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April 3, 2006

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

We are writing in response to the comment submitted on January 3, 2006, by Rothwell, Figg, Ernst & Manbeck, P.C. ("Comment"), in opposition to the above-referenced petition ("Petition"). With this submission, we are also providing the agency with a declaration from an expert dermatopathologist, Khanh P. Tran, M.D., in support of the finding that Efudex® (fluorouracil) Cream is approved for use in treating two distinct disease conditions that occur at two anatomically distinct sites of action.

As shown in the Petition and Valeant's subsequent filing, an abbreviated new drug application ("ANDA") for a generic version of Efudex® must be supported by a comparative clinical study in patients with superficial basal cell carcinoma ("sBCC"). The Comment contends that a clinical study in patients with actinic keratosis ("AK") should suffice, even though the generic product, if approved, would be labeled for use in treating sBCC.

The only new point raised in the Comment is the assertion that: "When two drug products release the same active ingredient, at the same site of action, at a comparable rate, the same concentration of active ingredient will be available regardless of the particular condition being treated." Comment at 3. The Comment includes a letter from an expert, Thomas J. Franz, M.D., who maintains that this proposition is applicable to locally acting topical drugs, just as it is applicable to drugs intended for systemic use.

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The Comment might have value here if there were a reliable way of demonstrating that two topical drug products do, in fact, release the same amount of drug at the same rate and to the same extent. At present, however, there is no validated method for measuring and comparing the pharmacokinetic ("PK") profiles of locally acting topical products. *See* 67 Fed. Reg. 35122, 35123 (May 17, 2002) (announcing the withdrawal of the draft guidance, *Topical Dermatological Drug Product NDAs and ANDAs – In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies*, because of scientific concerns about the validity of dermatopharmacokinetics, the primary method recommended in the guidance for demonstrating the bioequivalence of topical dermatological drugs).

For this reason, the bioequivalence of locally acting topical products must be supported by one or more comparative clinical trials. An equivalence trial, however, is designed only to show a lack of a difference around a pre-specified treatment parameter; it does not provide reliable or valid information on the rate and extent of absorption of the two products being tested. The clinical model used in an equivalence study would have to be extraordinarily sensitive to even begin to infer equivalent PK profiles from a finding of "no significant treatment difference."

AK studies, as shown in the Petition and Valeant's subsequent filing, tend to lack assay sensitivity. They suffer from high inter-observer variability, inclusion of inappropriate patients (*e.g.*, those who may lack the disease or may experience spontaneous improvement), and lack of blinding. *See, e.g.*, Reply Comment, Tab A at ¶¶ 25-31 (Oct. 21, 2005) (Declaration of Howard I. Maibach, M.D.). All of these factors tend to reduce observable differences between treatment groups and promote a conclusion that the products being compared are indistinguishable. To take such a conclusion and use it to find that the two products have equivalent PK profiles – and will have equivalent PK profiles at all other sites of action – is fatally flawed.

Here, the more sensitive model for an equivalence study is the sBCC model. An sBCC study relies on more objective parameters and, because it occurs at a deeper site of action, is more likely to challenge the release profiles of the test and reference products. An sBCC study is far more likely than an AK study to detect differences in the formulations. *See* 21 USC 355(j)(8) (alternative methods for demonstrating the bioequivalence of products not absorbed into the bloodstream

must be able to "detect a significant difference between the [proposed] drug and the listed drug in safety and therapeutic effect").[1]

As shown in Dr. Tran's declaration, AK and sBCC are distinct disease conditions that are anatomically different in meaningful ways. Dr. Tran is a practicing dermatopathologist who examines more than 100 skin biopsies and excisions weekly and routinely diagnoses AK, sBCC, and other skin disorders. According to Dr. Tran, AK is characterized by localized lesions of atypical squamous epidermal cells. sBCCs are "malignant, neoplastic proliferations of keratinocytes from the basal epidermis, which" – contrary to the Comment – "almost always exhibit multifocal growth within the papillary dermis." Tab A at ¶ 2; *see* Comment at 4. Although AK and sBCC both begin in the epidermis, they are "different diseases that exhibit different growth patterns and behavior." Tab A at ¶ 2.

The Comment suggests that once a basal cell carcinoma enters the papillary dermis, it is no longer considered to be an sBCC. Rather, according to the Comment, it becomes a form of carcinoma for which Efudex® is neither labeled nor approved. Again, as Dr. Tran explains, sBCC can and typically does extend into the papillary dermis. *Id.*

Finally, it is important to emphasize the importance of the clinical model to be used in this instance to support a finding of equivalence. As shown in the Petition and Dr. Maibach's declaration, even if two topical products are formulated to contain the same quantity and type of ingredients ("Q1/Q2 equivalent"), several factors may cause the products to perform differently once applied to the body. Contrary to the statement offered by Dr. Franz, one cannot "presuppose" that Q1/Q2 equivalent topical products will release their active ingredients at a comparable rate and to a comparable extent. Comment, Appendix 1.

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[1] Rothwell, Figg continues to assert that a clinical study in AK patients will be *more* sensitive and reliable than a study in sBCC patients, because the published success rate for AK is lower than that for sBCC. Comment at 6. As Valeant pointed out in its previous submission, no success rate for AK can be viewed with that level of precision because AK studies suffer from high variability and are based on the visual diagnoses of lesions by physicians. Reply Comment at 6. sBCC studies, on the other hand, typically use biopsies to confirm diagnoses and clinical cures, and are therefore much more objective.

Dr. Franz's position rests upon the mistaken premise that such products are necessarily "virtually identical in composition." *Id.* In fact, two fluorouracil cream products, formulated to be Q1/Q2 equivalent, may nonetheless have differences in particle size and distribution that may cause the products to release different amounts of active ingredient at different rates and to different extents. *See* Reply Comment, Tab A at ¶¶ 13, 16-24. Fluorouracil is a poorly soluble crystalline solid. The concentration and size of partially solubilized droplets in a fluorouracil cream product are thus critical to determining the dermal penetration and bioavailability of the active ingredient.

Accordingly, two fluorouracil cream manufacturers can start with the same set of ingredients and yet effectively produce two different products. Only when the two formulations are compared in a challenging clinical environment, capable of detecting differences in the products, can a conclusion of equivalence be reached. sBCC, and not AK, is the only model likely to surface real differences between the products.

In sum:

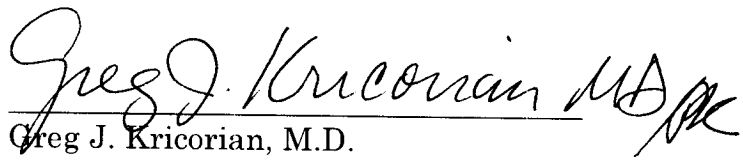
- A finding of clinical equivalence in an AK study is not synonymous with a finding that the two products release the same amount of drug at the same rate and to the same extent.

- The Comment asserts that AK and sBCC occur at the same anatomical site of action, which is not correct.

- The Comment assumes that Q1/Q2 equivalent products will release the same amount of drug, which fails to take into account other differences that can affect bioavailability.

The approval of a drug for use in treating sBCC should not be based on a leap of faith; it should be based on a well-controlled, comparative clinical study in patients with sBCC. The agency should not accept anything less.

Respectfully submitted,



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Attachment

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