

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19452/S015

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Hill Dermaceuticals, Inc.
Attention: Jerry S. Roth, President
2650 South Mellonville Avenue
Sanford, Florida 32773

MAY 5 1999

Dear Mr. Roth:

Please refer to your pending August 13, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Derma Smoothe/FS (fluocinolone acetonide, 0.01%) Topical Oil.

We are reviewing the Medical section of your submission and have the following comments and information requests:

1. The Sponsor should adequately demonstrate that the presence of peanut oil in Derma-Smoothe/FS does not pose a safety hazard when the product is used to treat atopic children. The Sponsor should also address the potential risk of peanut sensitization, which could possibly be caused by the chronic use of Derma-Smoothe/FS.
2. The Sponsor should provide adequate clinical and chemistry, manufacturing, and control (CMC) information to demonstrate that the level of peanut protein allergens in the Derma-Smoothe/FS product is replicable and consistent between batches.
3. The Sponsor should provide clinical narratives and the completed medical records for trial subjects with hypo-pigmentation, anaphylaxis, asthma, and exacerbations.
4. The Sponsor should provide a complete summary of all post-marketing reports of adverse reactions to Derma-Smoothe/FS since the approval of the drug product, with narratives for all reports of allergic/asthmatic reactions.
5. Please submit one copy of the current approved label, the proposed labeling pursuant to S-015, and the proposed patient package insert pursuant to S-015, if planned.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

TSI

5/5/99

Susan Walker, M.D.
Medical Team Leader
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:

Archival NDA 19-452/S-015

HFD-540/Div. Files

HFD-540/M. Wright

HFD-540/Wilkin

HFD-540/Walker

HFD-540/Toombs

HFD-540/DeCamp

HFD-540/Pappas

HFD-540/Hill

HFD-540/Jacobs

HFD-540/Bashaw

HFD-540/Srinivasan

HFD-540/Freidlin

Drafted by: mw/May 4, 1999; May 5, 1999

Initialed by: MJK/5/4/99

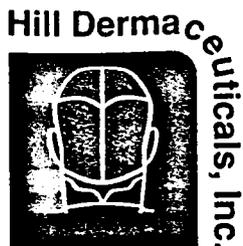
final: 5/5/99

filename: N19452S15IR

INFORMATION REQUEST (IR)

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ORIGINAL



NDA SUPPL AMEND
S-015 BC

"The Scalp Company"

Derma-Smoothie/FS Topical Oil
NDA 19-452
S-015

August 12, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850
Attn: Ms. Millie Wright
Project Manager



RE: Proposed Insert Label for Derma-Smoothie/FS
Pediatric indication

The changes specified in the proposed product insert for Derma-Smoothie/FS were made based on data previously submitted and other supporting documentation which are enclosed.

Please note the following information:

Nineteen of the 22 patients in the safety study had 50% to greater than 75% surface area involvement. Indicating that most of the subjects used Derma-Smoothie/FS on greater than 50% of the body strongly substantiates the safety of the product concerning adrenal suppression; that there was no adrenal suppression on any of the patients after twice daily treatment for 4 weeks. This is referenced to lines 57 to 66 of HD (Hill Dermaceuticals) draft label.

A cautionary statement on the use of Derma-Smoothie/FS on children between the ages of 2 to 6 years, we feel, is justifiable based on the safety study data for cortisol levels. The cautionary statement is proposed in place of lines 65-66 (FDA draft): Derma-Smoothie/FS should not be used in children below the age of 6 years.

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407-525-1887 FAX: 407-649-9213

Although the number of subjects is considerably less for the safety study than the efficacy study, a paired t-test analysis of the data by age comparison (≤ 6 years and ≥ 6 years) shows no difference between the age groups. (Attachment 1). We do not believe that the product should be disallowed for children between 2 to 6 years old. This statement is referenced to lines 66-67, 83-85, 213-214, and 272 of HD draft label.

In addition to the efficacy and safety studies conducted for Derma-Smoothe/FS, a clinical trial on the allergenicity of peanut oil-containing products, i.e., Derma-Smoothe/FS, on peanut-sensitive individuals was also performed. A summary of this clinical study has been included in the appropriate section of the proposed insert label, lines 69-76 and 139-145 of the HD draft label. The study involve the Prick test and Patch test with refined peanut oil and Derma-Smoothe/FS, followed by a 2-week twice daily treatment with Derma-Smoothe/FS. The results of the study show that all 13 patients did not react to the refined peanut oil prick test and patch test, and the Derma-Smoothe/FS prick test and patch test. Nine of these patients were RAST-test positive to peanuts prior to the study. One peanut-sensitive child had a flare of his atopic dermatitis during the 2 weeks treatment with Derma-Smoothe/FS, which is cited under the "Precaution" heading, lines 145-147 of the HD draft label.

Specific reference to the refined peanut oil used in the manufacture of Derma-Smoothe/FS:

- We have committed to testing each new lot of refined peanut oil by the S-ELISA method, for detection of all peanut allergens; referenced to lines 133-138, and 240-244 of HD draft label. (Attachment 2)
- Laboratory data used as basis for S-ELISA test kit. (Attachment 3)
- Published articles on clinical studies proving that peanut oil is not allergenic to peanut-sensitive persons. (Attachment 4)
- Summary of data on the clinical study sponsored by Hill Dermaceuticals, Inc. on the allergenicity of peanut oil-containing product (Derma-Smoothe/FS) on peanut-sensitive individuals, through the use of the Prick test, Patch test, and a 14-day twice daily application of the product. The results show that all patients did not react to the patch tests and prick tests with refined peanut oil and Derma-Smoothe/FS. (Attachment 5)

In place of FDA draft lines 120-121: "Patients with a history of allergic reactions to peanuts should avoid use of this product", the statement "Physicians should use the product with caution on peanut-sensitive individuals" is substituted (HD draft lines 149-150, and 245-246). This statement is appropriately justified by the submitted study on peanut allergenicity through prick and patch testing with refined peanut oil and Derma-Smoothe/FS on peanut-sensitive children.

Co-packaging with the moisturizing vehicle:

We intend to co-package Derma-Smoothe/FS with its vehicle. The vehicle is intended to be used as moisturizer in between treatments with Derma-Smoothe/FS. As I'm sure you fully appreciate, while the underlying cause of atopic dermatitis in pediatric patients is unknown, evidence suggests that dryness of the skin leads to the development of pruritus. This itching leads to scratching, skin trauma and changes that make the skin more easily irritated. When the pruritus occurs, it initiates a "spreading" itch, hence producing more irritation, further pruritus, and a cycle of itch-scratch-itch (Hurwitz, 1993).

The moisturizing vehicle has been used in the clinical studies and a beneficial effect was derived from its use. A secondary objective in the efficacy study on children with atopic dermatitis involving greater than 20% of the body (S-015, Aug 1998, pp. 51 & 55) was to evaluate the moisturizing effect of the vehicle. Vehicle-treated patients in the double-blind efficacy study reported improvement in their symptoms resulting from the moisturizing effect of the vehicle on the skin. In the study, 17 of 45 evaluable vehicle-treated patients had global improvements of 50% or greater (all disease parameters: erythema, scaling, lichenification and pruritus). One had complete clearing of his condition (100%) after 2 weeks use of the vehicle; 18 of 45 had global improvements of 20% to 50%, a total of 35 of 45 vehicle-treated patients with improvements greater than 20% over the initial disease condition.

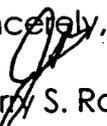
It is also important to point out that the Derma-Smoothe/FS-treated group had statistically significant improvement over the vehicle. The p-values for global improvements were $p=0.003$ and $p=0.0018$ after 2 weeks of treatment.

In our clinical viewpoint, and in the opinion of the clinical investigators who participated in the study, it is very important to keep the skin moisturized, particularly in between the twice daily application of Derma-Smoothe/FS. Data from the clinical trial noted above indicate that patients benefit from the moisturizing effects of the vehicle. Using the vehicle as moisturizing agent between treatments with Derma-Smoothe/FS serves 2 purposes: the first, to keep the skin moisturized preventing further irritation; and second, to minimize the potential of a person applying Derma-Smoothe/FS more frequently than twice a day and thus increasing the exposure of the patient to fluocinolone acetonide. While the vehicle itself could be sold over the counter as a cosmetic, we have decided not to market it in such a manner. Rather, we intend to co-package it with Derma-Smoothe/FS so that it can be used as it was in the clinical trial, as an emollient in between treatments or as often as needed.

We firmly believe that the co-packaging of Derma-Smoothe/FS with the moisturizing vehicle is consistent with the principles set forth in FDA's regulations concerning combination products, 21 CFR section 300.50. While this section of FDA's regulations concern fixed combination dosage form prescription drugs, the principles are consistent with our intent in co-packaging of Derma-Smoothe/FS with the moisturizing vehicle, i.e., to enhance the safety and effectiveness of Derma-Smoothe/FS in treating patients with atopic dermatitis, and to minimize exposure to the steroid especially in children. The clinical studies on efficacy and safety fully support the benefits to patients on the use of the vehicle as moisturizing agent in between treatments with Derma-Smoothe/FS, or as often as needed to prevent the skin from drying.

We are looking forward to a favorable outcome. Thank you.

Sincerely,


Jerry S. Roth
President
Hill Dermaceuticals, Inc.



TRIPlicate
SEI-015/OC

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
IND NDA 19-452
S-015

NEW CORRESP



July 19, 1999

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Ophthalmologic Drug Products/CDER
Food and Drug Administration
9201 Corporate Boulevard, HFD 540
Rockville, MD 20850
Attn: Chemistry Department

Re: Chemistry Request: S-ELISA (sandwich enzyme-linked immunosorbent assay) for peanut protein.

Dear Dr. Wilkin:

This is to assert that Hill Dermaceuticals, Inc. will not use any manufacturer that does not refine its peanut oil by heating it to 475^o Fahrenheit for fifteen (15) minutes.

Very truly yours,


Jerry S. Roth
President

JSR:med

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ORIGINAL

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NDA SUPPL AMENDMENT
SEI-015 BC

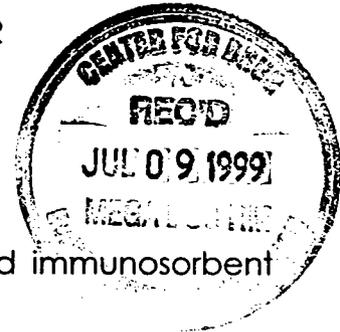
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"The Scalp Company"

Derma-Smoothe/FS Topical Oil
IND / NDA 19-452
6-015

July 8, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850
Attn: Chemistry Department



RE: Chemistry Request: S-ELISA (sandwich enzyme-linked immunosorbent assay) for peanut protein.

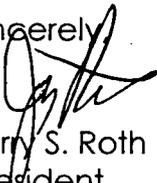
This submission contains the following items, as requested by the Agency, on 2 prior telephone conference calls.

1. Results of the ELISA test (commercially prepared as Veratox®) showing that refined peanut oil spiked with 500 ppm peanut extract is positively detected by optical density reading, with results, in ppm, too high to read.
Results showing that heating refined peanut oil spiked with 500 ppm peanut extract, at 475°F for 15 minutes, denatures the protein, as shown by 0.0 ppm reading. The optical density reading for this sample is very low in comparison to the known standards.
2. Letter from the University of Nebraska on test results for refined peanut oil samples spiked with 500 ppm peanut extract, after heating at 475°F, showing sample results at 0.0 ppm.
3. Hill Dermaceuticals, Inc. letter of commitment to test every new lot of refined peanut oil for peanut protein, prior to release. Raw material specification from for Refined Peanut Oil NF reflects this test (highlighted).

4. Letter from [redacted] approved manufacturer of refined peanut oil raw material, pertaining to their refining methods which have not changed for decades, and the commitment to advise Hill Dermaceuticals, Inc. of any changes in these methods.
5. Copy of the Veratox® (ELISA test) Insert, defining sample preparations and test procedures.

Should you have questions on any part of this submission, please call us at 800-344-5707. Thank you.

Sincerely,



Jerry S. Roth
President



Rosario G. Ramirez
Medical/Regulatory Affairs

ORIGINAL

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NC

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
NDA 19-452 / 5015

June 10, 1999

Jonathan K. Wilkin, MD
 Director
 Division of Dermatologic and Dental Drug Products / CDER
 Food and Drug Administration
 9201 Corporate Boulevard HFD 540
 Rockville, MD 20850
 Attn: Dr. Susan Walker



RE: Response to Information Request
Peanut Oil Allergenicity Study

Dear Dr. Walker:

This submission contains the requested items pertinent to the study on peanut protein allergenicity. The itemized requested information in the FDA correspondence is included.

Due to the urgency of the matter and the geographical limitation we are faced, most of the documentation enclosed are facsimile copies which were signed and dated by the primary investigator and sub-investigator. Each requested item was addressed as promptly and as completely as physically possible.

Thank you for your patience and cooperation. We are looking forward to a favorable review.

Sincerely,

Rosario G. Ramirez
 Rosario G. Ramirez
 Medical/Regulatory Affairs

407-525-1687 FAX: 407-649-9213

200-



TRIPlicate
nc

NEW CORRESP

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

Derma-Smoothe/FS Topical Oil *"The Scalp Company"*
NDA 19-452

June 8, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850
Attn: Ms. Millie Wright



RE: Chemistry: Sandwich enzyme-linked immunosorbent assay (S-ELISA)
for peanut protein.

Dear Dr. Wilkin:

As requested, peanut protein allergen was purchased from (insert enclosed) and used to spike the refined peanut oil raw material and Derma-Smoothe/FS finished product. These were then tested using the ELISA test kit. The results are enclosed.

The ELISA test used to detect peanut protein is a commercially prepared test kit from the (with a detection limit of 2.5 ppm (parts per million) peanut protein. The insert for the test kit is enclosed.

Also enclosed is a letter from Dr. Hefle, University of Nebraska, pertaining to peanut allergen tests and threshold level.

Thank you.

Sincerely,
Rosario G. Ramirez
Rosario G. Ramirez
Medical/Regulatory Affairs

Nancy Puglia
Nancy Puglia
Plant Manager

Enc.

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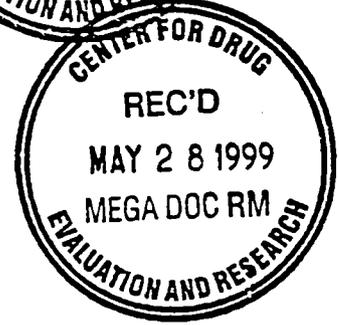
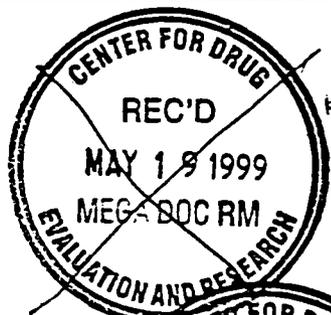


ORIGINAL

SEI-015/NC

NDA SUPPL AMEND

"The Scalp Company"



May 27, 1999

NDA 19-452 S-15 - Correspondence

VIA FACSIMILE AND FEDERAL EXPRESS

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: Safety of Refined Peanut Oil Used in Derma-Smoothe/FS

Dear Dr. Wilkin:

Thank you for your telephone call on Monday afternoon informing us of the postponement of the advisory committee meeting. I must say I was disappointed that we will be unable to proceed in a rapid fashion with the advisory committee's review of the safety of refined peanut oil used in Derma-Smoothe/FS. You may not fully appreciate how difficult it was to coordinate and accommodate the schedules and travel plans for professionals of the stature of those we were prepared to have attend the meeting that was scheduled for June 3, as they were coming from institutions around the country including and the University of Nebraska's Food and Sciences Department. We were quite fortunate to be able to assemble such a panel of outside experts on short notice. I am not sure that their schedules will permit them to attend the rescheduled advisory committee meeting, although we will certainly try to arrange their attendance at the meeting if you still think it necessary to discuss the safety of refined peanut oil.

Hill Dermaceuticals and our outside experts firmly believe that the safety of refined peanut oil used in Derma-Smoothe/FS is well established. In our view, there are no

Jonathan K. Wilkin, M.D.
May 27, 1999
Page 2 of 4

outstanding issues relating to safety of refined peanut oil and this matter does not warrant advisory committee review. The rescheduling of an advisory committee meeting to discuss the safety of refined peanut oil only serves to deprive the pediatric population of the benefits of Derma-Smoothe/FS Topical Oil for the treatment of atopic dermatitis.

Refined peanut oil is a major component in the formulation of Derma-Smoothe/FS. We have been using the same peanut oil manufacturer. Their process for refining peanut oil is the standard process which has been used for decades by the industry. [redacted] has informed us that their refining techniques for peanut oil have not changed for decades with the exception of adding automation and computerized controls. [redacted]

[redacted] (of the materials provided for the advisory committee.) It is a well-known and well-established fact from many studies that no detectable protein has been found in refined peanut oil and that it is the protein in peanuts that is the cause of peanut allergies.

In Monday afternoon's conversation, you specifically asked that we show that the refined peanut oil used in future manufacturing batches of Derma-Smoothe/FS meets the same specifications as those used in the Chicago Children's Hospital study. The test for peanut protein content in refined peanut oil was developed at the Food and Allergy Research and Resource Program at the University of Nebraska. The co-chairman of the Department, Dr. Susan Hefle, was one of the expert witnesses who was scheduled to present at the advisory committee meeting on June 3. Hill Dermaceuticals has recently tested three different lots of refined peanut oil manufactured by [redacted] as well as our finished Derma-Smoothe/FS product for the presence of peanut protein. Our specification for the peanut protein is not more than 2.5 ppm. (This specification is included in Section 3 of our supplemental application, "Chemistry and Manufacturing Controls," a labelling supplement and general correspondence submission dated May 14, 1999) and we have committed to testing each lot number of refined peanut oil for peanut protein levels. In each test case the results compare to the 0 ppm standard relative to the presence of peanut protein. (See summary of test results provided in Tab 2 of the materials provided for the advisory committee. Actual certificates of analyses are on file at Hill Laboratories.) Moreover, we have tested the lot of refined peanut oil and the finished Derma-Smoothe/FS product used in the Chicago Children's Hospital study and have confirmed that the product meets specification for peanut protein.

Please note that Hill is one of the few dermatology companies in the United States that does its own manufacturing and testing of its products. We have done this for over 10 years. We do not contract to outside manufacturers and have our own, in-house analytical laboratory and microbiology laboratory. We are fully confident that we have

Jonathan K. Wilkin, M.D.
May 27, 1999
Page 3 of 4

adequate controls in place to assure that the refined peanut oil raw material as well as our finished Derma-Smoothe/FS product meet the specification for non-detectable peanut protein. It is well known that the controls in a pharmaceutical company are much higher than those required in the food industry. The use of refined peanut oil has long been a staple in the U.S. food industry. It would seem that, if refined peanut oil were a problem, there would have been many reports of allergies relating to refined peanut oil and it would not be freely used in cooking the way it has been and continues to be. The first studies conducted on refined peanut oil were completed in 1980 and 1981 and are well documented. (Please refer to Section 2 of the Supplemental Application to NDA 19-452 dated May 14, 1999.) The Quality Assurance in a pharmaceutical company such as ours is far more stringent than that required of the food industry.

Finally, we have marketed Derma-Smoothe/FS using the same refined peanut oil vehicle since 1988. It has been marketed for both atopic eczema and scalp psoriasis and there have been almost [] units distributed. The product is marketed in a 4-oz. container which equates to about [] doses of Derma-Smoothe/FS that have been used. We have no reports of adverse event than even remotely resemble a peanut allergic reaction to our product. We are not aware of any adverse event reports that have been submitted to the Agency on this matter. In addition, we have a national sales force of representatives who visit, one by one, an average of 90% of the dermatologists in this country, routinely (every five weeks). While we realize this is anecdotal evidence, we have never been approached by any of these dermatologists or their patients about an allergic reaction (or even a suspected one) to the refined peanut oil in our product. When considered in conjunction with published literature and the Chicago Children's Hospital study this is certainly very compelling evidence as to the safety of the product.

Making Derma-Smoothe/FS available to children ages 2 - 12, suffering from atopic dermatitis has been a long, arduous process, ongoing since we first met for a conference in February of 1996. Of course, we had started working on it even prior to that conference. At that time, you gave us several difficult challenges to demonstrate safety. Those challenges were far greater and more exacting than what had ever been required for corticosteroids. As a reminder, you required greater than 50% whole body involvement to test for adrenal suppression. To my knowledge and from speaking with various experts in the field, this almost rewrites the chapter on the safety issue of adrenal suppression with corticosteroids. As you know, atopic dermatitis in children is a very difficult disease. Sometimes, I get the impression the agency thinks, "oh, well, there are other corticosteroids on the market;" however, all other corticosteroid products on the market are approved for less than 20% body surface involvement.

I hate to see further delays. The issue regarding peanut allergy was never raised during our discussions concerning the development of our product for the pediatric indication.

Jonathan K. Wilkin, M.D.
May 27, 1999
Page 4 of 4

There were issues of inflammatory news media releases about peanut allergies but nothing about refined peanut oil. Doctors routinely ask us about refined peanut oil sensitivity and are well comforted by the study and others concerning peanut protein. As stated above, I, as well as our outside expert consultants firmly believe that there are no unanswered issues concerning the safety of refined peanut oil used in our product. The pediatric population should not be deprived of the benefits of Derma-Smoothe/FS Topical Oil any longer because of a delay in the rescheduling of an advisory committee.

Your consideration in this matter would be greatly appreciated and I would welcome your prompt reply to this letter and our pending supplemental application. If there are any questions, please do not hesitate to call me.

Very truly yours,

HILL DERMACEUTICALS, INC.


Jerry S. Roth
President
JSR:med

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DUPLICATE

NDA SUPPL AMENDMENT
SEI-015 BM

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
IND / NDA 19-452

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products/CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850



RE: Supplemental application to NDA 19-452
Peanut Allergenicity Study

Dear Dr. Wilkin:

Hill Dermaceuticals, Inc., is submitting this supplemental application to the approved NDA 19-452, Derma-Smoothe/FS Topical Oil (0.01% Fluocinolone acetonide). The information provided refers to the investigational study on peanut sensitive children with atopic dermatitis. Derma-Smoothe/FS is an approved treatment for atopic eczema and scalp psoriasis in adults.

The target population being children, evaluation of safety with the use of Derma-Smoothe/FS was a primary concern. The study reported in this submission was conducted by Dr. Amy Paller at Children's Memorial Hospital in Chicago. This study is in conjunction with the study that will be conducted at

This submission includes requirement specified in the Clinical Data Section. Articles that support the study are included in Appendix 2. Some segments not pertinent to the report have been omitted. Thank you for your consideration and continued cooperation.

Sincerely,

Rosario G. Ramirez
Rosario G. Ramirez
Medical/Regulatory Affairs

Jerry S. Roth
President

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ORIGINAL

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
NDA 19-452

NDA SUPPL AMENDMENT

SET-015
B2

May 14, 1999



Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850

RE: LABELING Supplement and General Correspondence
Addendum to Supplemental application S-015

Dear Dr. Wilkin:

In response to the information requests from the Agency, the items listed below are addressed in this submission. Each numbered item, designated as a section, includes the relevant documentation in support of the subject matter.

1. Information to demonstrate that the presence of peanut oil in Derma-Smoothe/FS does not pose a safety hazard when the product is used to treat children with atopic dermatitis.
 - a. Peanut Allergenicity Study conducted by Dr. Amy Paller, which includes the study protocol, summary tables of results, and the case report forms on all subjects in the study.
2. Sponsor's response on the potential risk of peanut sensitization, which could possibly be caused by the chronic use of Derma-Smoothe/FS.

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3. Chemistry, manufacturing and controls (CMC) information to demonstrate that the level of peanut protein allergens in the Derma-Smoothe/FS product is replicable and consistent between batches.
 - a. ELISA test results from Hill Labs, including validation of test kit.
 - b. University of Nebraska letter from Dr. Susan Hefle on peanut oil test using ELISA method.
4. Clinical narratives and completed medical records for trial subjects that had hypopigmentation, anaphylaxis, asthma, and exacerbation.
 - a. Case report forms of patients that experienced hypopigmentation, anaphylaxis, asthma, and exacerbation of atopic dermatitis.
5. Summary of all post-marketing reports of adverse reactions to Derma-Smoothe/FS since the approval of the drug, with narratives for all reports of allergic/asthmatic reactions.
6. Copy of the current approved label, the proposed labeling pursuant to S-015, and the proposed patient package insert pursuant to S-015. Disk of the current approved insert and proposed insert is enclosed.

The protocols for the investigation of Derma-Smoothe/FS in peanut-sensitive patients (peanut allergenicity studies), from the _____ and the Children's Memorial Hospital, have been previously submitted under IND _____. The protocols submitted did not have designated protocol numbers, but were specifically associated to its affiliate center and primary investigator. A copy of each protocol is included.

The peanut allergenicity study conducted by Dr. Amy Paller at Children's Memorial Hospital has been completed; date of completion was first week of May, 1999. The study at _____ under the supervision of _____ is presently active.

Sincerely,


Rosario G. Ramirez
Medical/Regulatory Affairs

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"The Scalp Company"

NDA SUPPL AMENDMENT

Derma-Smoothe/FS Topical Oil
NDA 19-452

March 26, 1999



Chemistry Division
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850
Attention: Ms. Millie Wright
Project Manager

RE: Minor Chemistry amendment. Hard copy to the facsimile transmitted documentation.

Dear Ms. Wright:

Enclosed, please find the copy of the data requested by Dr. DeCamp regarding the article on Peanut oil and peanut-sensitive individuals, the letter from Dr. Hefle of University of Nebraska regarding the analysis of the refined peanut oil raw material sent by Hill, the (raw material) manufacturer's certificate of analysis, and certificates of analysis from Hill Laboratories and Celsis Laboratory.

This information was previously faxed February 8, 1999.

Sincerely,

Rosario G. Ramirez
R. G. Ramirez
Medical/Regulatory Affairs Director

2000 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

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ORIGINAL

"The Scalp Company"

IND / NDA 19-452 / S-015 NDA SUPPL AMENDMENT

SEI-015/BM March 10, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850



RE: General Correspondence: Request for Case Report Forms, and
Published articles.
Clinical study on Atopic dermatitis in children (2-12 yrs)

Dear Dr. Toombs;

Enclosed, please find copies of the case report forms requested for those patients that experienced adverse events. The case reports were compiled according to Protocol number and investigator. A brief explanation of the 6 patients from the Miami center is included.

Also enclosed is the information on the interpretation of Cortisol values after ACTH stimulation test, provided by []

The articles/publication copies referencing peanut oil and peanut allergy, as supporting documentation to this submission are enclosed in a separate binder.

Sincerely,
R. G. Ramirez
R. G. Ramirez
Medical/Regulatory Affairs

130



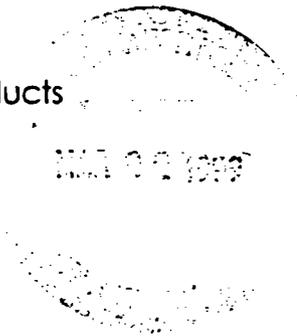
NEW CORRESP
SEI
S015 (BM)

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

Derma-Smoothe/FS Topical Oil *"The Scalp Company"*
IND / NDA 19-452
FDA Correspondence

March 1, 1999

Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850



Dear Dr. Toombs;

Enclosed, please find the tabulated cortisol values for the 22 patients evaluated. Included in this table is a column on the "Drug Use" approximated total amount used by each patient during the 4 weeks treatment period. I also included the age and gender of each patient, and the surface area involvement.

Case report forms (CRF) for 3 patients, Patient Nos. 1, 7 and 9 are also transmitted. Each patient's CRF has about 17 pages. The adverse effect documented can be found towards the end of the CRF, at visit 5 and visit 6. I will attempt to fax the complete CRF for each patient. I am also making a hard copy of these CRFs to be sent out to the agency.

I shall be speaking with a pediatric endocrinologist from California later this evening. Please advise for further requirement. Thank you.

Sincerely,
Nini Ramirez
Nini Ramirez

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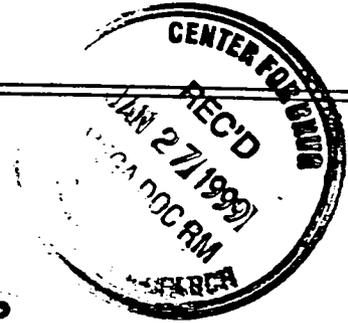


ORIGINAL

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
IND 1 NDA 19-452
S-015

SUPPL NEW CORRESP
SNC-015



January 26, 1999

Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850

Dear Dr. Toombs;

A revised tabulated summary of the clinical study protocols and study results for supplement 15 (S-015) NDA 19-452 is provided. This report is transcribed under Word Version 7.0. Two hard copies are enclosed.

Included in this report are all the data I have given you over the phone, including the efficacy evaluation and Physician Global evaluation for Protocol 25-S, Safety study, as you have requested. Mean scores for the efficacy parameters, as well as a list of the raw data are provided.

Thank you for your patience and consideration.

Sincerely,


Rosario G. Ramirez
Medical/Regulatory Affairs

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ORIGINAL

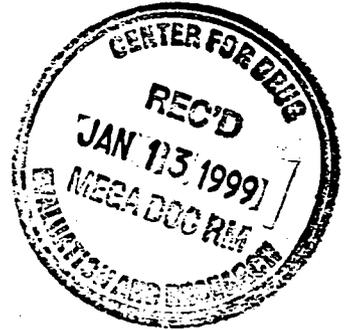
ET 1/22/99

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
IND / NDA 19-452
S-015

January 12, 1999

Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850



Dear Dr. Toombs;

As you have requested, a summary of the clinical study protocols and study results for supplement 15 (S-015) NDA 19-452 is provided. This report is transcribed under Word Version 7.0. A hard copy is also enclosed.

Included in this report are:

- A. Outline of the clinical study protocols (Protocols 25 and 25-S).
- B. Tabulated Investigator and Site information.
- C. Tabulated Patient Data according to site and investigator.

The above report is contained under the title heading 'Schematics of the Clinical Studies.doc' in the enclosed disk. Also contained in the disk is a copy of the currently used insert label for Derma-Smoothe/FS under the title heading 'Current Insert DSFS 1998.doc'.

To briefly summarize the Safety Study results (Studies 1 and 2), there was no adrenal suppression seen in any of the patients that participated in the studies. The results of the blood Cortisol tests show no statistically significant difference between the post-stimulation Cortisol level taken at the initial visit and the post-stimulation Cortisol level taken at the end of 4 weeks treatment with Derma-Smoothe/FS. This is true for all 25 patients enrolled and completed the study. The basal (early morning) Cortisol levels taken prior to stimulation, for the initial visit and after the 4th week treatment, were essentially similar. The basal Cortisol levels for the initial visit and last visit were in the normal range.

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page 2

The results of the Efficacy Studies (Studies 1 and 2) showed statistically significant difference between the active-treated group and the vehicle-treated group (placebo). This significance was very evident in the measure of clinical improvement after 2 weeks of treatment, from the condition at initial presentation (Physician's Global Evaluation). Statistical significance between treatment groups was also demonstrated in the primary parameters, erythema, scaling, pruritus and lichenification.

Of the 47 active-treated patients, 24 had clinical improvement of 75% to 100%, compared to only 6 of the 40 vehicle-treated patients.

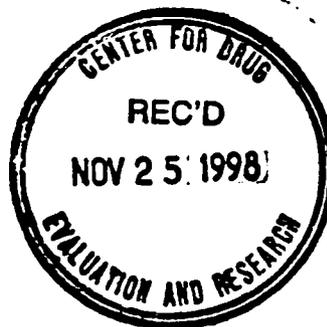
The tabulated data compiled for your review was prepared to include as much details as possible. The requested data on the average amount of drug used for each patient is submitted for the San Diego site (Safety Study). I am requesting your indulgence for a follow-up on the information on amount of drug use with the rest of investigational sites. Thank you for your consideration and continued cooperation.

Sincerely,


Rosario G. Ramirez
Medical/Regulatory Affairs



"The Scalp Company"



November 24, 1998

Derma-Smoothe/FS Topical Oil
IND/ NDA 19-452
S-015

Jonathan K. Wilkin, M.D.
Director
Division of Dermatological and Dental Drug Products, HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Re: Request for Expeditious Review of a Supplement for Pediatric Indication

Dear Dr. Wilkin:

This letter respectfully requests that you expeditiously review the above referenced supplement providing for a pediatric indication and dosing instructions for Derma-Smoothe/FS (fluocinolone acetonide) Topical Oil for the treatment of atopic dermatitis. This disease affects over 10% of the pediatric patient population. Pediatric dermatologists consider atopic dermatitis to be one of the most common diseases encountered in their pediatric patients as well as being one of the most difficult diseases to treat and keep under control.

As you know, Hill has recently completed pediatric trials on Derma-Smoothe/FS. The supplement which provides for use of our product in children ages 2-12 was submitted to your Division on August 13, 1998. The safety data from the trials indicate that in patients with 50% to 100% body involvement of atopic dermatitis there was no adrenal suppression when Derma-Smoothe/FS was applied twice a day for thirty (30) days. These results are significant, since to the best of our knowledge, no other topical corticosteroid has demonstrated the absence of adrenal suppression when tested in pediatric patients having 20% or more body involvement of atopic dermatitis.

Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products, HFD-540

Re: Proposed Pediatric Study Request

November 24, 1998

Page 2 of 2

We firmly believe that such information will be extremely beneficial to physicians when evaluating treatment options for their pediatric patients suffering from atopic dermatitis. Pediatric patients should have access to Derma-Smoothe/FS Topical Oil, since both in our view and in that of pediatric dermatology investigators who conducted the clinical trials, the product will provide a significant, new therapeutic option and benefit for use in the treatment of atopic dermatitis. Upon review of our supplement, I am confident that you will conclude that we have demonstrated Derma-Smoothe/FS to be safe and effective for the treatment of atopic dermatitis in children.

Again, as noted above, we respectfully request that you expeditiously review the above referenced supplement providing for a pediatric indication and dosing instructions for Derma-Smoothe/FS (fluocinolone acetonide) Topical Oil for the treatment of atopic dermatitis. Such an expeditious review will fulfill the spirit of pediatric initiatives mandated by the Congress and undertaken by the FDA. We hope that the review will be completed within four to six months of submission for the benefit of children suffering from atopic dermatitis.

If you have any questions, please contact either myself or Rosario G. Ramirez at (800)344-5707.

Very truly yours,


Jerry S. Roth
President

Enc

cc: Millie Wright
(301) 827-2075 (fax)

Mary Jean Kozma Fornaro
(301) 827-2075

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225
1/22/98

ORIGINAL

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
IND / NDA 19-452 / S-015

NDA SUPPL. AMENDMENT
B.M

September 30, 1998

Ms. Millie Wright
Project Manager
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850

RE: Supplemental application (S-015) to NDA 19-452: SUMMARY TABLES
on disk.

Dear Ms. Wright;

Enclosed, please find a 3.5 disk containing the requested Summary Tables
for Demographics, Efficacy and Safety results on the Pediatric studies. As
requested, the format is in Microsoft Word Program.

Thank you for your continued support and cooperation.

Sincerely,

R. G. Ramirez
Medical/Regulatory Affairs

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213



SEI-015 C
ORIGINAL

"The Scalp Company"

Derma-Smoothe/FS Topical Oil
IND NDA 19-452/S-015

September 18, 1998



Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard, HFD 540
Rockville, MD 20850

Re: Supplemental Application (S-015) To NDA 19-452: Request For Approval On The Indication *Atopic Dermatitis* On The Pediatric Age Group 2 to 12 Years

Dear Dr. Wilkin:

This letter is to request that, as the medical reviewers go over the supplemental application S-015 for Pediatric approval, we be given the opportunity to respond to any questions that may arise via teleconference, as we have in the past, so as to expedite the approval process as much as possible.

Thank you for your continued support and cooperation.

Very truly yours,

Jerry S. Roth
President

JSR:med

cc: Ms. Millie Wright
Dr. Ella Toombs, Medical Reviewer

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Notes
Action needed
M. H. P. M

2773 • 407-323-1887 • Fax: 407-649-9213
Santford, Florida

164



DUPLICATE

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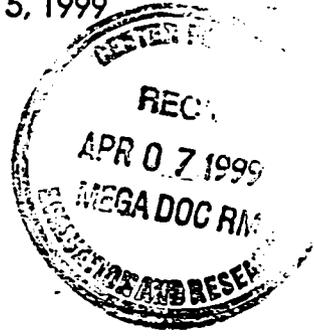
"The Scalp Company"

Derma-Smoothie/FS Topical Oil
IND / NDA 19-452

NDA SUPPL AMENDMENT
SEI-015/RC

April 5, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products / CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850
Attn: Mr. Ernie Pappas



RE: Chemistry Request: Validation of the sandwich enzyme-linked immunosorbent assay (S-ELISA) for peanut protein.

Dear Mr. Pappas:

In response to the FDA request for validation of the ELISA test (enzyme-linked immunosorbent assay) for peanut protein, the data submitted are results from tests performed by Hill Laboratories on the raw material peanut oil from [redacted] the drug product Derma-Smoothie/FS Topical oil, a grocery brand peanut (cooking) oil, and spiked Derma-Smoothie/FS samples. The ELISA test used to detect peanut protein is a commercially prepared test kit from the [redacted] with a detection limit of 2.5 ppm (parts per million) peanut protein. Internal validation of the ELISA test by [redacted] is presented in tables 3, 4 and 5.

The letter from Dr. Hefle from University of Nebraska, and the product insert for the ELISA test kit (Veratox), which were previously faxed to the agency on March 26, 1999, are enclosed.

Please advise if additional data is required. Thank you.

Sincerely,
Rosario G. Ramirez
Rosario G. Ramirez
Medical/Regulatory Affairs

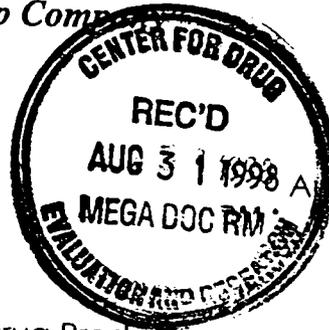
cc: Ms MILLIE WRIGHT



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SEI-015
NDA SUPPL AMENDMENT
DUPLICATE

"The Scalp Comp

Derma-Smoothe/FS Topical Oil
IND NDA 19-452
S-015



August 28, 1998

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850

RE: Amendment to a pending application : Supplemental application (S-015) to NDA 19-452: Request for approval on the indication atopic dermatitis on the pediatric age group 2 to 12 years.

Dear Dr. Wilkin;

In reference to the recently submitted supplemental application S-015, dated August 13, 1998, Hill Dermaceuticals, Inc. seeks to withdraw the line 'Smoothe Oil Moisturizing emollient is supplied in bottles containing 8 fluid ounces.' under the section HOW SUPPLIED (page 26 of the enclosed draft insert labels) in the product insert labeling. Enclosed are 4 draft copies of the amended insert label for Derma-Smoothe/FS; the pagination from the original supplement was retained.

Thank you for your continued cooperation.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

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2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213



Derma-Smoothe/FS Topical Oil ^{"The Scalp Company"}
IND / NDA 19-452 NDA NO. 19452 REF. NO. S-015
S-015
NDA SUPPL FOR SE1

August 13, 1998

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
CDER
Food and Drug Administration
9201 Corporate Boulevard HFD 540
Rockville, MD 20850

RE: Supplemental application to NDA 19-452: Request for approval on the indication *atopic dermatitis on the pediatric age group 2 to 12 years.*
EXPEDITIOUS REVIEW REQUESTED.

Dear Dr. Wilkin:

Hill Dermaceuticals, Inc., is submitting this supplemental application to the approved NDA 19-452, Derma-Smoothe/FS Topical Oil (0.01% Fluocinolone acetonide), to seek approval for the indication *Atopic dermatitis* in afflicted children 2 to 12 years of age. Derma-Smoothe/FS is an approved treatment for atopic eczema in adults.

This submission contains 2 clinical investigations: (1) Safety studies, and (2) Efficacy studies. These studies were conducted to prove that Derma-Smoothe/FS is a safe and effective treatment for atopic dermatitis (with greater than 20% involvement) on the pediatric population ages 2 to 12 years, with emphasis on the safety studies.

Topical corticosteroids are the mainstay of therapy for atopic dermatitis. As a topical corticosteroid preparation, Derma-Smoothe/FS (0.01% Fluocinolone acetonide) is *technically* an effective treatment for atopic dermatitis as evidenced from the extensive literature and publications based on research and clinical studies. The target population being children, evaluation of safety with Derma-Smoothe/FS use was made the primary and major concern of this application.

IND NDA 19-452
S-015
page 3

The contents of this submission include all sections pertinent to this application. Other sections are referred to the original NDA and supplements.

A claim for exclusivity for the additional indication atopic dermatitis in pediatric patients 2 to 12 years, is respectfully requested. As a previously approved NDA, this supplement is understood to be exempt from the application fee.

Thank you for your consideration and continued cooperation.

Sincerely,


Rosario G. Ramirez
Medical/Regulatory Affairs


Jerry S. Roth
President



"The Scalp Company"

Derma-Smoother/FS Topical Oil
IND _____ NDA 19-452
S-015

July 19, 1999

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Ophthalmologic Drug Products/CDER
Food and Drug Administration
9201 Corporate Boulevard, HFD 540
Rockville, MD 20850
Attn: Chemistry Department

Re: Chemistry Request: S-ELISA (sandwich enzyme-linked immunosorbent assay) for peanut protein.

Dear Dr. Wilkin:

This is to assert that Hill Dermaceuticals, Inc. will not use any manufacturer that does not refine its peanut oil by heating it to 475° Fahrenheit for fifteen (15) minutes.

Very truly yours,

Jerry S. Roth
President

JSR:med

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