CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-452/S017

ADMINISTRATIVE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION (ITEM 13)

Patent Information [21 CFR 314.50(h) and 314.53(c)(3)]

1. *Active Ingredients:* Fluocinolone acetonide

2. *Strengths:* Fluocinolone acetonide 0.01%

3. *Trade Name:* Derma-Smoothe/FS Topical Oil

4. *Dosage Form and Route of Administration:* topical oil preparation

5. *Applicant Firm Name:*

   The applicant, Hill Dermaceuticals, Inc., is a corporate entity doing business in the U.S. at 2650 S. Mellonville Avenue, Sanford, Florida 32773

6. *Applicable Patent Number(s):*

   No relevant patents [21 CFR 315.53(c)(3)] – The applicant, Hill Dermaceuticals, Inc., believes there are no patents which claim the drugs or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

27 JULY 2001

Date

Rosario G. Ramirez
Director, Regulatory Affairs
Hill Dermaceuticals, Inc.

Claimed Exclusivity [21 CFR 315.50(j)]

1. The applicant, Hill Dermaceuticals, Inc., claims three (3) years marketing exclusivity upon approval of this supplemental new drug application submitted pursuant to Section 505(b)(1) of the FD&C Act.

2. The applicant makes reference to 21 USC 355(c)(3)(D)(iii) in support of this claim.

Claimed Exclusivity – 21 USC 355(c)(3)(D)(iii)

i. *New clinical investigations:* The applicant certifies that to the best of its knowledge the open-label safety clinical investigations included in the application meet the definition of "new clinical investigation" set forth in 314.108(a).

ii. *Essential to approval:* The applicant is requesting 3 years of market exclusivity for the product Derma-Smoothe/FS, pursuant to 21 USC (c)(3)(D)(iii), based on the contained reports of new investigation, other than bioavailability studies, sponsored by the applicant, that is essential to the approval of this application.

iii. *Conducted or sponsored by:* The applicant certifies that it was the sponsor named in the Form FDA 1571 for Investigational New Drug Application (IND) 33,448 under which the new clinical investigation that are essential to the approval of this application was conducted.

27 July 2001

Date

Rosario G. Ramirez
Director, Regulatory Affairs
Hill Dermaceuticals, Inc.

EXCLUSIVITY SUMMARY for NDA # 19-452 SUPPL # 017

Trade Name Derma-Smoothe/FS Toical Oil, 0.01%

Generic Name fluocinolone acetonide

Applicant Name Hill Dermaceuticals, Inc. HFD-540

Approval Date _____

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 questions 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.)? **SE5**
   The purpose of the clinical study was to demonstrate the safety of the product for use in pediatric patients 2 to 5 years. Safety assessment, to evaluate HPA axis function involved analysis of morning plasma cortisol levels before and after ACTH stimulation, at baseline (prior to treatment) and at the end of 4 weeks.

   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**

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?

3 years

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

YES /___/ NO /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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).

YES / / NO /X*/

***Derma-Smoothe/FS is approved for same use for pediatric patients age 6 and above, but not for use in the 2 to 5 year old age group.**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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 #**NDA 19-452** **Derma-Smoothe/FS Topical Oil, 0/01%**

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).**N/A**

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /<u>X</u>/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

_____

_____

(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 26**–An Open Label Safety Study on Derma-Smothe/FS for Treatment of Atopic Dermatitis in Children 2 to 5 years of Age.

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 **Protocol 26** 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:**N/A**

NDA # _____ Study # _____

(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 **Protocol 26** YES /___/ NO /**X**/

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

NDA # _____ Study # _____

(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 26**

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(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #[redacted] 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 _____

(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: _____

_____

_____

_____ _____
Signature of Preparer Date
Title:_____

_____ _____
Signature of Office of Division Director Date

cc:
Archival NDA 19-452/S-017
HFD-540/Division File
HFD-540/Wright
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	019452	**Trade Name:**	DERMA-SMOOTHE FS
Supplement Number:	017	**Generic Name:**	FLUOCINOLONE ACETONIDE
Supplement Type:	SE5	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	CORTICOSTEROID
Action Date:	10/10/00		

Indication # 1 Atopic dermatitis in pediatric patients

Label Adequacy: Adequate for SOME pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): Studies below the age of 2 have not been conducted. Deferral has been granted until February 2003

Ranges for This Indication

Lower Range	Upper Range	Status	Date
2 years	5 years	Deferred	2/1/03

Comments: Studies still need to be conducted in the below age 2 pediatric population.

This page was last edited on 10/4/01

Signature ______________ ______ Date ______________

/S/ 10/9/01

DEBARMENT CERTIFICATION (ITEM 16)

Pursuant to 21 USC 335a(k)(1) the applicant, Hill Dermaceuticals, Inc., in Sanford, FL "did not and will not use in any capacity the services of any person debarred under subsections (a) or (b), in connection with [this] application."

27 JULY 2001

Date

Jerry S. Roth
President
Hill Dermaceuticals, Inc.

ENVIRONMENTAL IMPACT: Claim for Categorical Exclusion

Categorical exclusion based on specific criteria listed in 21 CFR, section 25.24, (c) 2 (i)(c) is claimed for the product Derma-Smoothe/FS Topical Oil.

21 CFR Ch.1 § 25.21 (c) *Human drugs and biological products.*

(2) Action on an amendment or supplement to an NDA of the following types if the drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect and if data available to the agency do not establish that, at the expected levels of exposure, the substance may be toxic to organisms in the environment.

(i) Changes specified in §314.70 (c).

Based on the above provisions, Hill Dermaceuticals, Inc. is claiming categorical exclusion for the product Derma-Smoothe/FS Topical Oil. The drug product has not changed with regards to formulation of the active component (0.01% Fluocinolone acetonide) or its excipients, has not changed the method of administration, nor the indications it was approved for. All other procedures, controls and tests for the drug product have not deviated from previous commitments (S-004, S-005, S-007, S-009, S-010, S-012, S-013).

FDA Fax Memo

Date: January 29, 2001

Subject: NDA 19-452/S-017/Derma-Smoothe FS

Hi NiNi and Criss,

The medical reviewer has the following information requests for the above submission:

1. Reasons for the two dropouts in Study 26 should be provided in detail.

2. The efficacy data have been collected and should be presented

3. Although the report for Study 26 does not discuss the data at the end of treatment (Week 4), 3 of the 13 patients with testing at Week 4 had low pre-stimulation cortisol levels (the label uses >7 µg/dL as normal). Such data should be presented in the label.

Additional labeling comments will be faxed to you at a later date.

If you have questions, please call.

Respectfully,

Millie

FDA Fax Memo

Date: July 26, 2001

Subject: NDA 19-452/S-017/Derma-Smoothe/FS Topical Oil (fluocinolone acetonide), 0.01% Information Request

Hi NiNi and Chris,

We have the following information requests:

1. Please provide a statement that the proposed changes in the supplement do or do not effect the CMC section as submitted in the NDA.

2. Please provide an environmental assessment statement should be submitted for the supplement, claiming categorical exclusion as required by 21 CFR 25.31(a). In doing so, you must indicate tat a claim categorical exclusion is submitted under 21 CFR 25.31(a) because your calculations show that the expected introduction concentrate (EIC) of the drug substance into the aquatic envifronment is less than 1 part per billion.

3. Please provide patent information

4. Please provide Debarment Statement.

5. Please provide Financial Disclosure information.

6.

If you have questions, please call.

Respectfully,
Millie

FDA Fax Memo

Date: August 7, 2001

Subject: NDA 19-452/S-017/Derma-Smoothe/FS Topical Oil (fluocinolone acetonide), 0.01% Information Request

Hi NiNi and Chris,

We have the following information requests:

[redacted]

2. Please provide the data (frequencies of the reactions listed) to support removal of one of the appearances of "hypopigmentation" in the ADVERSE REACTIONS, since the reactions are listed in order.
3. Please provide your clinical plan for the age group under 2 or request a waiver.

If you have questions, please call.

Respectfully,
Millie

FDA Fax Memo

Date: August 27, 2001

Subject: NDA 19-452/S-017/Derma-Smoothe/FS Topical Oil (fluocinolone acetonide), 0.01%
Information Request

Hi NiNi and Chris,
Review of your August 8, 2001 submission has been completed. We have the following information requests:

1. Removal of one of the appearances of "hypopigmentation" in the ADVERSE REACTIONS section is a correction of a previous error and is acceptable. As the reactions are supposed to be listed in the order of decreasing frequencies, it is imperative that their order of appearance be correct. The proposed draft label gives an order different from that in the topical corticosteroid class label of 1995, and therefore must have been supported by data. The class label of 1995 provides for this order:
   burning > itching > irritation > dryness > folliculitis > acneiform eruptions > hypopigmentation > perioral dermatitis > allergic contact dermatitis > secondary infection > skin atrophy > striae > miliaria

   [redacted]

   Therefore, the Applicant is again requested to provide the frequencies (controlled clinical trials or post-marketing reporting) to assure accuracy of the statement in terms of the order of adverse events. It is anticipated that this should be easily available from the Sponsor's database.

2. The Applicant may be granted deferred submission of required pediatric assessment in children <2. However, the Applicant should request the deferral, with certification indicating the grounds for deferral, a description of the planned studies, and evidence that these will be conducted with due diligence and at the earliest possible time (21 CFR 314.55(b)).

If you have questions, please call.

Respectfully,
Millie

FDA Fax Memo

Date: August 28, 2001

Subject: NDA 19-452/S-017/Derma-Smoothe/FS Topical Oil (fluocinolone acetonide), 0.01%
Information Request

Hi NiNi and Chris,

Review of your request for Categorical Exclusion, in your July 27 2001 submission, has identified deficiencies in your submission. Your request should comply with requirements in the Final Rule dealing with Environmental Assessments, published July 29, 1997 and effective August 28, 1997. Please refer to the Implementation section, second paragraph under #2 which reads as follows:

> Most applications will qualify for categorical exclusion under the new regulations because the expected introduction concentration (EIC) into the aquatic environment is less than 1 ppb. Information regarding the expected introduction concentration into the environment is normally at the end of EA format item 6. The standard EIC calculation is in included in the EA Industry Guidance on page 14 and the calculation should be based on the kg of the active moiety used in applicant's entire product line for that active moiety.

Please note that the Guidance Document referred above, for the calculation of EIC, can be found on CDER's web site. The title is *Guidance to Industry: For the Submission of an Environmental Assessment in Human Drug Applications and Supplements.* It was published November 1995.

If you have questions, please call.

Respectfully,
Millie

FDA Fax Memo

Date: October 1, 2001

Subject: NDA 19-452/S-017/Derma-Smoothe/FS Topical Oil (fluocinolone acetonide), 0.01% Labeling

Hi NiNi and Chris,
In the September 5, 2001 submission to NDA 19-452/S-017, you proposed changing the chemical name for the anhydrous form of fluocinolne acetonide. Your proposed change is not acceptable, as it is not the nomenclature that is required by the Agency. Therefore the wording in the Description section should remain as follows:

> Derma-Smoothe/FS® contains fluocinolone acetonide (6α, 11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione, cyclic 16,17 acetal with acetone, a synthetic corticosteroid for topical dermatologic use.

Please let us know if this is acceptable to you.

If you have questions, please call.

Respectfully,
Millie

FDA Fax Memo

Date: October 1, 2001

Subject: NDA 19-452/S-017/Derma-Smoothe/FS Topical Oil (fluocinolone acetonide), 0.01%
Information Request

Hi NiNi and Chris,
The submission for NDA 19-452 dated 9/5/01 states the following:

"Adverse events, probably or possibly related to the drug product, collected from recent pediatric studies show occurrence of burning, itching, irritation, erythema, papules and pustules in 6 patients, and slight change in pigmentation in 1 patient. "

Presumably each of those adverse events (except for hypopigmentation) occurred in more than one patient, and the order is consistent with class labeling.

Please clarify yes or no on this.

If you have questions, please call.

Respectfully,
Millie