The Affidavit of Howard Ira Maibach, M.D.
In Support of Citizen Petition, Docket 2004P-0448

This affidavit is made on my own personal knowledge and belief. I am over the age of 18 years, and otherwise *sui juris*. I testify as to the following matters based upon my own personal knowledge:

Educational Background – I earned my undergraduate and medical degrees from Tulane University. I completed a residency and fellowship at the Hospital of the University of Pennsylvania. Post-graduate positions include Assistant Instructor at The University of Pennsylvania School of Medicine, lecturer at the Graduate School of Medicine, University of Pennsylvania; Within the University of California, School of Medicine positions held have been: Assistant Professor of Dermatology, Associate Professor of Dermatology, Research Associate, Cancer Research Institute, Professor of Dermatology, Vice Chairperson of Dermatology, Chief of Occupational Dermatology Clinic. I am presently a Professor of the Department of Dermatology at The University of California.

I am the author of articles and textbooks, including Topical Corticosteroids.

Details concerning my educational and professional background are in the curriculum vitae and bibliography (Attachment 1).

AFFIDAVIT

In light of my experience in the field of dermatology and my expertise with topical corticosteroids, I have been asked by Mr. 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 in adults 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 older, and adults.

Derma-Smoothe/FS® Scalp Oil

1. *Derma-Smoothe/FS® 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. Even slight modifications of the excipients in the formulation may move a corticoid from weak to highly potent:

Table[1] Betamethasone valerate

Corticosteroid Class	Potency	Tradename
Class 2 Potent	0.1%	Betnovate
Class 3 Upper mid-strength	0.1%	Betatrex Valisone 0.1%, O
Class 5 Lower mid-strength	0.1%	Betatrex Valisone C,L
Class 6 Mild	0.1%	Valisone 0.1% C

2. 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 are based upon a surrogate marker, skin blanching (vasoconstrictor study), which is performed on normal skin, usually the forearm.

3. *Derma-Smoothe/FS® Scalp Oil* was approved for scalp psoriasis, with the use of occlusion with a shower cap. Reference is made to the supplemental application S-010 to NDA 19-452 for the indication of scalp psoriasis, approval date Feb 16, 1995 (Attachment A), and S-016/NDA 19-452 for indication specific labeling, approval date Nov 17, 2005 (Attachment B). The scalp differs significantly from the forearm, back or other body parts; the scalp 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. Moreover, potential safety issues cannot be validated by vasoconstrictor studies.

[1]Jacob SE, Steele T. Corticosteroid classes: A quick reference guide including patch test substances and reactivity. J. Am Acad Dermatol 2006;54:723-7.

This is a vital issue that should be addressed by the Agency. When the blood level system is not applicable, the clinical end point becomes the true marker of bioequivalence.

4. The formula for the *Derma-Smoothe/FS®* is precise. Even a slight variation in the 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. Variances in the vehicle's composition, if more occlusive, could produce folliculitis. Therefore, the sponsor for a generic equivalent should provide documentation that the generic product is not only '*not inferior*' but also '*equal to*' in efficacy and safety to the brand name drug through well-controlled clinical trials.

   The proprietary formulation of Derma-Smoothe/FS contains a specific quality of a specific surfactant (detergent). Because this surfactant can significantly affect the stability of the active ingredient fluocinolone acetonide, very tight controls and testing requirements are conducted on each manufactured batch of the finished product to ensure that the stability of fluocinolone acetonide is maintained throughout the product's shelf life.

   Note that the analytical assay test for fluocinolone acetonide in the finished product is a proprietary method developed by Hill. The proprietary method was developed because the Agency (Dermatology Division) did not accept the validity of the (USP) compendial method originally applied to test this product.

5. Derma-Smoothe/FS® was approved for the indication of scalp psoriasis based on well-controlled phase 3 clinical studies that involved treatment of the whole scalp and occlusion with a shower cap for a minimum of 4 hours. This unique approval included the drug product packaging assembly that included the shower cap. [S-010 to NDA 19-452 for the indication of scalp psoriasis, approval date Feb 16, 1995 (Attachment A), and S-016/NDA 19-452 for indication specific labeling, (approval date Nov 17, 2005 Attachment B)] There is no other topical corticosteroid product that is marketed with a shower cap, as part of the packaged finished product.

Derma-Smoothe/FS® (Body Oil)

6. *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 trials (Phase 4 safety studies) to assess the potential of Derma-Smoothe/FS to suppress the Hypothalamic-Pituitary-Adrenal (HPA) axis in pediatric patients with severe to moderate atopic dermatitis, (sNDA

017, approval date Oct 10, 2001, Attachment C) document that Derma-Smoothe/FS Body Oil appears, as **none of the patients in the study experienced adrenal suppression.** This favorable feature of the drug is attributed to the vehicle and formulation, so that maximum benefit is derived, such as the ability of this vehicle to cover a larger surface area with a lesser amount of drug, its ability to hydrate and enhance penetration of the active component, and the stability of the molecule in the vehicle, among others[2]

7. The safety data was presented to the FDA's Pediatric Advisory Committee,[3 4] showing that Derma-Smoothe/FS® Body Oil is the only topical corticosteroid product to prove systemic safety, demonstrating that the adrenal function is not compromised when treating >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.**

8. I have been informed by Hill that additional adrenal suppression studies on patients as young as 3 months of age have been conducted by the Sponsor (from April 2005 to Nov 2006) and submitted to the Agency. (Supplemental Application filed February 12, 2007). It is my further understanding that no adrenal suppression appeared in that patient population either.

   Thus, the percutaneous penetration available from Hill's FDA-approved product results from the amount of corticoid delivered to the skin and relates not only to the proprietary oil's characteristics but to the proprietary detergent.

9. As stated earlier, even a slight modification of the excipients in the formulation may move a corticosteroid from weak to highly potent. This should be considered when reviewing a generic version of the brand name drug, *Derma-Smoothe/FS® Body Oil*, as even a slight variance in the vehicle's composition may significantly affect the action of the corticoid in the body, and result in adrenal suppression in patients. **(Table; Topical Corticosteroids[5])** Therefore, the sponsor for a generic equivalent should provide proof that the generic product is not only '*not inferior*' but also '*equal to*' in efficacy and safety to the brand name drug through well-controlled clinical trials.

Refined Peanut Oil

[2] Brazzini, B; Pimpinelli, N, New and Established Topical Corticosteroids in Dermatology, Am J Clin Dermatol 2002;3 (1):47-58

[3] Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee Meeting on October 29, 2003 in Gaithersburg, Maryland and the March Joint Session with the Non-Prescription and Dermatolic Drugs Advisory Committee

[4] March 24, 2005 Joint Dermatologic & Ophthalmic Drug and Non-Prescription Drug Advisory Committee Meeting

[5] Maibach ed. Topical Corticosteroids.

10. Note that the Agency's Dermatologic Division has continually expressed to Hill Dermaceuticals (Attachment D) concern over peanut allergy since this product contains peanut oil. Two studies were conducted and submitted to the Agency 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). [Reports filed with FDA on May 21, 1999, February, 1999 and March, 1999). Any proposed generic product should demonstrate for their formulation the absence of peanut reaction in peanut-sensitive patients.

11. It is also important to consider the quality of the ingredients in the vehicle, i.e. the Hill proprietary 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 product.

12. In (June 1999) Hill implemented an analytical test, S-ELISA, for refined peanut oil, to verify that no protein is detected at 2.5 ppm (parts per million) level. However, the literature and experts suggest the importance of testing to even lower levels. Although not part of an official compendium for refined peanut oil testing, in 2007, Hill will implement a newer, more sensitive, analytical test for peanut protein content detection to as low as 1 part per million (microgram per gram). This validated method of testing and proprietary preparation will be the standard testing at Hill as of (March 2007) on every batch of refined peanut oil and will be so stated in its labeling. This is a proprietary technology.

13. The source of this highly-refined peanut oil is proprietary and not released for other manufacturers' use. To the best of my knowledge, this information is proprietary between Hill and the Agency's Division of Dental and Ophthalmic Drugs.

In conclusion, for these reasons, a generic product should have exactly the same qualitative and quantitative formulation as *Derma-Smoothe/FS®* because this FDA-approved formula has been demonstrated through adequate and well-controlled clinical studies not to cause adrenal suppression or immunologic contact urticaria, when used over as much as 90% body surface area in pediatric patients 3 months and older. Potential safety issues cannot be validated by vasoconstrictor studies. 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.

I DECLARE under penalty of perjury that the foregoing is true and correct.
Executed on this 1st day of March, 2007.

Howard Ira Maibach, M.D.

HOWARD I. MAIBACH, M.D. ATTACHMENT INDEX

		Tab Identifier
Attachment 1:	Curriculum Vitae and Bibliography of Howard I. Maibach, M.D.	Attachment 1
Attachment A:	Supplemental Application S-010 to NDA 19-452 for the Indication of Scalp Psoriasis (Feb. 16, 1995)	Attachment A
Attachment B	Supplemental Application S-016 to NDA 19-452 for Indication Specific Labeling (Nov. 17, 2005)	Attachment B
Attachment C:	Supplemental Application S-017 to NDA 19-452 for the Indication of Pediatric Patients 2 Years and Older (Oct. 10, 2001)	Attachment C
Attachment D:	Peanut Allergy Articles	Attachment D
Affidavit Reference 1:	Reference to Maibach Affidavit Point 4	Point 4 Reference
Affidavit Reference 2:	Reference of Footnote 1 of Maibach Affidavit: Jacob SE, Steele T. Corticosteroid classes: A quick reference guide including patch test substances and reactivity. J Am Acad Dermatol 2006;54:723-7.	Reference to Footnote 1
Affidavit Reference 3:	Reference to Footnote 2 of Maibach Affidavit: Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology. Am J Clin Dermatol 2002;3(1):47-58.	Reference to Footnote 2