# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 19452/S015

## ADMINISTRATIVE DOCUMENTS

Division Director Memorandum of NDA 19-452/S-015

Drug: Derma-Smoothe/FS Topical Oil, 0.01%
Active: Fluocinolone acetonide 0.01%
Sponsor: Hill Dermaceuticals, Inc.
Category: Low to medium potency topical corticosteroid
Proposed indication: Treatment of atopic dermatitis in children 2-12 years of age

AUG 18 1999

The Medical Review of NDA 19-452/S-015 Information Amendment (stamp date: June 12, 1999) concluded that the sponsor had demonstrated the safety and efficacy of Derma-Smoothe/FS Topical Oil, 0.01%, in the treatment of atopic dermatitis in children 6 years and older when used twice daily for up to four weeks. That review focused on: 1) the clinical allergenicity study results, 2) the quantification of peanut allergen in the bulk Peanut Oil, NF, and 3) post-marketing adverse event reporting. I will briefly comment on the insufficiency of these three pieces of information to adequately assess safety and the subsequent submissions of additional information that provide sufficiency.

In my assessment, the clinical allergenicity study indicates that those particular batches of bulk Peanut Oil, NF, from which the sample of "refined peanut oil" was taken, and from which the Derma-Smoothe/FS was prepared, are unlikely to present a significant safety concern. However, it is difficult to extend the results from those particular batches to other batches of Peanut Oil, NF, since it is not known whether the peanut allergen load might vary from batch-to-batch.

Second, the Sponsor had not established that a negative ELISA test result would assure the absence of clinically significant amounts of all clinically relevant peanut allergens as a batch-to-batch control test.

Finally, the absence of a post-marketing signal of allergic reactions to peanut allergen in drug products is not the same as evidence that such reactions do not occur. The absence of a post-marketing signal can result from the failure to recognize an association or the failure to report a recognized association. The absence of a post-marketing safety signal for vaginal products containing much smaller amounts of Peanut Oil, NF, would be insufficient to find a product containing 48% Peanut Oil, NF, safe for use on excoriated skin in children with atopic dermatitis. Differences in the surface:volume relationship between children and adults could also be important. Since peanut allergy may occur at a higher prevalence in pediatric patients with atopic dermatitis than in adults with either atopic dermatitis or any of the other conditions for which products containing peanut oil are prescribed, the absence of an allergic signal in an adequate study of a consistent product in children with atopic dermatitis could reasonably be extrapolated to adults with atopic dermatitis. However, extrapolation of the apparent absence of a safety problem from lower risk groups and lesser relative exposures to a group at higher risk for a particular safety problem and greater relative exposures is not sound, especially when the basis is postmarketing reports instead of carefully monitored clinical studies.

In sum, I could not find sufficient evidence for safety of Derma-Smoothe/FS Topical Oil, 0.01%, in the treatment of atopic dermatitis in children at the time of the Medical Review Information Amendment referred to above, given the incomplete assessments and insufficient assurances regarding the bulk manufacture and testing of each batch of Peanut Oil, NF.

Subsequently, we received information that the ELISA test used by the Sponsor for "quantification of peanut allergen" in the bulk Peanut Oil, NF, relies on rabbit polyclonal antibodies raised against a large number of proteins in a crude aqueous extract of at least 19 varieties of peanuts. This ELISA test is currently marketed as a screening test to detect whether peanut contamination in food commodities has occurred. Although the assay is said to be "very sensitive and specific for peanut", no claim has been made for sensitivity or specificity in the detection of clinically relevant allergens. Dr. Hefle, a consultant for Hill Dermaceuticals, has asserted in a memorandum of Aug 5 that "the antibodies have been shown in immunoblotting studies to specifically recognize all of the three major allergens of peanut, the one minor allergen of peanut, and, in addition, many other proteins in the peanut that are non-allergenic". No data

supporting the sensitivity and specificity for detecting all of the clinically relevant antigens have been presented. Dr Hefle did state that she "had her(sic) postdoc run an immunoblot of the rabbit anti-peanut protein against a peanut flour extract", and she enclosed a photocopy of the blot. Such qualitative data do not provide either sensitivity and specificity estimates nor the limit of detection of the specific allergens. The limit of detection for peanut proteins according to information from the manufacturer of the ELISA kit is 0.875 ppm, with a 1:25 sample extraction ratio. Hill Dermaceuticals has demonstrated that they are capable of testing for peanut protein at 2.5 ppm with accuracy. The Sponsor has also demonstrated that peanut oil spiked with peanut protein tested positive before heating at 475°F, but negative after heating at 475°F. Importantly, Hill has also asserted that they will only use Peanut Oil, NF, that has been heated at 475° F for at least 15 minutes. Such conditions should adequately decompose any remaining proteins such as allergens.

In sum, these additional tests and assurances, especially the assurance that Hill will not use any bulk manufacturer that does not refine its peanut oil by heating it to 475°F for at least 15 minutes, identified in the Addendum #2 to NDA 19-452/SE1-15 Chemistry Review #2 (stamp date: July 19, 1999), are sufficient evidence for batch-to-batch safety.

## Overview of the Risk-Benefit Calculus

Derma-Smoothe/FS (fluocinolone acetonide topical oil) Topical Oil, 0.01%, is one of many topical corticosteroid products for dermatologic use. In a superficial inspection, those who do not routinely provide care for patients with chronic skin disease might miss the additional benefit to the public health that may be expected to accrue from one more topical corticosteroid which might carry a small, but non-zero, risk of peanut allergy from the peanut oil-based vehicle. This is a specific instance of a not uncommon, regulatory problem, viz., the determination of the risk-benefit calculus when the benefits are modest and the risk of a significant adverse reaction may be very small, but non-zero. The first objective in the analysis is to bring further precision to the estimates of both the benefit and the risk. The second objective is to determine whether the risk can be reduced.

The advantage would be a product with demonstrated effectiveness which has a vehicle that is substantially different from other topical corticosteroid products for this age group and indication. Intolerance to topical corticosteroid vehicle components, such as parabens, propylene glycol, lanolin, and sorbic acid, can occur. Products lacking the offending ingredient provide a therapeutically satisfactory option for continuing therapy. In addition, some patients find some topical products much more appealing cosmetically than other products. Finding a topical that is preferred by a patient may enhance compliance, which in turn enhances control in chronic dermatoses such as atopic dermatitis. The additional choice provided by a new topical corticosteroid for atopic dermatitis in children is not trivial. Atopic dermatitis is common, chronic, and costly.

This NDA efficacy supplement did not provide adequate information at the time of submission to fix an estimate of the risk of peanut allergy from this product in atopic children with excoriated skin. While this NDA supplement was under review, the FDA communicated with the Sponsor regarding the evaluation of the risk of peanut allergy on multiple occasions, and the Sponsor undertook additional studies and tests and submitted the additional information cited above, sequentially, to the FDA. This information and assurances permit an estimate of negligible risk of peanut allergy. Even so, it is prudent to provide labeling to inform the prescribing clinician that 1) this product contains peanut oil, 2) this product may contain peanut protein below the level of detection, and 3) physicians should use caution in prescribing this product for patients with a history of allergic reaction to peanuts.

## Conclusions

There is now sufficient evidence for effectiveness and safety to approve Derma-Smoothe/FS (fluocinolone acetonide topical oil) Topical Oil, 0.01%, for the treatment of atopic dermatitis in children 6

years of age or older under the conditions of use described in the labeling. The information base in the labeling will be enhanced with information from Phase 4 studies

Lastly, the compendium for Peanut Oil, NF, refers to "the refined fixed oil", but does not explicitly require a heating step at a sufficient temperature and duration to ensure decomposition of allergic proteins. This could be a useful addition to the compendial specifications with advantages for the public health.

/S/

Jonathan Wilkin, M.D. 8/18/99
Director, Division of Dermatologic and
Dental Drug Products

cc: HFD-540 file
Archival NDA 19-452 (S-015)
HFD-540/DivDir/Wilkin
HFD-540/Medical TL/Walker
HFD-540/Pharm Tox TL/Jacobs
HFD-540/Pharm Tox/Hill
HFD-540/Chem TL/ DeCamp
HFD-540/Chem/Pappas
HFD-880/Biopharm/Bashaw
HFD-540/PM/Wright
HFD-354/USP:FDA/Mille, Yana

TEAM LEADER REVIEW

| | |
|---|---|
| Date of Submission: | August 14, 1998 |
| Medical Officer Review: | March 12, 1999 |
| Team Leader Review: | April 9, 1999<br>Revised April 28, 1999 |
| Drug: | Flucinolone acetonide 0.01% |
| Trade Name: | Derma-Smoothe F/S |

APR 28 1999

Background:

The current approved label[1] for Derma-Smoothe/FS states that the product is "a low to medium potency corticosteroid indicated for the treatment of atopic eczema and psoriasis of the scalp". The pediatric use section of the label states that safety and effectiveness in children and infants has not been demonstrated.

Adult and pediatric atopic dermatitis are similar diseases such that the efficacy of a product approved for use in adults can be extrapolated to children. However, the safety of the product cannot be extrapolated, therefore the sponsor must demonstrate that Derma-Smoothe F/S can safely be used in children.

Team Leader Review

The Medical Officer Review highlights several areas of clinical concern, which will be further discussed below.

- Derma-Smoothe contains 48% peanut oil.

The sponsor has not provided the agency with adequate evidence that the presence of Derma-Smoothe F/S does not pose a safety hazard for atopic children or peanut sensitive children. Peanut proteins have been demonstrated in both refined and crude peanut oil[2]. The presence or absence of these allergens may be dependent upon both the temperature and length of the processing method employed[3]. Therefore, peanut oil from different bulk sources could potentially have different specifications with regard to the peanut protein profile from batch to batch.

Approximately one third of children with refractory, moderate to severe atopic dermatitis have IgE mediated clinical reactivity to food proteins,[4] (milk, egg, wheat, soy, peanut, fish). One patient in the sponsor's clinical trial was recorded as suffering "anaphylactic reaction to nuts", while another withdrew due to an asthma reaction. These events were not explained adequately by the sponsor. Was an underlying sensitivity exacerbated by contact with the peanut oil in Derma-Smoothe F/S?

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[1] Based upon printed label revised 2/95 and submitted by Hill Dermaceuticals in final printed form.
[2] Olszewski A et al Clin Exp Allergy 1998 Jul;28(7):850-9
[3] Teuber SS et al J Allergy Clin Immunol 1997 Apr;99 (4): 502-7
[4] Eigenman et al Pediatrics 1998 Mar; 101 (3):E8

- Potential for sensitization to peanuts from chronic use of Derma-Smoothe F/S.

The sponsor should demonstrate that Derma-Smoothe F/S does not induce peanut sensitization in atopic children.

- Local hypopigmentation

Both patients (2/43) who experienced local hypopigmentation withdrew from the trial due to exacerbation. Details of these local cutaneous adverse events are insufficient.

Other Discipline Review Conclusions:

Statistical Review: Efficacy analysis supports the claim that Derma-Smoothe is more effective than vehicle.

Pharmacokinetics Review: There does not appear to be any measurable amount of HPA axis suppression. Insufficient data is presented to allow a claim in children less than 6 years.

**Regulatory Recommendation**:

The sponsor should be sent an Information Request as delineated below. The responses to these questions could affect approvability.

**Recommendations for Information Request to Sponsor**:

1. The sponsor should adequately demonstrate that the presence of peanut oil in Derma-Smoothe F/S 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 F/S.

2. The sponsor should provide adequate clinical and CMC information to demonstrate that the level of peanut protein allergens in the Derma-Smoothe F/S product is replicable and consistent between batches.

3. The sponsor should provide clinical narratives and the complete 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 F/S since the approval of the drug product, with narratives for all reports of allergic/asthmatic reactions.

TEAM LEADER REVIEW

/S/ 4/28/99

Susan J. Walker, M.D.
Clinical Team Leader

Cc: HFD-540 file
Archival NDA 19-452 (S-015)
HFD-540/DivDir/Wilkin
HFD-540/Derm TL/Walker
HFD-540/MO/Toombs
HFD-540/Pharm Tox TL/Jacobs
HFD-540/Pharm Tox/Hill
HFD-540/Chem TL/DeCamp
HFD-540/Chem/Pappas
HFD-540/PM/Wright

/S/ 4/28/99

EXCLUSIVITY SUMMARY FOR NDA # 19-452 SUPPL # 015

Trade Name: Derma-Smoothe/FS Topical Oil Generic Name fluocinolone, 0.01% AUG 17 1999

Applicant Name: Hill Dermaceuticals, Inc. HFD # 540

Approval Date If Known _____

## PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

*a) Is it an original NDA?*

YES /___/ NO /X/

*b) Is it an effectiveness supplement?*

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

*c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")*

YES /___/ NO /X/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: N/A

[Studies to establish safety in pediatric population down to age 6 years.]



cc: Original NDA 19-452/S-015 Division File/HFD-540 HFD-540/Wright HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The Sponsor did not specify the length of exclusivity requested.

*e) Has pediatric exclusivity been granted for this Active Moiety?*

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such) [Approved for adults, but not for pediatric popultion.]

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

**NDA# 19-452** **Derma-Smoothe/FS Topical Oil**

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

*N/A*

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?
YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation # 1, Study # **Protocol 25**

Investigation # 2, Study # **Protocol 25-S**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

   a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

   | | | |
   |---|---|---|
   | Investigation #1 | YES /___/ | NO /X/ |
   | Investigation #2 | YES /___/ | NO /X/ |

   If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

   _____ _____

   _____ _____

*b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?*

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /X/ |
| Investigation #2 | YES /___/ | NO /X/ |

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

*c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):*

Investigation # 1, Study # **Protocol 25**

Investigation # 2, Study # **Protocol 25-S**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

*a) For each investigation identified in response to question 3©: if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?*

Investigation #1 !

IND _____ ( YES /X/ ! NO /___/ Explain: _____

!

! _____

Investigation #2 !

!

IND _____ | YES /X/ ! NO /___/ Explain: _____

_____

*(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?*

*N/A*

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

/S/ 7/25/99

Signature Date

*Title:* Project Manager

/S/ 8/17/99

Signature of ~~Office~~ Date
Division Director

cc: Original NDA 19-452/S-015 Division File/ HFD-540 HFD-540/Wright HFD-93 Mary Ann Holovac

# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

| | | | |
|---|---|---|---|
| **NDA/BLA Number:** | 19452 | **Trade Name:** | DERMA-SMOOTHE FS |
| **Supplement Number:** | 15 | **Generic Name:** | FLUOCINOLONE ACETONIDE |
| **Supplement Type:** | SE1 | **Dosage Form:** | Oil; Topical |
| **Regulatory Action:** | AP | **Proposed Indication:** | Treatment of atopic dermatitis in pediatric patients |

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**
YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

**What are the INTENDED Pediatric Age Groups for this submission?**

____NeoNates (0-30 Days ) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

| | |
|---|---|
| **Label Adequacy** | Adequate for SOME pediatric age groups |
| **Formulation Status** | |
| **Studies Needed** | STUDIES needed. Applicant has COMMITTED to doing them |
| **Study Status** | Protocols are under discussion. Comment attached |

**Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission?** YES

COMMENTS:
Sponsor request pediatric age group 2 and up. Did not have data to support treatment in pediatric patients under the age of 6. Sponsor has agreed to conduct a phase 4 study looking at local safety on the phase. To obtain approval for lower age group, additional studies will be required 8/19/99

**This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MILDRED WRIGHT**

/S/
Signature

August 19, 1999
Date

CC:
NDA 19-452/S-015
DIV File
HFD-540/Wright

Hill Dermaceuticals, Inc.

*"The Scalp Company"*

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

## DEBARMENT CERTIFICATION

Pursuant to 21 USC 335 a (k) (1), the applicant, Hill Dermaceuticals, Inc., in Sanford Florida, "did not and will not use in any capacity the services of any person debarred under subsections (a) or (b), in connection with NDA 19-452, Derma-Smoothe/FS Topical Oil (0.01% fluocinolone acetonide)."

27 JULY 1999

Date

Jerry Roth
President
Hill Dermaceuticals, Inc.

# MEMORANDUM OF TELECON

MAR - 4 1999

**DATE:** March 4, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Ernest Pappas, M.S., Chemistry Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Chemistry Information Request/ELISA test

**Discussion:**
The following information was requested as validation of the ELISA test:
A detailed description was requested. It should include:
1) Complete methodology—principle, instrutments used, condition, assay-whole chromatogram
2) Validation data—spike samples to determine sensitivity, selectiveness, accuracy and precision of method

**Agreements Reached:**
The Sponsor will provide the requested information

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
Div File
HFD-540/M.Wright

# MEMORANDUM OF TELECON

MAR 10 1999

**DATE:** March 10, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Ella Toombs, M.D., Medical Reviewer
Mary Jean Kozma-Fornaro, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Clinical Information request

**Discussion:**
Dr. Toombs requested the following information:

1) For the articles that the Sponsor has found discussing peanut oil allergy, submit a synopsis of articles, along with the articles.
2) Please provide the CRFs requested in a previous t-con.
3) Further clarification of Protocols 25 and 25S.
4) Requested the demographics for Protocol 25S.
5) Clarified the bottle size for vehicle and drug and dosing in both protocols.

Also discussed the following:

1) Regulatory history of NDA
2) The fact that peanut allergy was not an exclusion criteria

**Agreements Reached:**
The Sponsor will

1) Fax a synopsis of the articles today and follow-up with a hard copy submission of the fax and e articles.
2) Fax the CRFs today and follow-up with a hard copy submission.
3) Will provide a descriptive summary of Protocols 25 and 25S.
4) Will provide the demographics for 25S.

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
Div File
HFD-540/M.Wright

# MEMORANDUM OF TELECON

MAR 26 1999

**DATE:** March 26, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Ernest Pappas, M.S., Chemistry Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** 3/26/99 Chemistry amendment

**Discussion:**
The amendment did not provided the information needed The Sponsor needs to

1) Call/ and ask for validation. Has to show
   a. That it goes down to 1 PPM.
   b. If 2.5 PPM is the lowest level it will have to be validated.
   c. Need to spike levels of protein and determine sensitivity and selectiveness.
   d. Need to know which protein it is detecting.

**Agreements Reached:**
The Sponsor will provide the requested information. Will call the middle of next week to give us a status update.

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
Div File
HFD-540/M.Wright

# MEMORANDUM OF TELECON

APR 21 1999

**DATE:** April 21, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Jerry Roth, President
Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Jonathan Wilkin, M.D., Division Director
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Advisory Committee Meeting

**Discussion:**
Dr. Wilkin informed the Sponsor that the advisory committee meeting scheduled for June 3rd and 4th has been cancelled for administrative reasons.

Mr. Roth expressed concern for delay and inquired if the meeting was the only way the peanut oil issue could be resolved.

Dr. Wilkin stated that he was open to resolving it otherwise, if they could present data to answer the Division's concerns. Concern remains about batch to batch consistency of batch peanut oil.

Mr. Roth reported that since the test is now commercially available, is would not be a problem to validate different batches.

Dr. Wilkin explained that even after the Advisory Committee meeting, we could still not be a 100% certain, but it does offer the opportunity for the Division and the Sponsor to make their presentations to the members. The Sponsor was encouraged to support data to support their position and opposed to "in my clinical experience" type of comments.

**Agreements Reached:**

1) Tracey Riley will inform the Division and Sponsor once the meeting date has been determined.

Minutes drafted by Millie Wright, P.M.

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Orig NDA 19-452/SE-015
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# MEMORANDUM OF TELECON

**DATE:** May 18, 1999 MAY 18 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Jerry Roth, President
Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Jonathan Wilkin, M.D., Division Director
Susan Walker, M.D. Dermatology Team Leader
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Information to be discussed at the Advisory Committee Meeting

**Discussion:**
Dr. Wilkin pointed out the package that arrived for the advisory committee meeting contained a summary of a clinical study that the Division had not reviewed (Tab 7). Minutes drafted by Millie Wright, P.M.

It was also discussed that this study had not been submitted to an IND. The Sponsor was directed to the IND regs in the CFRs. Mr. Hill stated that this was an over sight and that he had no problem submitting the protocol to the Agency.

It was further noted that the information contained in Tab 7 was inadequate for review—it was not a protocol, but only a synopsis of a protocol. The Division needs to see the complete protocol and study report, without which their claim can not be evaluated. Mr. Hill also established that the study is completed.

Mr. Hill stated his belief that the potential for allergic reaction due to the peanut oil in the product was not an issue prior to the submission of the NDA supplement. It only became an issue due to media coverage and doctors reaction to airline "peanut scare."

Dr. Wilkin confirmed that the potential for safety concerns due to the peanut oil in the product had been discussed in the February 1996 meeting.

If the required information can not be submitted in time for review, the Sponsor was informed of the possibility of a delay in the advisory committee meeting.

Mr. Roth wanted to know the drop-dead date to avoid the need for rescheduling the meeting.

Dr. Wilkin stated that this would depend on the material that was submitted for review.

**Agreements Reached:**

1. The requested information will be submitted by the end of the week.
2. Based on the material submitted, the Division will determine if the June advisory committee meeting needs to be rescheduled.

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Dr. Wilkin stated that he has never found it helpful to impute the motives of a Sponsor. It is the Agency's and the Sponsor's responsibility to look over the landscape of the product—the scientific data and come to a convergent point. One of the reasons for deferring the meeting was that there was a major piece of evidence included in the meeting package that the Division had not reviewed. This fact was not reported in your letter.

**Agreements Reached:**

1) Tracey Riley will inform the Division and Sponsor once the meeting date has been determined.
2) The Sponsor will provide documentation to the NDA to address the safety concerns identified by the Division.

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
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HFD-540/M.Wright

# MEMORANDUM OF TELECON

JUL 19 1999

**DATE:** July 19, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Jerry Roth, President
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Jonathan Wilkin, M.D., Division Director
Wilson DeCamp, Ph.D., Chemistry Team Leader
Ernest Pappas, M.S., Chemistry Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Bulk Peanut Oil

**Discussion:**
The Sponsor was asked if their suppliers would be restricted those who heat process the refined peanut oil. Specifically, heated to 475 degrees for 15 minutes. The rationale is that the heating denatures the peanut protein.

Mr. Roth replied that they had a commitment from the supplier that they wouldn't change from the heat processing method without notifying Hill.

Dr. Wilkin stressed that the Division did not want them using bulk peanut oil that hadn't been heat process.

**Agreements Reached:**
Mr. Roth will submit to the application their commitment to only use refine peanut oil that had been heated to 475 degrees for 15 minutes.

Minutes drafted by Millie Wright, P.M.

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# MEMORANDUM OF TELECON

JUL 2 1999

**DATE:** July 2, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**

Name: Jerry Roth, President
Rosario G. Ramirez, Medical/Regulatory Affairs
Nancy Puglia, Plant Manager, Chief Chemist
Representing: Hill Dermaceuticals, Inc.
AND

**Name:** Wilson DeCamp, Ph.D., Chemistry Team Leader
Ernest Papas, M.S., Chemistry Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Peanut Allergen/Testing for Presence in refined bulk peanut oil
Labeling: How Supplied Section

**Discussion:**

1) The rationale for a CMC study in which the peanut oil is spiked with the allergen, tested for the allergen prior to heat processing, tested again after it has been heated at 475 degrees for 15 minutes, and retested for the presence of the allergen afterwards was again reviewed with the Sponsor. It was stressed that the burden is with Hill to show the absence of the allergen.
2) The Sponsor was asked why the statement "tightly closed containers" is in the How Supplied section.
Response: The oil has a tendency to leak. This cap has been in use for 8-9 years. Once it ready to be dispensed, the cap used during shipping and storage is removed and a dispensing cap is attached.

**Agreements Reached:**

The Sponsor will conduct the study in which the oil is spiked with the known antigen, tested prior to heating and tested after heating. These results will be submitted to the NDA.

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
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# MEMORANDUM OF TELEPHONE COFERENCE

DEC 30 1998

| | |
|---|---|
| **DATE:** | **December 30, 1998** |
| **NDA:** | **19452/SE1** |
| **DRUG:** | **DermaSmoothe/FS** |
| **SPONSOR:** | **Hill Derm Pharmaceuticals**<br>**Dr. Nini Ramirez** |
| **FDA:** | **Dr. Ella Toombs, Medical Officer, HFD-540**<br>**Mary Jean Kozma-Fornaro, CPMS< HFD-540** |
| **SUBJECT:** | **Request Information and Clarification on Efficacy Supplement dated 8/18/98** |

**The following were requested of Dr Ramirez:**

1. **Copy of current Derma-Smoothe/FS label on disk.**
2. **Schematic detailing protocol investigative time frames. Include number of patients, number of patients per center, and date of entry and date of completion per center. Also provide details of when patient returned and what was done.**
3. **Provide the cortisol laboratory normal levels, baseline as well as post-stimulation levels.**
4. **Please clarify which areas of the skin were treated. If the skin was pre-moistened prior to application of Derma-Smoothe F/S, understand, reference to same will be included in the label.**
5. **Provide clarification on the amount of drug applied per patient and an average if possible. The BSA application per patient can also be used. Quantitative information is needed.**
6. **Provide a table of all local adverse events. Include all events regardless of whether you consider the event treatment related. Dr. Ramirez stated that all local adverse events were included.**

**Dr. Ramirez agreed to provide all of the information by the week of January 4, 1999. The information would be provided in table format.**

**Conversation ended amicably.**

**cc:**

**NDA 19452/S-015**
**HFD-540/Div File** 12/30/98
**HFD-540/Toombs**
**HFD-540/Wright**

# MEMORANDUM OF TELECON

AUG 26 1998

**DATE:** August 26, 1998

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Nancy Puglia, Plant Manager, Chief Chemist
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Wilson DeCamp, Ph.D., Chemistry Team Leader
Ernest Pappas, M.S., Chemistry Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Draft labeling submitted with application

**Discussion:**
In preparation for the filing meeting for this application, the following line was noted in the labeling under the How Supplied Section:

The Sponsor reported that the intent was to co-package Derma-Smoothe/FS Topical Oil with the over-the-counter moisturizer, Smoothe Oil Moisturizing emollient. The Agency informed them this was beyond the scope of an efficacy supplement and that co-packing would need to be explored separately.

**Agreements Reached:** The Sponsor agreed to submit revised labeling to remove the co-packing statement from the labeling.

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
Div File
HFD-540/M.Wright

540-WRIGHT

# MEMORANDUM OF TELECON

| | |
|---|---|
| **DATE:** | **September 28, 1998** |
| **DRUG:** | **Derma Smoothe FS** |
| **NDA:** | **19452/SE1** |
| **SPONSOR:** | **Hill Demaceuticals** |
| | **Nini Ramirez, MD** |
| **FDA:** | **Mary Jean Kozma Fornaro, CPMS, HFD-540** 9/28/98 |

**Dr. Ramirez was contacted to request for the clinical reviewer summary tables of the safety, efficacy and demographic data in MS Word format. Since the data is located at the sponsor facility, Dr. Ramirez stated she would have the requested information within a few days.**

**Conversation ended amicably.**

**cc:**

**NDA 19452**
**HFD-540 Division File**
**HFD-540/Toombs**
**HFD-540/Wright**

JAN 11 1999

# MEMORANDUM OF TELECON

**DATE:** January 11, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Ella Toombs, M.D., Medical Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Information request

**Discussion:**
Dr. Toombs requested the following information:

1) Outline of the clinical study Protocols (25 & 25S)
2) Tabulated investigator and site information
3) Tabulated patient data according to site and investigator

**Agreements Reached:**
The Sponsor will submit the requested information.

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
Div File
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# MEMORANDUM OF TELECON

**DATE:** January 20, 21, and 26, 1999 JAN 26 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Ella Toombs, M.D., Medical Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Protocols 25 and 25S

**Discussion:**
Dr. Toombs requested clarification on the following points during the telecons:

1) Difference between the protocols.
2) For Protocol 25—disposition, demographics (separate for 2-6 and 7-12), outcomes, and local adverse events,
3) Amount of drug received
4) Cortisol levels

**Agreements Reached:**
The Sponsor will submit the requested information.

Minutes drafted by Millie Wright, P.M.

CC:
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HFD-540/M.Wright

# MEMORANDUM OF TELECON

**DATE:** February 8, 1999

FEB - 8 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Jerry Roth, President
Rosario G. Ramirez, Medical/Regulatory Affairs
Nancy Puglia, Plant Manager, Chief Chemist
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Wilson DeCamp, Ph.D., Chemistry Team Leader
Ella Toombs, M.D., Medical Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Chemistry and Clincial Requests

**Discussion:**
Chemistry:

Please fax the COA for last batch of peanut oil that you accepted from vendor. The request is related to the possible sensitivity of children to a drug product containing peanut oil.

Clinical:

1) Clarified that it was a multi center study—not different studies.
2) Requested efficacy mean values for erythema.
3) Discussed AEs and patients that dropped out of study.

**Agreements Reached:**

The Sponsor will provide the requested information.

Minutes drafted by Millie Wright, P.M.

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# MEMORANDUM OF TELECON

FEB - 9 1999

**DATE:** February 9, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Jerry Roth, President
Rosario G. Ramirez, Medical/Regulatory Affairs
Nancy Puglia, Plant Manager, Chief Chemist
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Wilson DeCamp, Ph.D., Chemistry Team Leader
Ella Toombs, M.D., Medical Reviewer
Millie Wright, Project Manager
Barbara Hill, Ph.D., Pharmacology Reviewer
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Peanut Allergy

**Discussion:**

Sponsor was asked what had been done to address the potential for allergic reactions for patients that are allergic to peanuts.

Response: Do not think it is a problem. Reported that a study conducted by has confirmed that fact. It was also reported that they are planning to repeat the study.

Dr. Toombs asked if the study was done with oral or topical drug product?

Response: Both oral and topical. In their planned study, they will use topical—3-arm study: pure peanut oil, vehicle and drug product.

Dr. Hill asked how they were measuring the peanut protein:

Response: ELISA test

Discussion end amiably.

Minutes drafted by Millie Wright, P.M.

CC:
Orig NDA 19-452/SE-015
Div File
HFD-540/M.Wright

# MEMORANDUM OF TELECON

**DATE:** March 1, 1999 MAR - 1 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Ella Toombs, M.D., Medical Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Cortisol Values

**Discussion:**
Dr. Toombs requested clarification on the following points:

1) Explanation as to why the cortisol values differed.
2) Amount of drug applied.
3) 2 reported adverse events of hypopigmentation
4) Study methods for Protocol 25S

**Agreements Reached:**
The Sponsor will submit the following information:

1) Tabulated cortisol values for the 22 patients
2) Case report forms for patients # 1, 7, and 9.

Minutes drafted by Millie Wright, P.M.

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Div File
HFD-540/M.Wright

# MEMORANDUM OF TELECON

MAR - 2 1999

**DATE:** March 2, 1999

**APPLICATION NUMBER:** NDA 19-452/SE1-015

**Product:** Derma-Smoothe/FS Topical Oil

**BETWEEN:**
Name: Rosario G. Ramirez, Medical/Regulatory Affairs
Representing: Hill Dermaceuticals, Inc.
AND
**Name:** Ella Toombs, M.D., Medical Reviewer
Millie Wright, Project Manager
Representing: Division of Dermatologic and Dental Drug Products/HFD-540

**Topic:** Peanut Oil Allergy

**Discussion:**
The potential for peanut allergic individuals to have an allergic reaction to Derma-Smoothe/FS was discussed. The Division still sees this as a possibility. The Sponsor did not share this concern. Dr. Toombs requested that data to support their lack of concern be submitted. Suggestions were:

1) All adverse events that were allergic reactions to the drug
2) Literature search.

**Agreements Reached:**
The Sponsor agreeable to doing the above.

Minutes drafted by Millie Wright, P.M.

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