



Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

September 30, 2004

VIA FEDERAL EXPRESS

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Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SEP 30 2004

CITIZEN PETITION

Hill Dermaceuticals, ("Hill") Sanford, Fl., submits this Citizen Petition under the Code of Federal Regulations Part 21, Section 10.30 to request the Commissioner of Food and Drugs to take the following administrative action:

A. Action Requested

The Petitioner hereby requests that the Commissioner of Food and Drugs not approve any generic equivalent version of the Petitioner's proprietary drug product, DERMA-SMOOTHIE/FS® (fluocinolone acetonide 0.01% topical oil) unless and until Abbreviated New Drug Application ("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-SMOOTHIE/FS®. In addition, any ANDA applicant for fluocinolone acetonide topical ointment must demonstrate bioequivalence which can only be done by conducting studies with clinical endpoints, the same as those established by Petitioner, as discussed below.

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. Moreover, any approval of any generic equivalent(s) of Petitioner's DERMA-SMOOTHIE/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.

2004P-0448

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Petitioner specifically requests that the Commissioner withhold approval of any proposed generic equivalent(s) of the Petitioner's proprietary DERMA-SMOOTH/FS® (fluocinolone acetonide) topical oil 0.01% without safety, efficacy, bioequivalence¹ or bioavailability studies evidencing results mirroring those found by the original drug in light of its novel and innovative application and delivery systems. Petitioner also requests that the Agency apply inspectional requirements consistently and that each site conducting the proposed generic equivalent(s) requisite bioequivalence studies are subject to audit in order to determine whether these bioequivalence studies were conducted in compliance with the protocol and other good clinical practice requirements.

B. Statement of Grounds

Petitioner, Hill Dermaceuticals, manufactures and distributes DERMA-SMOOTH/FS® (fluocinolone acetonide) topical oil 0.01%. DERMA-SMOOTH/FS® has been approved by the Food and Drug Administration (hereinafter referred to as "FDA" or "the Agency") for use in adult patients with scalp psoriasis, and in pediatric patients over the age of two years with moderate to severe atopic dermatitis. As part of its original New Drug Application ("NDA") with the FDA, Hill Dermaceuticals conducted and submitted to the Agency three major clinical studies, involving 40 patients, 94 patients and 102 patients, respectively, which demonstrated the safety and effectiveness of the Product for both indications². DERMA-SMOOTH/FS® (Scalp Oil) is the only topical corticosteroid that is FDA approved for use under occlusion in treating scalp psoriasis. The use of the shower cap that is packaged with the product (two are included in the box) and the corresponding labeling associated with the use of the product under occlusion distinguish DERMA-SMOOTH/FS® from all other FDA approved topical corticosteroids.

Hill Dermaceuticals' significant experience in the development and manufacture of fluocinolone acetonide topical oil (please note that DERMA-SMOOTH/FS® is the only topical product currently approved by the FDA that uses a specially designed, proprietary peanut oil vehicle) makes it uniquely situated to comment and to provide insight on the issues involved with establishing the therapeutic equivalence of any proposed fluocinolone acetonide topical oil generic product. There are a myriad of safety, efficacy, chemistry, manufacturing and controls, and bioequivalency, and bioavailability issues that must be addressed by both ANDA applicants and the Agency prior to approval of any generic fluocinolone acetonide topical oil product.

¹ The FDA Advisory Committee on Pharmaceutical Science recently determined, in its April 14, 2004 meeting, that a drug will be considered bio-inequivalent if it does not meet or exceed any of three pharmacokinetic endpoints; (1) area under the curve to a specific time; (2) total area under the curve; (3) the maximum concentration of the drug. Specifically, the committee found that the "area under the curve" parameter should have the primary emphasis. For those products that are not systemically absorbed, the Agency has adopted alternative approaches that utilize validated surrogate markers and/or relevant clinical endpoints to establish bioequivalence.

² A chart is attached hereto as Appendix "A" which summarizes the conduct and outcome of the three major clinical studies conducted on DERMA-SMOOTH/FS®.

Statutory and Regulatory Requirements

Section 505(j)(2)(A) of the Federal Food, Drug and Cosmetic Act (“FDCA” or “the Act”) provides that with respect to drugs containing only one active ingredient, any person filing an ANDA must demonstrate, among other things, that the proposed abbreviated new drug includes information: (1) to show that the conditions of use prescribed, recommended or suggested in the labeling have been previously approved in the reference listed drug (“RLD”); (2) the active ingredient is the “same”; (3) the dosage form, route administration is the same; (4) to show that the product is bioequivalent; and (5) the proposed labeling has been previously approved. The statutory requirements are paralleled in FDA’s implementing regulations at 21 CFR §314.94.

Inactive Ingredients for Topical Products

In addition to requirements regarding the “sameness” of active ingredients, FDA’s regulations also address inactive ingredient requirements for topical dosage forms. A drug product intended for topical use must contain the same inactive ingredients as the RLD, unless the applicant identifies and characterizes the differences and can demonstrate that the differences do not affect the safety and effectiveness of the proposed drug product. *See* 21 C.F.R. §314.94(a)(9)(v).

To meet requirements for approval, an ANDA applicant must meet the applicable statutory and regulatory requirements. The importance of these requirements as they relate to proposed ANDAs for fluocinolone acetonide topical oil are discussed below.

Pharmaceutical Equivalence Requires That Any Manufacturer Meet Strict Specifications for Processing, Manufacturing and Testing

As you may know, DERMA-SMOOTH/FS® is formulated with a specially designed, proprietary refined peanut oil. Importantly, the proprietary refined bulk peanut oil NF used in DERMA-SMOOTH/FS® is heated at a specific high temperature for a period of time to decompose the allergenic proteins. In addition, proprietary peanut oil used in Derma-Smooth/FS® is routinely tested for peanut proteins using a sandwich enzyme-linked immunosorbent assay test (S-ELISA) kit, which can detect peanut proteins to a very low level. Hill Dermaceuticals fully characterized the proprietary peanut oil and blend of other oils that comprise the vehicle for DERMA-SMOOTH/FS®, and specifically established an upper limit for the amount of peanut protein that can be present in the vehicle.

Hill Dermaceuticals, of course, would also expect that any other company pursuing a product using another non-proprietary source of peanut oil as the vehicle would be required 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. ANDA applicants for a generic version of DERMA-SMOOTH/FS® must demonstrate that their product meets strict specifications to ensure that peanut protein is not present in the product (or present in quantities that do not raise safety concerns).

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. Hill Dermaceuticals knows that 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.)

In addition, DERMA-SMOOTHIE/FS®'s dosage form has unique properties. During the course of formulating, developing and subsequently marketing DERMA-SMOOTHIE/FS®, Hill Dermaceuticals has identified that the detergent used in the product is a particularly critical formulation and processing component. The order of addition of the components and other related manufacturing process parameters, e.g., temperature and mixing time can significantly affect the formulation and absorption of the drug product through the skin or scalp. Hill Dermaceuticals has identified that minor changes in the detergent used in the formulation can give rise to loss of product stability. The detergent likely has an impact on the stability of the active ingredient, fluocinolone acetonide. Consequently, Hill Dermaceuticals now places a representative sample lot of DERMA-SMOOTHIE/FS® into its accelerated and room temperature stability program when a new lot number of detergent is used in the manufacturing process. In addition, Hill Dermaceuticals believes that accelerated stability testing alone may not be indicative of product stability at the end of the expiration dating period. Manufacturers of a generic version of fluocinolone acetonide topical oil must ensure that their products meet appropriate specifications throughout the products' labeled expiration dating period.

DERMA-SMOOTHIE/FS® (Scalp Oil) is the only topical corticosteroid that is FDA approved for use under occlusion in treating scalp psoriasis. The use of the shower cap that is packaged with the product (two are included in the box) and the corresponding labeling associated with the use of the product under occlusion distinguish DERMA-SMOOTHIE/FS® from all other topical corticosteroids. Again, any manufacturer must conduct a trial using the proposed formulation under occlusion with a shower cap in order to establish the therapeutic equivalence of any generic versions of fluocinolone acetonide topical oil 0.01% product to Hill Dermaceutical's DERMA-SMOOTHIE/FS®. In addition, since Hill Dermaceuticals was required to establish the compatibility of the shower cap with DERMA-SMOOTHIE/FS®, any generic manufacturer of fluocinolone acetonide should also establish that the shower cap is compatible with its formulation.

Bioequivalence Requirements Should Not Be Waived For ANDA Applicants for Fluocinolone Acetonide Topical Oil

Among other requirements, an ANDA manufacturer must provide information that shows that the drug product is bioequivalent to the RLD upon which the applicant relies. See 21 C.F.R. §314.94 (j) The core of the bioequivalence concept is an absence of significant difference in the extent and rate of which two different drug products' active ingredients "become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. See 21 C.F.R. §320.1(e).

Because of the unique issues related to a topical oil containing fluocinolone acetonide, the Agency should not grant a bioequivalence waiver for any fluocinolone acetonide ANDA. FDA's requirements for a bioequivalence waiver for topical products are quite limited. Only if a topical product meets the following requirements can a bioequivalence study be waived:

[It] [c]ontains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and

[It] [c]ontains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

21 C.F.R. §320.22(b)(3).

Since formulation, manufacturing and processing parameters for fluocinolone acetonide topical oil may significantly affect systemic or local availability for products intended to act locally, we firmly believe that a bioequivalence waiver is not scientifically or legally warranted and should not be granted for ANDA applicants for fluocinolone acetonide topical oil.

Pharmacodynamic Requirements

In the past, the Agency has accepted the use of the vasoconstriction assay (skin blanching test) as a surrogate marker to establish the therapeutic equivalence of corticosteroid creams and ointments that contain the general indication for treating corticosteroid responsive dermatoses. While this pharmacodynamic test is appropriate for certain dosage forms containing corticosteroids, it is not a valid surrogate marker for a topical oil that is used to treat scalp psoriasis or atopic dermatitis, the indications clinically proven by Hill Dermaceuticals for DERMA-SMOOTH/FS® that are more specific than the general indication of corticosteroid responsive dermatoses. The vasoconstrictor assay has never been validated as a surrogate marker to predict clinical efficacy in either of these two diseases.

Studies With Clinical Endpoints Are Necessary to Establish the Therapeutic Equivalence of Any Fluocinolone Acetonide Topical Oil Product

Since fluocinolone acetonide topical oil is intended for local, topical use and is not systemically absorbed, the only way a company seeking approval for a generic version of DERMA-SMOOTH/FS® can establish therapeutic equivalence is to conduct studies with clinical endpoints in patients afflicted with two distinct dermatological conditions: (1) scalp psoriasis and (2) atopic dermatitis. Hill Dermaceuticals was required by FDA to conduct separate and distinct clinical trials to support each of the

specific indications for use. Other topical dosage forms containing corticosteroids, e.g., ointments and creams that carry the class labeling general indication of *corticosteroid responsive dermatoses* have been supported using multiple point vasoconstrictor assays to demonstrate pharmacodynamic effects of the drug. Such vasoconstrictor assays are not a valid surrogate maker for drugs use to treat scalp psoriasis nor for widespread atopic dermatitis.

Because DERMA-SMOOTHIE/FS® is labeled for the specific indications of the dermatological conditions being treated: (1) scalp psoriasis and (2) atopic dermatitis and the unique nature of the dosage form (DERMA-SMOOTHIE/FS® is the only topical oil approved by FDA), companies desiring to establish the therapeutic equivalence of any generic version of fluocinolone acetonide topical oil 0.01% product to Hill Dermaceuticals' DERMA-SMOOTHIE/FS® must be required to conduct trials in the specific disease states just as Hill was required to do. Generic companies cannot use a less rigorous test, i.e., the multiple point vasoconstrictor assay to establish therapeutic equivalence when Hill Dermaceuticals was required to conduct clinical trials in the specific disease state as a condition of approval.

Scalp Psoriasis

With respect to the indication of **Scalp Psoriasis** in order to demonstrate therapeutic equivalence with DERMA-SMOOTHIE/FS®, any generic formulation of fluocinolone acetonide topical oil must conduct studies as follows:

1. A comparison study with DERMA-SMOOTHIE/FS® applying either the reference or test product, once a day, wetting the hair and scalp with water, applying a thin film of the respective study product to the **entire scalp** and covering the scalp with a **shower cap overnight (or for a minimum of 4 hours.)** Efficacy is graded on a weekly basis with the primary efficacy assessment evaluated after week 3 of treatment.

DERMA-SMOOTHIE/FS® is the only corticosteroid formulation that is proven safe and effective under these treatment conditions. In order to establish therapeutic equivalence, any generic formulation must conduct a clinical study under the same treatment conditions and regimen.

2. Inclusion criteria must be a minimum of 20% scalp involvement. The entire scalp must be graded, not just target areas.

It is well established that the physiology of the scalp is complex and quite different from other parts of the body. Hill Dermaceuticals firmly believes that a study with clinical endpoints is necessary to establish the therapeutic equivalence of any generic versions of fluocinolone acetonide topical oil 0.01% product to Hill Dermaceutical's DERMA-SMOOTHIE/FS®.

Atopic Dermatitis

With respect to the indication of **Atopic Dermatitis**, in order to demonstrate therapeutic equivalence with DERMA-SMOOTHIE/FS®, any generic formulation of fluocinolone acetonide topical oil must conduct studies as follows:

1. Since DERMA-SMOOTHIE/FS® includes information on the safety and efficacy of the product in children having widespread body involvement 50 –90%, any generic version of the product must conduct a study in this patient population to demonstrate the safety of the generic formulation. As noted above, the product formulation and processing can impact availability and release of the corticosteroid fluocinolone acetonide; any generic version of DERMA-SMOOTHIE/FS® must demonstrate safety and effectiveness in children having widespread body involvement 50 – 90%.

Safety studies must be conducted on the particular generic formulation to study possible adrenal suppression. Patients should have widespread body involvement 50 - 90% (average of approximately 70%) of atopic dermatitis and use a generic fluocinolone acetonide topical oil 0.01% twice daily for 4 weeks. The Cortrosyn stimulation test and any other appropriate test of adrenal function should be performed.

2. Comparative efficacy studies (which also include a vehicle control) must be conducted in adults and children having greater than 20% body involvement.

As noted above, Hill Dermaceuticals was required by the FDA to conduct clinical trials to demonstrate efficacy both for atopic dermatitis and psoriasis of the scalp using valid clinical endpoints. Any manufacturer wishing to market fluocinolone acetonide should be required to demonstrate efficacy for both of these disease conditions using the same clinical endpoints and not a less rigorous test, the multiple point vasoconstrictor assay, which is not a valid surrogate marker in the specific FDA approved disease states approved in the labeling for DERMA-SMOOTHIE/FS®) to establish therapeutic equivalence.

Peanut Oil Safety Issues

Peanut Oil Specifications. Hill Dermaceuticals has characterized the its specially developed, proprietary peanut oil and blend of other oils that comprise the vehicle for DERMA-SMOOTHIE/FS®. In addition, the Agency required Hill Dermaceuticals to conduct a number of safety studies regarding the use of its now proprietary peanut oil in the formulation. The Agency has recently requested that Hill conduct additional safety studies in peanut sensitive pediatric patients. Hill Dermaceuticals understands that there are foreign commercial sources of peanut oil that have not undergone a refinement process to break down peanut proteins. Any manufacturer of a generic version of fluocinolone acetonide topical oil must set

appropriate limits and conduct studies to establish the safety of the specific source of peanut oil used in the generic formulation.

Testing in Confirmed Peanut Sensitive Pediatric Patients. Any generic formulation of fluocinolone acetonide topical oil must conduct studies to establish the safety of their specific source of peanut oil as follows:

1. In children with severe, widespread atopic dermatitis with known peanut sensitivities – the following three tests, the Skin Prick Test, the Skin Patch Test (both of which establish peanut sensitivity) followed by 7 days of twice daily treatment of the proposed generic formulation;
2. In children and adults (both documented to be peanut sensitive by the Skin Prick test and by the RAST test.) The generic formulation must also be patch-tested using Finn chambers.

Safety Issue - Adrenal Suppression

As you can surely appreciate, manufacturing process parameters and formulation issues can significantly affect the topical oil formulation and have an impact on the absorption of the drug product through the skin or scalp. Thus, Hill Dermaceuticals firmly believes that generic manufacturers must also demonstrate that those specific formulations do not cause adrenal suppression in pediatric patients after widespread body involvement 50 - 90% as explained above.

It is important to note that the FDA Pediatric Advisory Subcommittee recently recognized the widespread adrenal suppression potentially caused by topical corticosteroids.³ Petitioner was the only pharmaceutical company that presented safety data to the subcommittee demonstrating that patients two years and above, showed no adrenal suppression whatsoever when administered DERMA-SMOOTH/FS® (Eczema Oil).

Packaging Issues

DERMA-SMOOTH/FS® (fluocinolone acetonide), because it contains a specially designed, proprietary blend of several oils, is difficult to package. Hill Dermaceuticals has developed packaging that maintains the identity, strength, purity and potency of the Product and minimizes the possibility of leakage. Hill Dermaceuticals has two different closure systems – one for shipping and one with a spout that is dispensed to the patient so that the product can be easily applied in a thin film. Other manufacturers must ensure that their products are packaged in a manner to maintain the identity, strength, purity and potency of their product and that minimizes the possibility of leakage and that permits dosing of a thin film of the product.

³ Referring to the Pediatric Advisory Subcommittee of the Anti-infective Drug Advisory Committee Meetings that took place on October 29th and 30th in Gaithersburg, Maryland.

Indication for Atopic Dermatitis. Hill Dermaceuticals markets DERMA-SMOOTHIE/FS® (Eczema Oil) (soon to be renamed), which is a separate package presentation for use in treating a second, separate and distinct indication, atopic dermatitis. DERMA-SMOOTHIE/FS® (Eczema Oil) is not packaged with the two shower caps as is DERMA-SMOOTHIE/FS® (Scalp Oil) and has distinct labeling, including patient instructions. Hill Dermaceuticals has taken such steps in the effort to avoid potential confusion in the market and to assist in the prevention of any safety issues that could arise should pediatric patients mistakenly use the product under occlusion. Hill Dermaceuticals believes that any manufacturer of a generic version of fluocinolone acetonide topical oil must also use such a dual packaging configuration in order to meet the statutory and regulatory requirements for the labeling of the generic product. *See* 21 U.S.C. §355(j)(2)(A)(i) and (v) and 21 C.F.R. § 314.94(a)(4).

Shower Caps Included in the Package with the Indication for Scalp Psoriasis. DERMA-SMOOTHIE/FS® (Scalp Oil) is the only topical corticosteroid that is FDA approved for use under occlusion in treating scalp psoriasis. It was approved as a specific treatment regimen for the treatment of scalp psoriasis and not the general indication of corticosteroid responsive dermatoses. The use of the shower cap that is packaged with the product (two are included in the box) and the corresponding labeling associated with the use of the product under occlusion distinguish DERMA-SMOOTHIE/FS® from all other topical corticosteroids. The shower caps included in the box are required to be specifically labeled. Moreover, the Agency required Hill to conduct specific stability studies demonstrating the compatibility of the shower cap with the finished product. Hill Dermaceuticals believes that any manufacturer of a generic version of fluocinolone acetonide topical oil must also label and test the shower cap as Hill was required to do so.

Assay Methodology

Hill Dermaceuticals was not permitted by chemists in the Division of Dermatologic and Dental Drug Products to use the USP assay for fluocinolone acetonide in assaying the potency of DERMA-SMOOTHIE/FS®. FDA chemists were concerned that the USP assay for fluocinolone topical solution (there is no assay for fluocinolone acetonide topical oil) would not yield accurate, consistent or reproducible assay results if used in testing a topical oil formulation. Hill Dermaceuticals developed a proprietary assay method for fluocinolone acetonide in the topical oil dosage form. Companies seeking approval of a generic version of fluocinolone topical oil must develop their own an appropriate assay method for the proposed generic product.

Such Regulatory Requirements are Necessary to Protect the Public Health

The information and requirements set forth in this Citizen Petition are necessary to ensure that any generic version of DERMA-SMOOTHIE/FS® meets appropriate approval requirements. 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 Dermaceuticals is willing and able to compete in the marketplace as long as all companies seeking approval to market a generic version of DERMA-SMOOTH/FS® are required to meet appropriate regulatory requirements for approval.

C. Environmental Impact

According to 21 C.F.R. § 25.31(a), this Citizen Petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic Impact Statement

According to 21 C.F.R. § 10.30(b), Petitioner will, upon request by the Commissioner, submit economic impact information.

E. Certification

The undersigned certifies that, to the best of his/her knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Citizen Petition.

Respectfully submitted,

Signature



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Appendix "A"

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Protocol No. Title	Protocol No. 001 Double-blind comparative study of Derma-Smoothe/FS and its vehicle in patients with atopic dermatitis	Protocol No. 22-A PS Double-blind, comparative, parallel group study of Derma-Smoothe/FS on patients with psoriasis of the scalp.	Protocol No. 26 Double-blind, comparative efficacy and safety study of Derma-Smoothe/FS on atopic dermatitis in pediatric patients
No. of studies	2 independent studies	2 independent studies, multicenter	2 independent studies, multicenter
Population	40 adult patients	94 adult patients	102 pediatric patients
Study Design	Double-blind, comparative, parallel study, active versus vehicle. Each subject is his own control. 14 days treatment.	Double-blind, comparative, parallel study, active versus vehicle. 2 treatment groups. 14 days treatment, once daily. Occlusion of treated area with plastic shower cap.	Double-blind phase, 2 weeks: active versus vehicle Open-label phase, 2 weeks: active treatment, vehicle between treatments. Twice daily treatment. Cortisol study performed. 2 weeks post-treatment interval with vehicle use only.
Efficacy analysis	Vehicle treated subjects showed fair to good improvement of treated sites, although not as significant as those seen with Derma-Smoothe/FS treatment (good to excellent improvement)	After 7 days, both vehicle and active groups showed statistically significant improvement from baseline. This supports the contention that the vehicle provides beneficial effects. The active group showed significant improvement over the vehicle group after 2 weeks of treatment.	Consistent findings of significant improvement of atopic dermatitis from baseline, on both vehicle and active groups. The active group showed significant improvement over the vehicle group after 2 weeks of treatment.
Safety analysis	No adverse events were seen on either treatment side. No exacerbations noted on the vehicle side.	The incidence of adverse event: 1 vehicle-treated subject reported burning on the hairline area.	The incidence of adverse event on double-blind phase: 3 vehicle-treated subjects reported mild to moderate papule, pustule, burning,
Safety			

analysis		1 active-treated subject reported folliculitis in treated area	itching and irritation on treated areas. 3 active-treated subjects reported exacerbation of atopic dermatitis. The incidence of adverse event on open-label phase: 2 subjects reported mild to moderate papule, pustule, burning, itching and irritation on treated areas. Another 2 subjects reported severe papule, pustule, burning, itching and irritation on treated areas.
Supplement No. Date of submission	Original NDA submission February 28, 1985	Supplement No. 10 October 28, 1993	Supplement No. 15 August 13, 1998