



Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

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VIA FACSIMILE AND U.S. MAIL

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Docket No. 2004P-0448

Re: Requirements that Must Be Met to Establish Therapeutic Equivalence of Generic Versions Fluocinolone Acetonide 0.01% topical oil to Derma-Smoothe/FS® Scalp Oil and Body Oil

It has come to our attention that there is now currently at least one Abbreviated New Drug Application ("ANDA") submitted to the Office of Generic Drugs seeking acceptance for filing and approval for a generic version of Derma-Smoothe/FS® Scalp Oil and Body Oil (fluocinolone acetonide 0.01% topical oil.)

As you know, on September 30, 2004, Hill Dermaceuticals, Inc. ("Hill") submitted a Citizen Petition requested that the Commissioner of Food and Drugs not approve any generic equivalent version of the Petitioner's proprietary drug product, Derma-Smoothe/FS® Scalp Oil and Body Oil (fluocinolone acetonide 0.01% topical oil) unless and until ANDA applicants comply with statutory requirements to demonstrate that any proposed generic equivalent product has the same active ingredient, labeling, and conditions of use as the reference listed drug, Derma-Smoothe/FS®. In the petition we also requested that any ANDA applicant for fluocinolone acetonide topical oil must demonstrate bioequivalence which can only be done by conducting studies with clinical endpoints, the same as those established by Petitioner.

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On March 26, 2005, the Agency issued an interim response to the Citizen Petition noting that the Agency was unable to reach a decision due to the need to address other Agency priorities and that the Agency will respond as soon as possible given the numerous demands on the Agency's resources. As of today, the Agency has provided no substantive response to the Citizen Petition. This is a cause of significant concern to us and Hill intends to amend its Citizen Petition in the very near future.

Hill is sending this letter to emphasize some issues that we think are critical to establishing pharmaceutical and bioequivalence with respect to a generic equivalent version of our proprietary drug product, Derma-Smoothe/FS® Scalp Oil and Body Oil (fluocinolone acetonide 0.01% topical oil) and that we will vigorously pursue with the Agency, through the administrative and legal processes, if necessary, to ensure that the statutory requirements for approval of ANDAs are met. FDA must ensure that there is a level playing field so that all firms, large and small, innovator and generic can equally compete in the marketplace.

First, studies with clinical endpoints are necessary to establish bioequivalence and therapeutic equivalence as opposed to the vasoconstriction assay (skin blanching test) which the Agency has used as a surrogate marker to establish the therapeutic equivalence of corticosteroid creams and ointments that contain the general indication for treating corticosteroid responsive dermatoses but is not validated as a surrogate marker for the specific approved indications of scalp psoriasis or atopic dermatitis. Vasoconstrictor assays cannot and have not been conducted on the scalp. There is no validated method for such studies. All of the vasoconstrictor assays that were performed to date were conducted on the forearms. The scalp is far more permeable than the forearm and it is inappropriate to conduct a vasoconstrictor assay on the scalp. Given that the scalp is the intended treatment area for Derma-Smoothe/FS® Scalp Oil, bioequivalence/therapeutic equivalence can only be established through the conduct of a study on the scalp under the prescribed conditions of use measuring the relevant clinical endpoints.

Second, any approval of any generic equivalent(s) of Petitioner's Derma-Smoothe/FS® must also be preceded by evidence that the proposed equivalent has the same safety and efficacy profile under use for the specific indications of widespread scalp psoriasis and/or atopic dermatitis and not for corticosteroid responsive dermatoses. Hill understands that one of the current ANDA applicant(s) may be seeking approval based on demonstrating equivalence on only one of the specified indications, i.e., atopic dermatitis and not psoriasis of the scalp. As you well know, an ANDA is required to have the same conditions of use set forth in the labeling, but can "carve out" certain labeling statements that are protected by patent or market exclusivity. There is no patent or unexpired exclusivity associated with the approved indications of atopic dermatitis and not psoriasis of the scalp, thus a generic applicant is required to have the same labeling as the reference listed drug.

Third, Hill firmly believes that while a vasoconstrictor assay may be an appropriate surrogate marker for certain corticosteroid responsive dermatoses conditions, it is not a generally accepted surrogate marker for either atopic dermatitis or psoriasis of the scalp. Thus the only way to establish bioequivalence is for a generic applicant to conduct a non-inferiority comparison to Derma-Smoothe/FS® using relevant clinical endpoints to show efficacy and safety to patients with wide spread scalp psoriasis with a minimum of 4 hours occluding with a shower cap.

Fourth, the formulation of the product plays a role in delivering the product to the site of action, conditioning the skin and patient acceptance in being able to wash the oily formulation out of the hair when the dosage regimen is completed. The ratio of different oils in the formulation as well as the presence of the detergent has been shown in clinical studies to impact the safety and efficacy of the product. Since Derma-Smoothe/FS® Scalp Oil is the only topical corticosteroid approved for use under occlusion (with shower caps supplied in the package) any changes in the oil composition can increase adverse events such as folliculitis when the product is used under occlusion as specified in the approved labeling. The reference listed drug formulation has been demonstrated to be

safe and effective under occlusion. Given that any proposed generic product may have a different ratio of oils and other excipients, which can impact safety and efficacy, studies with appropriate clinical endpoints are necessary to establish equivalence.

Fifth, the reference listed drug is formulated with a specially designed, proprietary refined peanut oil. Hill expects the Agency to require any other company pursuing a product using another non-proprietary source of peanut oil as the vehicle to set an upper limit for the amount of peanut protein that can be present in the vehicle. Any such test used to measure peanut oil, of course, must be appropriated, validated and be capable of quantifying very low levels of peanut protein.

As we noted in the original Petition, this issue is of particular concern if the peanut oil used in the formulation is from a foreign supplier. The Agency must require foreign suppliers of peanut oil to implement appropriate specifications and controls to ensure the safety of peanut sensitive patients who use fluocinolone acetonide topical oil. The Agency recognizes the importance of this issue that was raised as a result of a study published in the New England Journal of Medicine and the responses published to the study. (NEJM, March 13, 2003, and July 17, 2003.)

Sixth, It is important to note that Derma-Smoothe/FS® Scalp Oil and Derma-Smoothe/FS® Body Oil are not interchangeable and indication specific and there is separate labeling for each product. The Derma-Smoothe/FS® Scalp Oil is not approved for children. Hill was required to conduct extensive efficacy and safety studies on patients with wide spread atopic dermatitis in peanut allergic patients testing peanut oil showing it is safe on a regular basis. Currently the Hill is conducting safety studies on patients 3 months to 2 years of age for adrenal suppression. Derma-Smoothe/FS® is the only topical oil with 50-90% body involvement that shows no adrenal suppression. This data is on file with dermatology division and was presented at the Pediatric Advisory Committee Meeting on October 23 – 24, 2003, as well as in the fall of 2004. Since the formulation can have a significant impact on peanut sensitive individuals as well as on

adrenal suppression, in order to establish equivalence, the Agency must require a manufacturer of a generic version of Derma-Smoothe/FS® to conduct these types of studies.

In summary, there are significant safety issues associated with overexposure to corticosteroids, i.e., adrenal suppression. In addition, peanut sensitive individuals who are exposed to peanut protein can experience, serious, life-threatening anaphylactic reactions. The Agency must institute such appropriate regulatory requirements to ensure that all generic products meet the standards of identity, strength, quality and purity and are therapeutically equivalent so that public confidence is maintained and the public health is protected. Hill is willing and able to compete in the marketplace as long as all companies seeking approval to market a generic version of Derma-Smoothe/FS® are required to meet appropriate regulatory requirements for approval.

Sincerely yours,



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