Appendix A

APPENDIX A

Dr. Howard I. Maibach Letter on Bioequivalence and Safety Issues Pertaining to Generic Versions of Derma-Smoothe/FS®

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE
DEPARTMENT OF DERMATOLOGY

Howard I. Maibach, M.D.
Professor

SAN FRANCISCO, CALIFORNIA 94143-0989

Office Telephone (415) 476-2468
Private Study (415) 673-9693
Facsimile (415) 753-5304

Division of Dermatology and Dental Drug Products
NDA 19-452

February 2, 2006

Gary J. Buehler, R.Ph.
Director
Office of Generic Drugs (HFD-600)
The Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

Dear Mr. Buehler:

I have been asked by Jerry Roth, President of Hill Dermaceuticals, Inc., to comment on bioequivalence and safety issues for your consideration, pertaining to possible generic versions of ***Derma-Smoothe/FS® Scalp Oil,*** approved by The Food and Drug Administration ("FDA") for *widespread scalp psoriasis* for age(s) ≥12 and ***Derma-Smoothe/FS® Body Oil*** which is FDA-approved for *widespread* (50%-90% involvement) *atopic dermatitis/eczema* in children ≥2 years of age and adults.

Comments of this formulation's uniqueness follow:

Derma-Smoothe/FS® Scalp Oil

Derma-Smoothe/FS® Scalp Oil is unique due to its vehicle, a blend of oils, primarily a proprietary refined peanut oil. This vehicle, the subject of extended discussions with the Agency has the following characteristics:

1. A sensitive chemical analytical assay implemented as required by the Division of Dermatology and Dental Drug Products, to ensure that individuals allergic to peanuts will not develop immunologic contact urticaria (ICU) syndrome on touching this formulation.

2. The active corticosteroid, fluocinolone acetonide, 0.01%, is insoluble in peanut oil, which led to a proprietary formulation. A specific quality of a specific surfactant (detergent) with

very tight controls and testing on each batch is used to ensure that the stability of fluocinolone acetonide is maintained throughout the product's shelf life.

3. The source of this highly refined peanut oil is proprietary information. Other peanut oils cannot and should not be assumed to be identical in refinement or processing.

This appears highly, clinically relevant in that the Derma-Smoothe/FS formulation has now been shown to be stable since 1990 and has not been associated with a single report of immunologic contact urticaria. (Attachment 5 provides a short summary of the clinical manifestations of Contact Urticaria Syndrome and why the sponsor has gone to extremes to avoid this). In addition, and quite importantly, there are no other commercialized corticosteroid products that have indication specific labeling, i.e., psoriasis of the scalp and widespread atopic dermatitis.

Derma-Smoothe/FS® Scalp Oil is the only corticosteroid in an oil delivery system. In corticosteroid products and other topical products, vehicles play a vital role in how the products react on, and in, the skin as to clinical potency, percutaneous absorption and tolerance.

Unlike with many oral and parenteral medications, the excipients of most topical formulations alter thermodynamic activity and interact with compartments within the stratum corneum and other parts of the skin. Slight modifications of the excipients in the formulation may move a corticoid from weak to highly potent.

The application method is unique. The product is applied to the entire scalp which is occluded with a shower cap supplied with the product, and left on for a minimum of 4 hours or overnight. This is the only corticosteroid preparation labeled for the scalp with occlusion (Phase 3 clinical studies on Derma-Smoothe/FS for the indication psoriasis of the scalp), and the only corticosteroid product available on the market for this type of treatment modality, i.e. packaged and labeled for occlusion. In this vehicle, local cutaneous problems associated with occlusion of corticosteroids have not been reported, in contradistinction to other corticoid occlusion strategies.

Most topical corticosteroids that the office of Generic Drugs reviews have been approved for the general indication of *corticosteroid-responsive dermatoses.* The bioequivalence of these products have been based upon a surrogate marker, skin blanching vasoconstrictive study, which is performed on normal skin, usually the forearm.

Derma-Smoothe/FS Scalp Oil is indicated specifically for scalp psoriasis. The scalp differs significantly from the forearm, back or other body parts; it is far more vascular and diseases do not present themselves the same way on the scalp as elsewhere. To my knowledge, vasoconstrictor assays have not been conducted on the scalp.

The formula for the Derma-Smoothe/FS® Scalp Oil Vehicle is precise. Even a slight variation in the quantitative formulation, despite meeting generic regulatory requirements, [Code of Federal Regulations, Title 21, section 314.94 (9)(v)] may create highly, clinically relevant safety issues (contact urticaria syndrome), especially when used with occlusion. Therefore, the sponsor for a generic equivalent should provide proof that the generic product is not inferior in efficacy or safety through well controlled clinical studies.

Derma-Smoothe/FS® Body Oil

Derma-Smoothe/FS® Body Oil, (fluocinolone acetonide, 0.01%) is approved for children and adults for the specific indication ***widespread atopic dermatitis/eczema > 50% - 90% body involvement.*** Clinical studies (Phase 4 clinical studies for the efficacy and safety of Derma-Smoothe/FS in pediatric patients with severe to moderate atopic dermatitis) document that ***Derma-Smoothe/FS® Body Oil*** is safe in terms of adrenal suppression. None of the patients in the study experienced such suppression.

The safety data was presented to the FDA's Pediatric Advisory Committee, showing that ***Derma-Smoothe/FS® Body Oil*** is the only product to be proven adrenal safe, showing that the adrenal function is not compromised when treating greater than 50% - 90% of the body in children as young as 2 years, with moderate to severe atopic dermatitis. To my knowledge, **Derma-Smoothe/FS Body Oil** is the only "modern" corticoid product to be proven free of adrenal suppression when treating such large surface areas.

For instance, pediatric approval for Elocon (mometasone furoate) required the labeling to state "use with caution in pediatric patients 2 years or older." Moreover, HPA axis suppression was observed in about 16% of pediatric patients 6 to 23 months who were otherwise normal (not suppressed) before treatment. Suppression was seen after 3 weeks of treatment over a mean body surface area ("BSA") of 41%.

The few other topical corticosteroids with pediatric studies, Aclovate (aclometasone diproprionate) and Cutivate (Fluticasone propionate), showed HPA axis suppression after 3 to 4 weeks of twice daily treatment in pediatric patients at least 1 year old and 3 months old, respectively.

Thus, to my knowledge, the only "modern" topical corticoid that has not shown adrenal suppression when treating large body surface areas (up to 90%) is ***Derma-Smoothe/FS® Body Oil.***

It is my further understanding that adrenal suppression studies are being conducted by the Sponsor on patients as young as 3 months of age; at this point (February 1, 2006), no suppression has appeared.

Peanut Oil

It is quite important to note that the Agency has expressed concern over peanut allergy since this product contains peanut oil. There were 2 studies conducted for Derma-Smoothe/FS in known peanut-sensitive individuals, using Prick and Patch tests. Results of both studies showed no reaction to Prick or Patch testing (Peanut allergy studies). Any proposed generic product should demonstrate for their formulation the absence of peanut reaction in peanut sensitive patients.

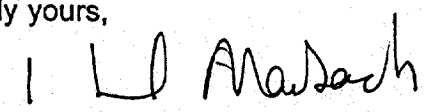
It is also important to consider the quality of the ingredients in the vehicle, i.e. refined peanut oil. As previously stated, the source, refining process, and even the quality control of peanut oil cannot be assumed to be exact from one manufacturer to the next. The qualitative evaluation of this ingredient must be the same as the reference drug product to ensure the generic product is exactly the same as the reference product. Testing for peanut proteins in Refined Peanut Oil NF is conducted using a sandwich enzyme-linked immunosorbent assay test (S-ELISA) and must be conducted by the ANDA applicant on all Refined Peanut Oil NF lots to ensure the generic products label claim, of no detectable peanut proteins to as low as 2.5 parts per million (ppm), is the same as the

reference product Derma-Smoothe/FS. If the test is not conducted by the ANDA applicant, they do not conform to the reference products approved labeling statement: Derma-Smoothe/FS does not have detectable proteins at 2.5 ppm. If the ANDA applicant does not perform appropriate peanut protein testing then appropriate clinical safety studies should be conducted.

For these reasons, a generic product must have exactly the same qualitative and quantitative formulation as Derma-Smoothe/FS because this FDA-approved formula has been demonstrated through adequate and controlled clinical studies not to cause adrenal suppression or immunologic contact urticaria.

Potential safety issues cannot be validated by Vasoconstrictor studies. I think this is a vital issue that should be addressed by the Agency. If there are any questions, I would be pleased to attempt to answer them.

Very truly yours,



Howard I. Maibach, M.D.