

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40259

APPROVAL LETTER

JUL 29 1999

Ferndale Laboratories, Inc.
Attention: Deborah L. Therese
780 West Eight Mile Road
Ferndale, MI 48220

Dear Madam:

This is in reference to your abbreviated new drug application dated June 24, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocortisone Acetate Cream USP, 2.5%.

Reference is also made to your amendments dated February 22, April 27, June 30, and July 28, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug product, Hydrocortisone Acetate Cream USP, 2.5% can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

DL
1/8/99
Douglas L. Spohn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

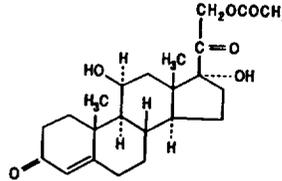
40259

DRAFT FINAL PRINTED LABELING

HYDROCORTISONE ACETATE CREAM USP, 2.5%

DESCRIPTION

The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and anti-pruritic agents. Hydrocortisone acetate is a member of this class. Hydrocortisone Acetate has a molecular formula of $C_{23}H_{32}O_6$, a molecular weight of 404.50 and a CAS registry number of 50-03-3. The chemical name is: Pregn-4-ene-3,20-dione, 21-(acetyloxy)-11, 17-dihydroxy-, (11 β)- and the chemical structural formula is presented below:



Each gram of the cream contains hydrocortisone acetate 25 mg (2.5% w/w) in a water washable cream containing the following inactive ingredients: aquaphor, isopropyl palmitate, stearic acid, cetyl alcohol, polyoxyl 40 stearate, potassium sorbate, triethanolamine lauryl sulfate, propylene glycol and purified water.

CLINICAL PHARMACOLOGY

Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See DOSAGE AND ADMINISTRATION).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE

Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS—Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression:

Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy, Teratogenic Effects, Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids.

Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged period of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

Burning	Hypertrichosis	Maceration of the skin
Itching	Acneiform eruptions	Secondary infection
Irritation	Hypopigmentation	Skin atrophy
Dryness	Perioral dermatitis	Striae
Folliculitis	Allergic contact dermatitis	Miliaria

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

Topical corticosteroids are generally applied to the effected area as a thin film two to four times daily depending on the severity of the condition.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED

Hydrocortisone Acetate Cream, USP 2.5% is supplied in the following:
1 oz (28.4 g) tubes (NDC 0496-0791-04)
2 oz (57 g) tubes (NDC 0496-0791-03)

JUL 29 1994

Rx Only.

Store at controlled room temperature 15°C - 30°C (59°F - 86°F).

FERNDAL LABORATORIES, INC.
FERNDAL, MICHIGAN 48220

Iss. 0998
MG #14144

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40259

CHEMISTRY REVIEW(S)

APPROVAL PACKAGE SUMMARY FOR 40-259

ANDA: 40-259

FIRM: Ferndale Laboratories, Inc.

DRUG: Hydrocortisone Acetate

DOSAGE: Cream

STRENGTH: 2.5%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 5/26/99

BIO STUDY/BIOEQUIVALENCE STATUS: Bio waiver was granted 5/25/99

METHODS VALIDATION: The drug product is compendial ~~Methods~~ Verification acceptable 3/11/98

STABILITY: The firm has provided 3 months satisfactory stability data at 40°C/75%RH and 24 months room temperature at 25°C/60%RH for each package. Also cycle study submitted for all packaging sizes. The sample will be tested at top, middle and bottom.

LABELING REVIEW STATUS: Labeling is satisfactory 5/21/99

STERILIZATION: N/A

BATCH SIZES: The firm has submitted the master formula and manufacturing process for maximum production batch kg. Also provided a copy of the exhibit batch PD 96120 for kg. The firm will be using the same drug substance manufacturer, same equipment and same process.

COMMENTS: The Application is Approvable.

REVIEWER: Nashed E. Nashed, Ph.D.

DATE: 7/16/99

SUPERVISOR: Paul Schwartz, Ph.D.

PJ 7/19/99

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 40-259

3. NAME AND ADDRESS OF APPLICANT

Ferndale Laboratories, Inc.
780 West Eight Mile Road
Ferndale, MI 48220

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that in their opinion and to the best of their knowledge, there are no patents that claim the listed drug referred to in this application and is not entitled to a period of marking exclusivity.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Hydrocortisone Acetate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original 6/24/97
Amendment 6/17/98
Amendment 4/27/99
Amendment 6/30/99
Amendment 7/28/99

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory

11. Rx or OTC

Rx

12. RELATED DMF's:

DMF's

13. DOSAGE FORM

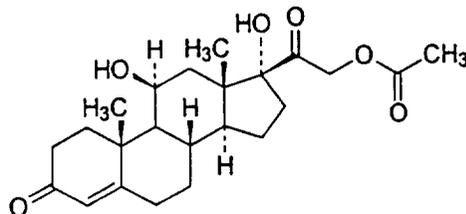
14. POTENCY

Cream

2.5%

15. CHEMICAL NAME AND STRUCTURE

Hydrocortisone Acetate. Pregn-4-ene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-, (11 β)-. C₂₃H₃₂O₆. 404.51. 50-03-3. Glucocorticoid, anti-inflammatory. USP 23, page 758.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER:

DATE COMPLETED:

Nashed E. Nashed, Ph.D.

7/16/99

Supervisor: Paul Schwartz, Ph.D.

7/19/99

cc: ANDA 40-259
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed, Ph.D./7-16-99

HFD-627/P.Schwartz, Ph.D./7-19-99

Nashed 7/21/99
Schwartz 7/21/99

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40259

BIOEQUIVALENCY REVIEW(S)

Hydrocortisone Acetate

Topical Cream, 2.5%

Reviewer: Gur J.P. Singh

ANDA #40-259

File #: 40259W.697

Ferndale Laboratories, Inc.

780 West Eight Mile Road

Ferndale, MI 48220

Submission Date:

June 24, 1997

REVIEW OF A WAIVER-REQUEST**BACKGROUND**

The firm is seeking waiver of *in vivo* bioequivalence study requirements for its hydrocortisone acetate 2.5% topical cream. The reference product cited in this application is hydrocortisone acetate 1% topical cream manufactured by Park Davis (ANDA #89914).

The basis for this application is a suitability petition (Docket #90P-0049/CP) approved under FD&C Act section 505(j)(2)(C) on June 22, 1990. It allowed manufacturing of hydrocortisone acetate 2.5% cream, which is a higher strength product compared with the listed drug, 1% hydrocortisone acetate cream (Park Davis) cited in the petition.

COMMENTS

1. The reference listed formulation of hydrocortisone acetate 1% cream manufactured by Park Davis has been discontinued. The reference listed drug for this product currently listed is manufactured by Purepac (ANDA #86052-001).
2. Because the reference listed formulation of hydrocortisone acetate 1% cream cited in the suitability petition (Docket #90P-0049/CP) has been withdrawn, this application for approval of hydrocortisone acetate 2.5% cream has not been submitted following appropriate procedure. Submission of this application falls under CFR 314.122, as it relies on a listed drug that is no longer marketed. The sponsor should follow the procedure outlined in CFR 314.122. On November 11, 1997, the firm was requested to submit a citizen petition (see the telephone conversation record, vol 1.1). However on January 16, 1998, the firm was advised to submit a new 505(j) information and labeling citing the new reference listed drug given in the 17th edition of the Orange Book. The sponsor has not submitted the required information.

RECOMMENDATIONS

1. The request for waiver of *in vivo* bioequivalence study requirements for Ferndale Laboratories' hydrocortisone valerate 2.5% topical cream will not be considered due to comments #1 and 2.
2. The Division of Labeling and Program Support should take appropriate action based on comments 1 and 2.

Gur J.P. Singh, Ph.D.
Division of Bioequivalence
Review Branch II.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Handwritten initials and date: JSI, U, 2/24/1998, and a signature.

CONCUR: JSI Date: 2/25/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence.

GJP SINGH/ 2/25/98/ 40259W.697
cc. ANDA #40259 (original, duplicate), HFD-630 (OGD), HFC-130 (JAllen), HFD-600 (Hare), HFD-655(Nerurkar, Singh), Drug file.

2.1
P. Schwartz

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-259

APPLICANT: Ferndale Laboratories

DRUG PRODUCT: Hydrocortisone Acetate Cream USP, 2.5%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40259

CORRESPONDENCE

FERNDALE LABORATORIES, INC.
780 WEST EIGHT MILE ROAD • FERNDALE, MICHIGAN 48220
(248) 548-0900 • (800) 621-6003 TOLL FREE • FAX (248) 548-0708

Handwritten signature
JUN 23 1998

June 17, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**MINOR AMENDMENT and
BIOEQUIVALENCY AMENDMENT**

RE: *Amendment to unapproved abbreviated new drug application (ANDA), Hydrocortisone Acetate Cream USP, 2.5% (ANDA 40-259).*

Dear Sir:

Please refer to your facsimiles dated November 17, 1997 and March 2, 1998 (copies attached) regarding our abbreviated new drug application (ANDA) dated June 24, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocortisone Acetate Cream USP, 2.5%. Please refer, also, to telephone conversation records identified in your March 2, 1998 letter as volume 1.1.

Pursuant to 21 CFR 314.120(a)(1) Ferndale Laboratories, Inc. hereby amends ANDA 40-259 with new information—new 505(j) information to show sameness (sections II to VI) to the new reference listed drug given in the 18th edition of The Orange Book, draft labeling and revisions to submitted Chemistry, Manufacturing, and Control information..

Two copies of this amendment are provided, one for the archival copy of the application and one for the review copy of the application. In addition, pursuant to 21 CFR 314.96(b), a true and accurate field copy of this amendment has been submitted to the local FDA district office.

If you have any questions about this amendment, please telephone me at (248) 548-0900, ext. 568 or fax me at (248) 548-8427.

Sincerely,

Handwritten signature of Stephen J. Goldner

Stephen J. Goldner, Esq.
Vice President, Regulatory Affairs

Attachments

Handwritten note:
Madeline
6-23-98



CELEBRATING OUR 100TH YEAR

*Naanda J. Mitchell for
8/15/97*

June 24, 1997

Mr. Doug Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Re: Hydrocortisone Acetate Cream 2.5%

Dear Mr. Sporn:

Ferndale Laboratories, Inc., herewith submits an original abbreviated new drug application (ANDA) seeking approval to market Hydrocortisone Acetate Cream 2.5%. This ANDA is being filed under a Suitability Petition assigned a docket number of 90P-0049/CP and approved by the Agency on June 22, 1990 (See Section II for basis of ANDA and copy of an FDA approval letter).

Ferndale Laboratories' ANDA is organized per the Office of Generic Drugs' Policy and Procedure Guide 30-91 and the FDA letter to industry dated October 14, 1994. This ANDA consists of four (4) volumes. The table of contents in this application is based on that included in the procedure guide 30-91 and includes reference to twenty (20) sections. If any information is not applicable to this ANDA, then N/A is indicated in the table of contents. Page numbers are provided only for those items included.

Ferndale Laboratories is filing an archival copy (blue folders) of the ANDA that contains all required information and a technical review copy (red folders) which contains all information as the archival. Ferndale Laboratories is requesting a waiver from conducting a bioequivalence study, this information is included in Section VI of this application.

This ANDA contains two general narratives, one for the manufacturing procedure and the other for the packaging procedures for Hydrocortisone Acetate Cream 2.5%. The narratives are included in Section XII.

A stability summary report is included in Section XVI. The summary includes all tests conducted for each of the three package sizes intended for distribution with results included and statements regarding compliance to established shelf-life specifications. This data supports Ferndale Laboratories' request for a tentative expiration date of two years (24 months) for each of the three (3) package sizes.



RECEIVED

JUL 03 1997

GENERIC DRUGS

Mr. Doug Sporn, Director, Office of Generic Drugs
Re: ANDA for Hydrocortisone Acetate Cream 2.5%
June 24, 1997
Page 2

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 810-548-0900, ext 568 and 810-548-8427 (fax).

We hereby authorize AAC Consulting Group Inc. (Suite 850, 7475 Wisconsin Avenue, Bethesda, Maryland 40814, (301) 986-4440, Attention: Mr. Tony Celeste) to act as our representative in all matters pertaining to this application.

We certify that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to the Detroit District Office. This "field copy" was contained in a burgundy folder.

Sincerely,

FERNDAL LABORATORIES, INC.



Stephen J. Goldner, Esq.,
Vice President, Regulatory Affairs

FERNDALE LABORATORIES, INC.
780 WEST EIGHT MILE ROAD • FERNDALE, MICHIGAN 48220
(248) 548-0900 • (800) 621-6003 TOLL FREE • FAX (248) 548-0708

June 30, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

RE: **Facsimile Amendment — Response to fax of June 17, 1999**
ANDA 40-259
Hydrocortisone Acetate Cream USP, 2.5%
(Hydrocortisone Acetate 2.5% w/w)

Dear Sir:

Ferndale Laboratories, Inc. is submitting a minor amendment to its pending application in response to your comments in the correspondence dated June 17, 1999.

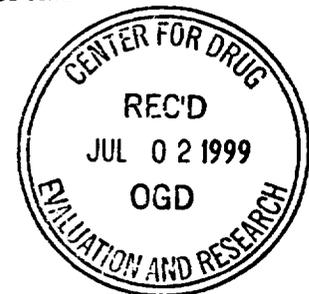
In regards to your comments of June 17, 1999 and our conference call of June 25, 1999:

1. Please conduct the blend uniformity on all the production batches and provide your specification including limits.

Response:

Blend uniformity will be conducted on production batches until sufficient data has been collected and presented to the Detroit District Office to allow the discontinuance to this testing. Blend uniformity testing will have the following specification:

The average of 6 assays will be between _____ % of label claim.
The _____ will be less than or equal to _____ %.



CELEBRATING OUR 100TH YEAR

2. Please revise your specification for the drug product to include specifications for viscosity and pH.

Response:

Ferndale Laboratories, Inc. has revised its specifications to include viscosity and pH as originally submitted. The specification for viscosity at 25°C (Initial 2 rpm) is _____ cP. The specification for pH (20% aqueous slurry at 25°C) is _____.

3. Please tighten your specifications for the drug product for hydrocortisone, cortisone acetate, any other individual impurity and total of any other individual impurities based on your data.

Response:

Ferndale Laboratories, Inc. has tightened its specifications for impurities testing. The following specifications were acceptable per our conference call of June 25, 1999:

Hydrocortisone does not exceed _____ %, Cortisone Acetate does not exceed _____ %, Any other individual impurity does not exceed _____ % and the sum of the total impurities observed does not exceed _____ %.

4. Please revise your stability specifications to include viscosity and pH.

Response:

Ferndale Laboratories, Inc. has revised its specifications to include viscosity and pH as originally submitted. The specification for viscosity at 25°C (Initial 2 rpm) is _____ cP. The specification for pH (20% aqueous slurry at 25°C) is _____.

5. Please tighten your stability specifications for hydrocortisone, cortisone acetate, any other individual impurity and total of any other individual impurities.

Response:

Ferndale Laboratories, Inc. has tightened its specifications for impurities testing. The following specifications were acceptable per our conference call of June 25, 1999:

Hydrocortisone does not exceed _____ %, Cortisone Acetate does not exceed _____ %, Any other individual impurity does not exceed _____ % and the sum of the total impurities observed does not exceed _____ %.

6. Please provide quantitative results for other impurity tests (individual and total) at 24 months.

Response:

Copies of the revised stability reports showing quantitative results for the above are provided for your review.

The review copy for the application was faxed to Mr. Joseph Buccine. In addition, pursuant to 21 CFR §314.70(a), a true and accurate field copy has been submitted to the local FDA district office.

If you have any questions, please feel free to telephone me at 248-548-0900 ext. 541 or fax me at 248-548-8427.

Sincerely,

A handwritten signature in cursive script, appearing to read "Deborah L. Therese".

Deborah L. Therese
Associate Manager, Regulatory Affairs

FERNDALE LABORATORIES, INC.
780 WEST EIGHT MILE ROAD • FERNDALE, MICHIGAN 48220
(248) 548-0900 • (800) 621-6003 TOLL FREE • FAX (248) 548-0708

April 27, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AM

RE: **Minor Amendment — Response to Letter of September 22, 1998**
ANDA 40-259, Hydrocortisone Acetate Cream USP, 2.5%
(Hydrocortisone Acetate 2.5% w/w)

Dear Sir:

Ferndale Laboratories, Inc. is submitting a minor amendment to its pending application in response to your comments in the correspondence dated September 22, 1998. Our formal response has been delayed due to on-going discussions with the Agency concerning the amount of Potassium Sorbate in the formulation. This concern has now been resolved so that the formulation may remain as originally submitted. It is our belief that the resolution of the bioequivalency comment reduces the level of the deficiencies to minor from major as indicated in the original correspondence.

In regards to your comments of September 22, 1998:

1. Please include the minimum fill test in the certificate of analysis according to USP.

Response:

Minimum Fill testing is part of the specifications for both the 1 ounce and 2 ounce packaging sizes. Minimum Fill testing is not performed on the Professional Sample. Per USP, Minimum Fill is performed on containers with a **labeled** content of not more than 150 g.. The Professional Sample package is not labeled with the contents of the container in compliance with the CFR provision that Professional Samples under 8 grams need not have the weight of the contents declared.

The results of the Minimum Fill testing can be found in the certificates of analysis (completed worksheets) submitted June 24, 1997 for the 1ounce package size (Volume II, pp. 275 - 279) and for the 2 ounce package size (Volume II, pp. 280 - 284) on pages 278 and 283, respectively. For your convenience, the Certificates of Analysis have been included in this amendment.



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APR 26 1999

GENERIC DRUGS

2. Please tighten the limits for the impurities and related substances for the release of the finished drug product.

Response:

Ferndale Laboratories, Inc. has tightened the limits for the impurities and release specifications for the release of the finished drug product to:

- Hydrocortisone is not more than %
- Cortisone Acetate is not more than %
- Other Individual Impurities are not more than % for any other individual impurity and not more than % for the other individual total impurities.

3. Please tighten your impurities limits and specifications for the stability and provide all available room temperature stability data.

Response:

Ferndale Laboratories, Inc. has tightened the limits for the impurities and stability specifications of the finished drug product to:

- Hydrocortisone is not more than %
- Cortisone Acetate is not more than %
- Other Individual Impurities are not more than % for any other individual impurity and not more than % for the other individual total impurities.

4. DMF is deficient. The DMF holder has been notified.

Response:

It is Ferndale Laboratories, Inc. understanding the all deficiencies in DMF have been addressed and is now acceptable to the Agency.

5. Please provide limits and specifications for individual impurities for the drug substance.

Response:

The drug substance is manufactured by . Their plan of action to comply with the "Other Impurities" requirement was to submit a chromatographic impurity assay capable of detecting and quantitating the impurities in their Hydrocortisone Acetate which may be present at % or greater. monitors potential impurities using the method submitted to the USP to fulfill their "Other Impurities" commitment for Hydrocortisone Acetate USP. They also proposed impurity limits of NMT % total and NMT % for individual impurities. The proposed method to the Hydrocortisone Acetate USP monograph can be found in Pharmacopeial Forum, Volume

Ferndale Laboratories, Inc. is submitting a copy of the Certificate of Analysis from the manufacturer for a recently received lot of Hydrocortisone Acetate USP listing and quantitating the "Other Impurities."

6. Please add blend uniformity testing as an in-process control.

Response:

Blend uniformity is used as process validation tool. Blend uniformity testing will be performed on the first three lots produced with the intent to market. Ferndale Laboratories, Inc. also commits to performing testing as part of process validation studies when deemed appropriate.

7. Your bioequivalence waiver request has been denied. Please respond to the FAX dated July 21, 1998 from the Division of Bioequivalence.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified.

Concentration of potassium sorbate in the test product is greater than its concentration previously approved for topical dermatologic formulations.

Due to this deficiencies in the composition of the test product does not support a waiver of in vivo bioequivalence study requirements. You should provide evidence that the presence of potassium sorbate (%) does not compromise the safety and efficacy of the test product, in relation to the reference product.

Response:

On March 31, 1999, the Division of Bioequivalence accepted the waiver request submitted for this product. This acceptance was based upon on-going telephone and FAX exchanges of information between the Agency and Ferndale Laboratories, Inc.

8. Your labeling is deficient. Please respond to the FAX dated July 1, 1998 from the Labeling Review Branch.

1. CONTAINER (Professional Sample, 28.4 g, 57 g)

Revise to express the active ingredient in the "Each gram contains" statement to read, ...25 mg (2.5% w/w)...

2. CARTON (Professional Sample, 28.4 g, 57 g)

See CONTAINER comment.

3. INSERT

a. See CONTAINER comment.

b. CLINICAL PHARMACOLOGY (Pharmokinetics)

Revise the first sentence of the third paragraph to read, ...pathways similar to systemically...

Please revise your labels and labeling, as instructed above, and submit in final print.

Response:

Ferndale Laboratories, Inc. has revised its labeling and is submitting computer generated labeling for the insert, tubes, and cartons. These graphics for the tubes and cartons are the actual size and color of the labeling proposed for the marketed product. To aid in the review process, a photocopy of the labeling is also being provided.

Ferndale Laboratories, Inc. has revised its product specifications to delete viscosity and pH testing. These test were originally performed for information only. Specifications were submitted earlier in the application. Ferndale has evaluated the results of the 24 month CRT stability studies for this product. Ferndale has concluded that while the product will meet the specifications that were proposed for viscosity and pH, the test results do not provide meaningful information concerning the safety, efficacy, and purity of the product.

Two copies of this report are provided, one for the archival copy of the application and one for the review copy of the application. In addition, pursuant to 21 CFR §314.70(a), a true and accurate field copy has been submitted to the local FDA district office.

If you have any questions, please feel free to telephone me at 248-548-0900 ext. 541 or fax me at 248-548-8427.

Sincerely,



Deborah L. Therese
Associate Manager, Regulatory Affairs

FERNDALE LABORATORIES, INC.

780 WEST EIGHT MILE ROAD • FERNDAL E. MICHIGAN 48220
(248) 548-0900 • (800) 621-6003 TOLL FREE • FAX (248) 548-0708

July 28, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: **Facsimile Amendment — Response to call of July 28, 1999**
ANDA 40-259
Hydrocortisone Acetate Cream USP, 2.5%
(Hydrocortisone Acetate 2.5% w/w)

Dear Sir:

Ferndale Laboratories, Inc. is submitting a minor amendment to its pending application in response to your comments to your communication of July 28, 1999.

In regards to your comments of July 28, 1999, we have revised our Post-Approval Stability Commitment to include the stipulation that an extension of the expiration dating will be based on three (3) post-approval production batches.

The review copy for the application was faxed to Mr. Joseph Buccine. In addition, pursuant to 21 CFR §314.70(a), a true and accurate field copy has been submitted to the local FDA district office.

If you have any questions, please feel free to telephone me at 248-548-0900 ext. 541 or fax me at 248-548-8427.

Sincerely,



Deborah L. Theres
Associate Manager, Regulatory Affairs



CELEBRATING OUR 100TH YEAR