 25.31.

VI. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner of Food and Drugs.

VII. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Kim D. Lamon, M.D., Ph.D.
President and Chief Scientific Officer
Valeant Pharmaceuticals International
3300 Hyland Avenue
Costa Mesa, CA 92626
Fax: (714) 668-3139
Phone: (714) 545-0100

Greg J. Kricorian, M.D.
Director, Medical Affairs
Valeant Pharmaceuticals International
3300 Hyland Avenue
Costa Mesa, CA 92626
Fax: (714) 668-3139
Phone: (714) 545-0100

cc: David M. Fox
Philip Katz
Brian R. McCormick
Hogan & Hartson LLP