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

Re: Docket No. 2004P-0557

Reply Comment of
Valeant Pharmaceuticals International

We are writing in response to the comment submitted May 5, 2006, by Rothwell, Figg, Ernst & Manbeck, P.C. ("Comment") to the above-referenced citizen petition ("Petition").

Valeant's Petition requests that the Food and Drug Administration ("FDA") require that any application for a generic version of Efudex® (fluorouracil) Cream contain bioequivalence data from a comparative clinical study in patients with superficial basal cell carcinoma ("sBCC").

Rothwell, Figg argues that a study in patients with actinic keratosis ("AK") should suffice, asserting that if two products "have already been found to be bioequivalent based on measurements in the upper and mid epidermis [*i.e.*, in patients with AK], then they will also be bioequivalent in the lower epidermis [*i.e.*, in patients with sBCC]." Comment at 1. This reasoning is flawed. Among other things, it is based on a fundamental misunderstanding of the nature of the comparative clinical studies conducted to show bioequivalence for locally active, topical products such as Efudex Cream.

When measuring the pharmacokinetics of systemically absorbed drugs, a demonstration of bioequivalence in the blood generally may be extrapolated to all sites of action. This is because pharmacokinetic studies constitute an actual measure of the rate and extent of absorption of active ingredients into the body. If

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two products deliver the same amount of an active ingredient into the blood, then all "downstream" effects usually can be assumed to be the same. This assumption cannot be made based on a comparative clinical study of products that act locally.

A comparative clinical study shows whether two products treat a condition in a like manner; it does *not* constitute an actual measure of the active ingredient within the live tissue of the skin. In fact, it is possible that two products may produce similar clinical results despite being inequivalent in the active ingredient's rate or extent of absorption. More importantly, there can be differences between the products that, although not significant in terms of treating one condition, have a meaningful impact on the treatment of another condition. Such differences would only be detected in a comparative clinical study in the second condition.[1]

For instance, two products that deliver different amounts of an active ingredient may nonetheless appear equivalent in treating one condition, because both may provide sufficient amounts to treat that condition. If the products were compared in their ability to treat another, more difficult condition, the results might be different. Unless the products are tested in that second condition, however, such differences would remain hidden. That is why the agency has in the past required comparative clinical studies to be conducted in the most difficult to treat conditions for which products are intended. *See, e.g.*, Petition at 11-13.

Fick's Laws of Diffusion say nothing to the contrary. Fick's first law stands for the proposition that the diffusion of a topical drug is a function of (1) the rate at which the drug partitions out of the formulation and into the stratum corneum; (2) the rate at which it diffuses through the stratum corneum; and (3) the concentration gradient, defined by the amount of drug in the formulation *vs.* the amount in the skin. *See* Comment at 3. Where two products are different in ways that alter one or more of those values, however, the outcomes of Fick's equation and the diffusion of the products will be different.[2]

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[1] It is not surprising that FDA's regulations characterize comparative clinical studies as "the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence." 21 CFR 320.24(b)(4).

[2] Additionally, as Rothwell, Figg concedes, Fick's first law describes an idealized setting that often does not hold true in practice. *See* Comment at 3 ("For *steady-state conditions*, this can be described with Fick's first law of diffusion . . . .") (emphasis added). Far from the unlimited supply of drug contemplated by Fick, in the clinical setting, topical drugs are applied in inconsistent amounts and routinely are rubbed or washed off.

With regard to Efudex Cream, for example, a proposed generic product that has the same active and inactive ingredients may contain fluorouracil particles that are different sizes than those in Valeant's product. As discussed below, differences in particle size would alter the surface area of the drug, thereby altering the amount of drug in the dissolved state and the rate at which the drug partitions out of the formulation – the first variable in Fick's law. A comparative clinical study in AK patients may not detect such differences, because of the ease with which that condition is treated and the well-documented insensitivity of AK studies. For these reasons, equivalence in treating AK patients cannot be relied upon to conclude that the active ingredient in two products is being absorbed to the same rate and extent. Therefore, a comparative clinical study must be conducted in patients with sBCC.

I. Particle Size is Critical to the Bioavailability of Efudex Cream

The delivery of a topical drug begins immediately upon the product's application to the skin. At that moment, the portion of the drug that is in solution at the product's interface with the skin partitions out of the formulation and into the stratum corneum. This creates, in effect, a deficit in the formulation near the skin, causing drug *not* in solution to solubilize, move through the formulation, and into the stratum corneum. This entire process continues according to the laws of thermodynamics, driven by the rate at which the drug can solubilize. *See generally* G.L. Flynn, *General Introduction and Conceptual Differentiation of Topical and Transdermal Drug Delivery Systems*, in Topical Drug Bioavailability, Bioequivalence, and Penetration, 379 (V.P. Shah & H.I. Maibach, eds., 1993) (attached at Tab 1).

The rate at which a drug can solubilize is determined in large part by the surface area of the drug particles. As a general rule, greater surface area means a higher rate at which a drug can solubilize. And the smaller a drug's particle sizes, the greater the drug's total surface area is in relation to its mass. Thus, drugs with smaller particle sizes tend to exhibit greater solubility.

The fluorouracil in Efudex Cream is a crystalline solid that is only sparingly soluble in water. *See Description*, Efudex Cream Labeling. To achieve better epidermal penetration, Valeant increases the surface area of the drug by reducing its particle sizes. This is accomplished by micronization to meet a specific product specification for particle size. The typical change in particle size achieved by micronization is a 10-30 fold reduction in dimension. Because volume (mass) is

preserved, the number of particles is increased 1,000 (10^3) to 27,000 (30^3) fold, and the corresponding surface area by 10-30 fold.

The micronized particles are then partially dissolved in propylene glycol, and the partially solubilized "droplets" are dispersed throughout the oil phase of Efudex Cream's oil-in-water formulation. The concentration and size of the partially solubilized droplets ultimately determine the epidermal penetration and bioavailability of the active ingredient.

If a proposed generic version of Efudex Cream contains different size particles, the drug's surface area, and the amount of dissolved drug available for diffusion, will be different. This likely would affect the rate at which the drug can solubilize and partition into the skin (changing the first value in Fick's equation). A product with particles larger than Efudex Cream's may have reduced therapeutic potency, because the drug will be slower or less likely to become available in the epidermis (as much as 10-30 fold). Similarly, a product with smaller particles may be super-potent in comparison, and may become unstable or even separate due to super-saturation of the active ingredient.

II. AK Studies are Insufficiently Sensitive to Detect Product Differences

Comparative clinical studies in AK patients are not sufficiently sensitive to detect particle size or other differences between products that may be significant in the treatment of sBCC patients. AK is an extremely prevalent, pre-cancerous condition caused by overexposure to the sun. Treatment often involves applying a topical product like Efudex Cream to lesions twice daily for two to four weeks, during which time the condition may resolve on its own. *See* Petition at 12; *Dosage and Administration*, Efudex Cream Labeling. A study using such a treatment regimen to compare the ability of two products to treat AK may easily lead to a conclusion of equivalence, even where there are differences that would cause the two products to perform differently in the treatment of sBCC.[3]

AK studies also cannot bear the reliance Rothwell, Figg places on them because of their inherent methodological limitations. As described in Valeant's October 21, 2005, response to Rothwell, Figg ("Reply Comment") and the attached declaration of Howard I. Maibach, M.D., AK studies depend on investigators'

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[3] *See generally* Petition, Tab G (R.I. Ceilley & J.Q. Del Rosso, *Topical Chemotherapy for the Treatment of Skin Cancer*, in Cancer of the Skin, 620 (D.S. Rigel, *et al.*, eds., 2005)) (describing the similar efficacy rates for different strengths and formulations of fluorouracil in the treatment of AK).

visually diagnosing the condition and counting patients' lesions – a methodology that has been found to suffer from very high inter-observer variability. In one study, for example, two different investigators counted 30 and 105 lesions, respectively, *on the same patient*. *See* Reply Comment, Tab A9 (M.A. Weinstock, *et al.*, *Reliability of Counting Actinic Keratoses Before and After Brief Consensus Discussion*, Arch. Dermatol. 137: 1055-58 (2001)). Accordingly, although AK studies may be sufficient to demonstrate the efficacy of products in treating AK, they cannot be relied upon to demonstrate equivalence in absorption or in treating sBCC.

III. Bioequivalence Must be Established in sBCC

Rothwell, Figg continues to assert that "[f]or every one patient who uses Efudex® to treat sBCC, sixty patients use Efudex® to treat AK[,]" Comment at 6 (emphasis removed), and then argues that the agency could (and presumably should) recommend "that a study be performed in the one condition in which the drug product is most commonly used by patients . . . ." *Id.* at 4.

Rothwell, Figg's statistic, even if true, is irrelevant. The relative frequency with which a product is prescribed for various conditions plays no role in determining an appropriate bioequivalence methodology. *See* Petition at 11; Reply Comment at 2. Efudex Cream is approved to treat both AK and sBCC. Under the law, any generic version of the product must be approved for the same conditions of use, and with the same labeling, except for cases not relevant here (such as to protect patent rights). *See* 21 USC 355(j)(2)(A); 21 CFR 314.94(a)(8)(iv). Because any generic version of Efudex Cream will be labeled for the treatment of sBCC, it is imperative that the product be bioequivalent in the treatment of that condition.

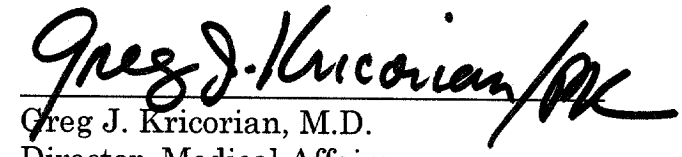
This is important, not just as a matter of law, but because of the risks associated with sBCC – a cancer that grows, invades other local tissues (including the papillary dermis), and is capable of metastasizing to other parts of the body. *See* Petition, Tab B (P.G. Lang & J.C. Maize, Sr., *Basal Cell Carcinoma*, in Cancer of the Skin, 101). Surgery and other aggressive treatments are the standard of care for treating sBCC patients. *See id.* at 118-23. Where a generic version of Efudex Cream might be prescribed, therefore, it is critically important that the product be bioequivalent in the treatment of sBCC.

IV. Conclusion

Rothwell, Figg has seized upon Fick's Laws of Diffusion to argue that a showing of equivalent rates of diffusion at one site of action allows one to assume equivalent rates of diffusion at another site of action. But for the reasons discussed above, a comparative clinical study in treating AK provides no data about rates of diffusion. Moreover, because the solubility of Efudex Cream and a proposed generic product would be affected by differences in particle size, there could be meaningful differences in their rates of diffusion. And because a comparative clinical study in AK patients simply cannot be relied upon to detect such differences, a study in sBCC patients must be conducted.

As always, we appreciate your time and courtesy in this matter.

Respectfully submitted,



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