CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-200

Name: Griseofulvin Oral Suspension USP, 125 mg/5 mL

Sponsor: Stiefel Laboratories, Inc.

Approval Date: March 2, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

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Statistical Review	
Microbiology Review	
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Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

APPROVAL LETTER

ANDA 65-200

MAR 2 2005

Stiefel Laboratories, Inc.
Attention: Mary Jane Carr
Route 145
Oak Hill, NY 12460

Dear Madam:

This is in reference to your abbreviated new drug application dated November 24, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Griseofulvin Oral Suspension USP, 125 mg/5 mL. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated July 1, September 3, September 8, September 23, October 8, October 22, October 25, and December 2, 2004.

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 Division of Bioequivalence has determined your Griseofulvin Oral Suspension USP, 125 mg/5 mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Grifuvin V®, 125 mg/5 mL, of Johnson & Johnson).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted in 1000 mL of water containing 5.4 mg of SLS per mL using USP apparatus II (Paddle) at 25 rpm. The test product should meet the following specification:

> Not less than —% (Q) of the labeled amount of griseofulvin in the dosage form is dissolved in 30 minutes.

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

Under Section 506A of the Act, 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/2/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-200
Division File
Field Copy
HFD-610/R. West 3/2/05
HFD-610
HFD-610/Orange Book Staff

HFD-640/M.Bennett/ 1/18/2005
HFD-643/S.Furness/ 11.21.05
HFD-617/R.Nguyen/ 11/21/05
HFD-613/M.Shin/ MS. 1-18-05
HFD-613/L.Golson 1/11/05

\\CDSNAS\OGDS11\FIRMSNZ/Stiefel/Ltrs&rev/65200.apltr.doc

F/T by: RTN/01/04/05

APPROVAL

cmc satisfactory
2/7/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

LABELING

Description

Griseofulvin is an antibiotic derived from a species of *Penicillium*. Each 5 mL of Griseofulvin Oral Suspension, USP contains 125 mg of griseofulvin microsize and also contains alcohol 0.2%, docusate sodium, FD&C Red No. 40, FD&C Yellow No. 6, orange cream flavors, magnesium aluminum silicate, menthol, methylparaben, propylene glycol, propylparaben, saccharin sodium, simethicone emulsion, sodium alginate, sucrose, and purified water.

Clinical Pharmacology

Griseofulvin Oral Suspension, USP acts systemically to inhibit the growth of *Trichophyton, Microsporum,* and *Epidermophyton* genera of fungi. Fungistatic amounts are deposited in the keratin, which is gradually exfoliated and replaced by noninfected tissue.

Griseofulvin absorption from the gastrointestinal tract varies considerably among individuals, mainly because of insolubility of the drug in aqueous media of the upper G.I. tract. The peak serum level found in fasting adults given 0.5 gm occurs at about four hours and ranges between 0.5 and 2.0 mcg/mL.

It should be noted that some individuals are consistently "poor absorbers" and tend to attain lower blood levels at all times. This may explain unsatisfactory therapeutic results in some patients. Better blood levels can probably be attained in most patients if administered after a meal with a high fat content.

Indications and Usage

Major indications for Griseofulvin Oral Suspension, USP are:

- Tinea capitis (ringworm of the scalp)
- Tinea corporis (ringworm of the body)
- Tinea pedis (athlete's foot)
- Tinea unguium (onychomycosis; ringworm of the nails)
- Tinea cruris (ringworm of the thigh)
- Tinea barbae (barber's itch)

Griseofulvin Oral Suspension, USP inhibits the growth of those genera of fungi that commonly cause ringworm infections of the hair, skin, and nails, such as:

- *Trichophyton rubrum*
- *Trichophyton tonsurans*
- *Trichophyton mentagrophytes*
- *Trichophyton interdigitalis*
- *Trichophyton verrucosum*
- *Trichophyton sulphureum*
- *Trichophyton schoenleini*
- *Microsporum audouini*
- *Microsporum canis*
- *Microsporum gypseum*
- *Epidermophyton floccosum*
- *Trichophyton megnini*
- *Trichophyton gallinae*
- *Trichophyton crateriform*

Note: Prior to therapy, the type of fungi responsible for the infection should be identified. The use of the drug is not justified in minor or trivial infections which will respond to topical anti-fungal agents alone.

It is *not* effective in:

- Bacterial infections
- Candidiasis (Moniliasis)
- Histoplasmosis
- Actinomycosis
- Sporotrichosis
- Chromoblastomycosis
- Coccidioidomycosis
- North American Blastomycosis
- Cryptococcosis (Torulosis)
- Tinea versicolor
- Nocardiosis

Contraindications

This drug is contraindicated in patients with porphyria, hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Two cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy. Griseofulvin should not be prescribed to pregnant patients.

Warnings

Prophylactic Usage: Safety and efficacy of prophylactic use of this drug has not been established.

Chronic feeding of griseofulvin, at levels ranging from 0.5-2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes result in an enhanced effect. Lower oral dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Although studies in other animal species have not yielded evidence of tumorigenicity, these studies were not of adequate design to form a basis for conclusions in this regard.

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice,but this has not been seen in other species. Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and cocarcinogenicity with methylcholanthrene in cutaneous tumor induction in laboratory animals.

Reports of animal studies in the Soviet literature state that a griseofulvin preparation was found to be embryotoxic and teratogenic on oral administration to pregnant Wistar rats. Rat reproduction studies done in the United States and Great Britain have been inconclusive in this regard, and additional animal reproduction studies are underway. Pups with abnormalities have been reported in the litters of a few bitches treated with griseofulvin. Because the potential for adverse effects on the human fetus cannot be ruled out, additional contraceptive precautions should be taken during treatment with griseofulvin and for a month after termination of treatment. Griseofulvin Oral Suspension, USP should not be prescribed to women intending to become pregnant within one month following cessation of therapy.

Suppression of spermatogenesis has been reported to occur in rats but investigation in man failed to confirm this.

Precautions

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hemopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense natural or artificial sunlight. Should a photosensitivity reaction occur, lupus erythematosus may be aggravated.

Drug Interactions: Patients on warfarin-type anti-coagulant therapy may require dosage adjustment of the anticoagulant during and after griseofulvin therapy. Concomitant use of barbiturates usually depresses griseofulvin activity and may necessitate raising the dosage.

The concomitant administration of griseofulvin has been reported to reduce the efficacy of oral contraceptives and to increase the incidence of breakthrough bleeding.

Adverse Reactions

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria and rarely, angioneurotic edema and may necessitate withdrawal of therapy and appropriate countermeasures. Paresthesias of the hands and feet have been reported rarely after extended therapy. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion and impairment of performance of routine activities.

Proteinuria and leukopenia have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

When rare, serious reactions occur with griseofulvin, they are usually associated with high dosages, long periods of therapy, or both.

Dosage and Administration

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4 to 6 weeks; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; tinea unguium - depending on rate of growth - fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis since in some forms of athlete's foot, yeasts and bacteria may be involved. Griseofulvin will not eradicate the bacterial or monilial infection.

Adults: A daily dose of 500 mg will give a satisfactory response in most patients with tinea corporis, tinea cruris, and tinea capitis.

For those fungus infections more difficult to eradicate such as tinea pedis and tinea unguium, a daily dose of 1 gram is recommended.

Children: Approximately 5 mg per pound of bodyweight per day is an effective dose for most children. On this basis the following dosage schedule for children is suggested:

Children weighing 30 to 50 pounds - 125 mg to 250 mg daily.
Children weighing over 50 pounds - 250 mg to 500 mg daily.

How Supplied

Griseofulvin Oral Suspension, USP (microsize) 125 mg per 5 mL in bottles of 4 fl oz (120 mL) (NDC 0145-2568-04).

Dispense Griseofulvin Oral Suspension, USP in a tight, light-resistant container as defined in the USP.

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]

STIEFEL®

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

Stock No. 2568-4
87889 Rev. 1104

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	65-200
Date of Submission:	November 24, 2003 (Original draft labeling)
Applicant's Name:	Stiefel Laboratories, Inc.
Established Name:	Griseofulvin Oral Suspension USP, 125 mg/5 mL
Proposed Proprietary Name:	None

Labeling Deficiencies:

CONTAINER:

- Revise the storage temperature statement to as follows:

  "Store at 20°-25° (68° – 77°F) [see USP Controlled Room Temperature]

PROFESSIONAL PACKAGE INSERT

- Please specify the flavors contained in your formulation.
- [we are requesting that you revise your labeling to be the same as the attached package insert.

Please revise your labels and labeling, as instructed above and submit in final. Please note that the electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website:

http://www.fda.gov/cder/guidance/5004fnl.htm.

Although the guidance specifies labeling to be submitted in PDF format, we request that labeling also be submitted in MS Word format to assist our review."

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Copy of Reference Listed Drug labeling removed.

FOR THE RECORD:

1. MODEL LABELING

[ ]

2. USP ITEM

Yes

3. PROPRIETARY NAME

N/A

4. PATENTS/EXCLUSIVITIES

There are no unexpired patents or exclusivities.

[Vol. 1.1 page 12]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

[Vol. 1.2 page 1778]

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Stiefel Research Institute, Inc.
Route 145,
Oak Hill, New York 12460

[Vol. 1.2 page 2003]

7. CONTAINER/CLOSURE

Container	Amber type III glass bottle	
Closure	[redacted] child-resistant, white	
	Product contact components of [redacted], CRC: Screw Cap: [redacted] Liner: [redacted]	Non-product contact component of the [redacted] CRC: Outer Cap: [redacted] Colorant – white [redacted] Tamper-evident ring: [redacted] Colorant [redacted]

[Vol. 1.3 page 2332]

8. PACKAGING CONFIGURATIONS

RLD: 4 fl oz (120 mL) Bottle
ANDA: 4 fl oz (120 mL) Bottle

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at room temperature
ANDA: Store at room temperature

I recommended the sponsor to revise as follows:

"Store at 20°-25° (68° – 77°F) [see USP Controlled Room Temperature]; [redacted]

Date of Review: **Dates of Submission:**

Primary Reviewer: [signature] 7-28-04
Melaine Shin Date:

Team Leader: [signature] 7/28/04
Lillie Golson Date:

cc: ANDA: DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
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REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	65-200
Date of Submission:	September 8, 2004 (\\CDSESUBOGD1\N65200\N_000\2004-09-08) September 23, 2004 (No E-submission) October 8, 2004 (\\CDSESUBOGD1\N65200\N_000\2004-10-08) October 25, 2004 ((\\CDSESUBOGD1\N65200\N_000\2004-10-25)
Applicant's Name:	Stiefel Laboratories, Inc.
Established Name:	Griseofulvin Oral Suspension USP, 125 mg/5 mL
Proposed Proprietary Name:	None

Labeling Deficiencies:

CONTAINER:

Satisfactory as of October 8, 2004 submission.

PROFESSIONAL PACKAGE INSERT

We note that you have submitted the package insert in final print on October 25, 2004 based on the previously faxed deficiency letter, however, due to some complicated issues with the reference listed drug for your product, we are asking you to refer back to your original submission of the package insert dated November 24, 2003 when you make the following revisions.

1. DESCRIPTION

   - Please specify the flavors contained in your formulation.

2. WARNINGS

   - In the fourth paragraph, replace ".....Great Britain [redacted] " with the following:

     "...Great Britain have been inconclusive in this regard, and additional animal reproduction studies are underway."

   - In the fifth paragraph, delete the following informaiton:

[ ]

3. ADVERSE REACTIONS

- Delete "[redacted]," from the first sentence.

4. HOW SUPPLIED

- Add the storage temperature recommendation as follows:

"Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]

Please revise your labeling, as instructed above and submit in final. Please note that the electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the guidance for industry regarding electronic submissions (Providing Regulatory Submissions in Electronic Format - ANDAs, issued 6/2002) available at the following website:

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Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FOR THE RECORD:

The text in bold has been added to the NA review #1.

1. MODEL LABELING

[redacted] **I am advised by the Division to use the currently approved labeling for ANDA 62-483. The most currently approved labeling for ANDA 62-483 comes from S-011/approved on 4/13/1993.**
I can not use [redacted] **Once this issue is resolved, the firm should revise their labeling.**

Therefore, although the firm has submitted a FPL that is satisfactory based on the previous deficiency letter, it is necessary to issue this deficiency letter #2 to the firm to revert back to their original labeling without the current updates we were hoping to incorporate into the labeling.

2. USP ITEM

Yes

3. PROPRIETARY NAME

N/A

4. PATENTS/EXCLUSIVITIES

There are no unexpired patents or exclusivities.

[Vol. 1.1 page 12]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement.

[Vol. 1.2 page 1778]

6. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Stiefel Research Institute, Inc.
Route 145,
Oak Hill, New York 12460

[Vol. 1.2 page 2003]

7. CONTAINER/CLOSURE

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Closure	[redacted] child-resistant, white	
	Product contact components of [redacted] CRC: Screw Cap: [redacted] Liner: [redacted]	Non-product contact component of the [redacted] CRC: Outer Cap: [redacted] Colorant – white [redacted] Tamper-evident ring: [redacted] Colorant [redacted]

[Vol. 1.3 page 2332]

8. PACKAGING CONFIGURATIONS

RLD: 4 fl oz (120 mL) Bottle
ANDA: 4 fl oz (120 mL) Bottle

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at room temperature

ANDA: Store at 20°-25° (68° – 77°F) [see USP Controlled Room Temperature];

Date of Review: **November 10, 2004** **Dates of Submission:** September 8, 2004
September 23, 2004
October 8, 2004
October 25, 2004

Primary Reviewer: _____ 11-15-04
Melaine Shin Date:

Team Leader: _____ 11/15/04
Lillie Golson Date:

cc: ANDA: DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
v:\FIRMSNZ\ Stiefell\ltrs&rev\65200NA2.Labeling.doc

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	65-200
Date of Submission:	November 24, 2004
EDR Path:	\\CDSESUBOGD1\N65200\N_000\2004-11-24
Applicant's Name:	Stiefel Laboratories, Inc.
Established Name:	Griseofulvin Oral Suspension USP, 125 mg/5 mL
Proposed Proprietary Name:	None

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? E-submission

CONTAINER LABELS/PROFESSIONAL PACKAGE ONSERT – 125 mg/5mL Bottle

Satisfactory in final print as submitted November 24, 2004

\\CDSESUBOGD1\N65200\N_000\2004-11-24\PI. Onsert.pdf

REVISIONS NEEDED POST-APPROVAL: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Grifulvin V Oral suspension

NDA Number: 62-483

NDA Drug Name: Grifulvin V

NDA Firm:. Johnson & Johnson

Date of Approval of NDA Insert and supplement #: S-011 Approvable on April 13, 1993.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

FOR THE RECORD:

Note to the Microbiologist: Please confirm if firm's proposal for

Old	Proposed
•	
•	
•	

I got the confirmation from the microbiologist, Connie Mahon from HFD-520, that the above terms

are the [redacted] See e-mail in file. The firm also submitted supporting documents on September 23, 2004.

1. GENERAL

   The generic labeling contained [redacted] and I requested the supporting documentation to justify the changes. The firm submitted the documents on September 23, 2004 and it appears to be adequate. However, I asked the microbiologist to concur with the firm's proposal and it is confirmed.

2. MODEL LABELING

   [redacted] and I'm advised by the Division to use the currently approved labeling for ANDA 62-483. The most currently approved labeling for ANDA 62-483 comes from S-011/approved on 4/13/1993.

   I can not use [redacted] Once this issue is resolved, the firm should revise their labeling.

   Therefore, although the firm has submitted a FPL that is satisfactory based on the previous deficiency letter, it was necessary to issue another deficiency letter to the firm to revert back to their original labeling without the current updates we were hoping to incorporate into the labeling.

3. USP ITEM

   Yes

4. PROPRIETARY NAME

   N/A

5. PATENTS/EXCLUSIVITIES

   There are no unexpired patents or exclusivities.

   [Vol. 1.1 page 12]

6. INACTIVE INGREDIENTS

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   [Vol. 1.2 page 1778]

7. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Stiefel Research Institute, Inc.
   Route 145,

Oak Hill, New York 12460

[Vol. 1.2 page 2003]

8. CONTAINER/CLOSURE

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[Vol. 1.3 page 2332]

9. PACKAGING CONFIGURATIONS

RLD: 4 fl oz (120 mL) Bottle
ANDA: 4 fl oz (120 mL) Bottle

10. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at room temperature
ANDA: "Store at 20°-25° (68° – 77°F) [see USP Controlled Room Temperature]

Date of Review: December 9, 2004 **Date of Submission: November 24, 2004**

Primary Reviewer: [signature] 12-17-04
Melaine Shin Date:

Team Leader: [signature] 12/17/04
Lillie Golson Date:

cc: ANDA 65-200
DUP/DIVISION FILE
HFD-613/MShin/LGolson (no cc)
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

CHEMISTRY REVIEWS

ANDA 65-200

Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL

Stiefel Laboratories, Inc.

Marco A. Bennett, Ph.D.
Division of Chemistry III, Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **65-200**

2. REVIEW #1

3. REVIEW DATE: 29-MAR-2004

4. REVIEWER: Marco A. Bennett

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	24-NOV-2003
Acceptable for Filing Notice	01-JAN-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	24-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	**Stiefel Laboratories, Inc**
Address:	Route 145 Oak Hill, NY 12460 Corporate Headquarters: 255 Alhambra Circle, Suite 1000 Coral Gables, FL 33134
Representative:	Mary Jane Carr
Telephone:	Phone: (518) 239-6901 Fax: (518) 239-8402

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name: Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL

9.

LEGAL BASIS FOR SUBMISSION:

The application is based on Grifulvin V® (Griseofulvin Oral Suspension) microsize suspension 125 mg/5 mL manufactured by J AND J (NDA # 62-483). The firm states that there are no unexpired patents or exclusivity periods for the reference listed drug product (pp. 12-13).

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 125 mg/5 mL (2.5%w/v)

13. ROUTE OF ADMINISTRATION: Oral

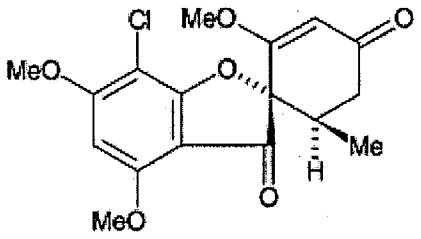
14. Rx/OTC DISPENSED: ✓ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

✓ Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name: Spiro[benzofuran-[2](3 H),1'-2cyclohexene]-3,4'-dione, 7-chloro-2',4,6-trimethoxy-6'-methyl-, (1'S-trans)-.7-Chloro-2',4,6-trimethoxy-6'b-methylspiro[benzofuran-2(3 H), 1'-[2]cyclohexene]-3,4'-dione

Molecular Formula: $C_{17}H_{17}ClO_6$

Molecular Weight: 352.77

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate	02-FEB-2004	
	III			3,4	Adequate	21-OCT-2002	
	III			3,4	Adequate	29-APR-2002	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	-	-
EES	Pending	-	-
Methods Validation	N/A	-	-
Labeling	Pending	-	-
Bioequivalence	Pending	-	-
EA	N/A	-	-
Radiopharmaceuticals	N/A	-	-

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ✓ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 65-200

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Recommended for Approval (MINOR)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Grifulvin V® (Griseofulvin Oral Suspension) microsize suspension 125 mg/5 mL manufactured by J AND J (NDA # 62-483).

Drug Product

Stiefel states that the manufacturing of Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL involves the [redacted]

The drug product is intended for oral administration. Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL contains Purified Water, USP, FD & C Yellow # 6, FD & C Red # 40, Sucrose, NF, Saccharin Sodium, USP, Propylene Glycol, USP, Propylparaben, NF, Sodium Alginate, NF, Magnesium Aluminum Silicate, NF, Methylparaben, NF, Docusate Sodium, USP, Simethicone Emulsion, USP, Alcohol, USP, Menthol, USP, and Orange Cream Flavor [redacted] as inactive ingredients. The formulation did not include the use of any novel inactive ingredients.

Stiefel states that the finished drug product is packaged in 4 fl. oz. (120 mL) amber glass bottles and capped with a plastic child resistant closure with a

tamper-evident ring. The proposed tentative expiration date of ——— is supported by 6 months of accelerated stability data and 6 months of CRT stability data.

Drug Substance
The drug substance is Griseofulvin, USP. It has molecular formula $C_{17}H_{17}ClO_6$ and molecular weight of 352.77 grams per mole. Griseofulvin, USP is manufactured ———————.

B. Description of How the Drug Product is Intended to be Used
N/A

C. Basis for Approvability or Not-Approval Recommendation
The application is not approvable for minor CMC issues.

III. Administrative

cc: ANDA 65-200
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/MBennett/3/29/2004 4/5/2004

HFD-643/RAdams/4/5/04 M. Sardaman for 4/6/04
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F/T by: mda/4/6/04

TYPE OF LETTER: NOT APPROVABLE - MINOR

Redacted 19 page(s)

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information from

CHEMISTRY REVIEW #1

5. The Drug Substance Drug Master File (DMF # ———) has been reviewed and found inadequate. The DMF holder has been informed of the deficiencies. Please be aware that the application cannot be approved until deficiencies regarding this DMF have been addressed satisfactorily by the holder.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

Chemistry Assessment Section

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 65-200
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/MBennett/3/29/2004 4/5/2004

HFD-643/RAdams/4/5/04 M Scott Andrews for 4/6/04

HFD-617/MAnderson/4/6/04 Mark Anderson 4/7/04

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F/T by: mda/4/6/04

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 65-200

Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL

Stiefel Laboratories, Inc.

Marco A. Bennett, Ph.D.

Division of Chemistry III, Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: **65-200**

2. REVIEW #2

3. REVIEW DATE: 24-AUG-2004

4. REVIEWER: Marco A. Bennett

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	24-NOV-2003
Acceptable for Filing Notice	01-JAN-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment Submission	01-JUL-2004
Telephone Amendment	03-SEP-2004
Telephone Amendment	02-DEC-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	**Stiefel Laboratories, Inc**
Address:	Route 145 Oak Hill, NY 12460 Corporate Headquarters: 255 Alhambra Circle, Suite 1000 Coral Gables, FL 33134
Representative:	Mary Jane Carr
Telephone:	Phone: (518) 239-6901 Fax: (518) 239-8402

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL

9. LEGAL BASIS FOR SUBMISSION:
The application is based on Grifulvin V® (Griseofulvin Oral Suspension) microsize suspension 125 mg/5 mL manufactured by Johnson & Johnson (NDA # 62-483). The firm states that there are no unexpired patents or exclusivity periods for the reference listed drug product (pp. 12-13).

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Oral Suspension

12. STRENGTH/POTENCY: 125 mg/5 mL (2.5%w/v)

13. ROUTE OF ADMINISTRATION: Oral

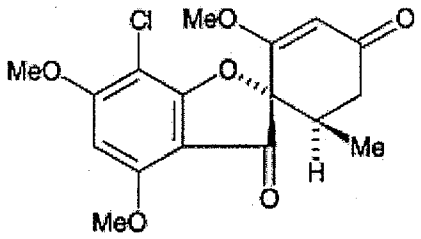
14. Rx/OTC DISPENSED: ✓ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___✓___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name: Spiro[benzofuran-[2](3 H),1'-2cyclohexene]-3,4'-dione, 7-chloro-2',4,6-trimethoxy-6'-methyl-, (1'S-trans)-.7-Chloro-2',4,6-trimethoxy-6'b-methylspiro[benzofuran-2(3 H), 1'-[2]cyclohexene]-3,4'-dione
Molecular Formula: $C_{17}H_{17}ClO_6$
Molecular Weight: 352.77

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	16-AUG-2004	-
	III			4	-	-	-
	III			4	-	-	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A	-	-
EES	Acceptable	01/06/05	S.Adams
Methods Validation	N/A	-	-
Labeling	Acceptable	12/17/04	M.Shin
Bioequivalence	Acceptable	12/21/04	N.Tran
EA	N/A	-	-
Radiopharmaceuticals	N/A	-	-

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ✓ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-200

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommended for Approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Grifulvin V® (Griseofulvin Oral Suspension) microsized suspension 125 mg/5 mL manufactured by Johnson & Johnson (NDA # 62-483).

Drug Product

Stiefel states that the manufacturing of Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL involves the

[redacted]

The drug product is intended for oral administration. Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL contains Purified Water, USP, FD & C Yellow # 6, FD & C Red # 40, Sucrose, NF, Saccharin Sodium, USP, Propylene Glycol, USP, Propylparaben, NF, Sodium Alginate, NF, Magnesium Aluminum Silicate, NF, Methylparaben, NF, Docusate Sodium, USP, Simethicone Emulsion, USP, Alcohol, USP, Menthol, USP, and Orange Cream Flavor [redacted] as inactive ingredients. The formulation did not include the use of any novel inactive ingredients.

Stiefel states that the finished drug product is packaged in 4 fl. oz. (120 mL) amber glass bottles and capped with a plastic child resistant closure with a

tamper-evident ring. The proposed tentative expiration date of 18 months is supported by 6 months of accelerated stability data and 6 months of CRT stability data.

Drug Substance
The drug substance is Griseofulvin, USP. It has molecular formula $C_{17}H_{17}ClO_6$ and molecular weight of 352.77 grams per mole. Griseofulvin, USP is manufactured [redacted]

B. Description of How the Drug Product is Intended to be Used
N/A

C. Basis for Approvability or Not-Approval Recommendation
Approval is recommended.

III. Administrative

cc: ANDA 65-200
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/MBennett/8/24/2004; 9/1/2004; 1/7/2005 1/18/2005

HFD-643/SFurness/8/30/04; 1/7/05 1/21/05

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F/T by:

TYPE OF LETTER: APPROVABLE

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information from

CHEMISTRY REVIEW #2

CHEMISTRY REVIEW

Chemistry Assessment Section

cc: ANDA 65-200
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/MBennett/9/1/2004; 1/7/2005 1/18/2005

HFD-643/SFurness/9/13/04; 1/7/05 1/21/05

HFD-617/RNguyen/ 1/21/05

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F/T by: RTN/01/07/05

TYPE OF LETTER: APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-200
Drug Product Name	Griseofulvin Oral Suspension
Strength	125 mg/5 ml
Applicant Name	Stiefel Laboratories
Address	Coral Gables, FL
Submission Date(s)	November 24, 2003
Amendment Date(s)	N/A
Reviewer	Nhan L. Tran
First Generic	Yes
File Location	V:\firmsnz\stiefel\ltrs&rev\65200N1103.DOC

I. Executive Summary

This application references Grifulvin V® Oral Suspension and includes one fasting and one fed bioequivalence (BE) study. The fasting study is a single-dose two-way crossover study using 52 male and female normal healthy volunteers given a dose of 250 mg (10 ml). The results (point estimate, 90% CI) of the fasting BE study are LAUCt of 109.2, 102.3%-116.4%; LAUCi of 108.9, 102.2-116.1%; and LCmax of 111.6, 105.6-117.9%. The fed BE study is a single-dose two-way crossover study using 18 male and female normal healthy volunteers given a dose of 250 mg (10 ml). The results of the fed BE study are LAUCt of 104.3, 99.2-109.7%; LAUCi of 104.3, 99.2-109.6%; and LCmax of 105.9, 97.1-115.4%. These studies are incomplete due to analytical method deficiencies. The dissolution (1000 mL water with 5.4mg/ml SLS, paddle at — rpm) testing is incomplete as the paddle speed is too fast to be discriminating. Application is deficient.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Griseofulvin Oral Suspension, USP (microsize), 125 mg/5 ml
Reference Product	Grifulvin V® microsize Suspension 125 mg/5 ml
RLD Manufacturer	Ortho Dermatological
NDA No.	62-483
RLD Approval Date	January 26, 1984
Indication	For the treatment of ring-worm infections of the hair, skin and nails.

B. PK/PD Information (from the PDR)

Bioavailability	Variable
Food Effect	Increase the bioavailability
Tmax	About 4 hrs
Metabolism	Griseofulvin is oxidatively demethylated and conjugated with glucuronic acid, principally in the liver. The major metabolite, 6-desmethylgriseofulvin, is inactive
Excretion	Renally
Half-life	9-24 hours
Relevant OGD Or DBE History	No ANDA has been submitted. Two protocols: One submitted by Stiefel on 7/22/1997 and the other one by ——— ——— submitted on 04/01/2002. In those protocols, the DBE recommended two BE studies (fast and fed) for bioequivalence determination. There are two Control Documents and they are under review (CD 03-496 by ———and CD 03-929 by———)
Agency Guidanc	None
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent
Analyte name	Griseofulvin
Internal Standard	
Method description	LC/MS/MS
QC range	30 ng/ml to 1200 ng/ml
Standard curve range	10 ng/ml to 1600 ng/ml
Limit of quantitation	10 ng/ml
Average recovery of Drug (%)	N/A--On-line extraction
Average Recovery of Int. Std (%)	N/A--On-line extraction
QC Intraday precision range (% CV)	6.6 To 7.6
QC Intraday accuracy range (%nominal)	95 to 104
QC Interday precision range (% CV)	7.9 to 8.8
QC Interday accuracy range (% nominal)	103.3 to 107.8
Bench-top stability (hrs)	12.3
Stock stability (days)	579
Processed stability (hrs)	188
Freeze-thaw stability (cycles)	5
Long-term storage stability (days)	575
Dilution integrity	%CV=3-5.4, % nom=109-112 for x5 & x10
Specificity	Yes
SOPs submitted	N/A
Bioanalytical method is acceptable	No—See Deficiency Comments
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chromatograms	Serial

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	AA04793
Study Design	Randomized, single dose, 2-way crossover
No. of subjects enrolled	54
No. of subjects completing	52
No. of subjects analyzed	52
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 45 (-2) Female: 7
Test product	Griseofulvin Microsize Oral suspension
Reference product	Grifulvin V
Strength tested	125 mg/5 ml
Dose	250 mg (10 ml)

Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	Point Estimate	90% Confidence Interval
AUC_{0-t}	109.2	102.3 – 116.4
AUC_{∞}	108.9	102.2 – 116.1
C_{max}	111.6	105.6 – 117.9

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, **Table 6**								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual numb		% of total assays	
	T	R	T	R	T	R	T	R
No information submitted.								
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	AA05458
Study Design	Single dose, randomized, cross-over
No. of subjects enrolled	18 plus two (2) alternates
No. of subjects completing	19
No. of subjects analyzed	18 as specified in the protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 15 (-1 dropout) Female: 4
Test product	Griseofulvin Microsize Oral suspension
Reference product	Grifulvin V
Strength tested	125 mg/5 ml
Dose	250 mg (10 ml)

Summary of Statistical Analysis, Fed Bioequivalence Study		
Parameter	Point Estimate	90% Confidence Interval
AUC_{0-t}	104.3	99.2 – 109.7
AUC_{∞}	104.3	99.2 – 109.6
Cmax	105.9	97.1 – 115.4

Reanalysis of Study Samples, Fed Bioequivalence Study Additional information in Appendix, Table 17								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual numbe		% of total assays	
	T	R	T	R	T	R	T	R
No information was submitted								
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

F. Formulation

Location in appendix	**Section B**
Are inactive ingredients within IIG limits?	No
If No, list ingredients outside of limits	Orange cream Flavor ——— is not listed in the current IIG.
If a tablet, is the product scored?	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes—See Notes
If not acceptable, why?	N/A

Notes: Even the Orange Cream Flavor ——— is not listed in the current IIG, the reviewer has contacted Martin Sheimer, Chief Regulatory Support Branch to ask him if he was aware of this before accepting for filing. He

indicated that he was aware of it and has asked the firm to submit a breakdown of each inactive ingredient in the flavor, and he has reviewed the composition and it is found acceptable as each of the ingredient is listed either in GRAS List or FEMA List. The Orange Cream flavor is also found acceptable to review Chemist in CMC review. In addition the total concentration of the flavor in the formulation is within the limits —— specified by the FDA (per Memorandum by Nasser Mahmud, former Chief, Regulatory Support Branch on October 14, 1999).

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	Water containing 5.4 mg of SLS per ml
Volume (mL)	1000
USP Apparatus type	Paddle
Rotation (rpm)	—
Firm's proposed specifications	— %/30 min
FDA-recommended specifications	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Dissolution rate is too fast for f2 calculation
Is method acceptable?	No
If not then why?	Too fast to be discriminating as almost 90% of the labeled content is dissolved in 5 minutes.

F2 metric, lower strengths compared to highest strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A			

F2 metric, test compared to reference	
Strength	F2 metric
N/A	

H. Waiver Request(s)

None

I. Deficiency Comments

1. Please provide a table that identifies every missing sample in the BE studies (fasting and fed). Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis.

2. Please provide the Standard Operating Procedures (SOPs) of the analytical method, the SOP for chromatographic acceptance criteria and verification of chromatograms, and SOPs for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for

defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study. Otherwise, the Division of Bioequivalence will not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

3. The dissolution testing conducted by the firm is incomplete. The firm is requested to conduct dissolution testing using the paddle method at 25 RPM in 1000 ml of water containing 5.4 mg of SLS per ml. Suggested sampling times: 10, 20, 30 and 45 minutes and until at least [redacted] % of the labeled drug is dissolved.

4. The potency of the reference product used in the studies was not provided.

J. Recommendations

1. The *in vivo* bioequivalence studies conducted under fasting and non-fasting conditions by Stiefel on its griseofulvin suspension, 125mg/5 ml, lot # L0299, comparing it to the reference product Grifulvin V® 125mg/5 ml (Ortho), lot # 13C973, is incomplete to the Division of Bioequivalence due to Deficiencies 1-4.

2. The dissolution testing conducted by Stiefel on its griseofulvin suspension, 125 mg/5 ml is incomplete. The firm is requested to conduct the dissolution testing in 1000 mL of water containing 5.4 mg of SLS per ml, using apparatus II (paddle) at 25 rpm.

3. Hence, the application is incomplete.

9-29-04

Nhan L. Tran, Reviewer, Branch III, Date signed

9/29/2004

YC Huang, Team Leader, Branch III, Date signed

9/29/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	AA04793
Study Title	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability of Stiefel and Ortho Griseofulvin Microsize Oral Suspension in Healthy Adult Volunteers Following Administration of a 250 mg Dose under Fasting Conditions
Clinical Site	[redacted]
Principal Investigator	[redacted], MD
Study/Dosing Dates	June 12 – June 29, 2003
Analytical Site	[redacted]
Analytical Director	[redacted]
Analysis Dates	July 7 – July 11, 2003
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	30 days

Treatment ID	Test	Reference
Test or Reference	Test	Reference
Product Name	Griseofulvin Oral Suspension	Grifulvin V
Manufacturer	Stiefel Laboratories	Ortho Dermatological
Batch/Lot No.	L0299	13C973
Manufacture Date	March 2003	N/A
Expiration Date	February 28, 2005	March 2005
Strength	125 mg/5 ml	125 mg/5 ml
Dosage Form	Suspension	Suspension
Batch Size	[redacted]	N/A
Potency	103% - 106%	Not reported
Formulation	See Appendix Section B	N/A
Dose Administered	250 mg (10 ml)	250 mg (10 ml)
Route of Administration	Oral	

No. of Sequences	~~2~~
No. of Periods	~~2~~
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	**AB: 4,7,8,9,14,15,18,20,22,23,26,30,32,34,35,36,37,39,40,42,43,47,48,50,51,52,53** **BA:1,2,3,5,6,10,11,12,13,16,17,19,21,24,25,27,28,29,31,33,38,41,44,45,46,49,54**
Blood Sampling Times (hrs)	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60, & 72
Blood Volume Collected/Sample	5 ml
Blood Sample Processing/Storage	Stored at -20^0 C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hrs
Length of Confinement	36 hrs
Safety Monitoring	Yes

Comments on Study Design: Acceptable

b) Clinical Results

Table 1 Demographics of Study Subjects

Age (year)		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
Mean	33	Mean	71.8	<18	0%			Caucasian	83.3%
SD	8	SD	8.4	18-40	80%	Male	87%	Afr. Amer.	7.4%
Range	19-45	Range	49-91	41-64	20%	Female	13%	Hispanic	9.3%

Table 2 Dropout Information

Subject #	Reason	Period	Replaced?
21	After dosing in Period 1	2	No
46	Did not return for Period 2	2	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Headache	2 (Subj. #50 &52)	1 (Subj. #21)
Nausea		1 (Subj. #21)
Dizziness	1 (Subj. #35)	1 (Subj. #21)
Total:	3	3

No serious adverse occurred during the conduct of the study. All adverse events were mild in nature.

Table 4 Protocol Deviations

No major or important protocol deviation was noted.

Comments on Dropouts/Adverse Events/Protocol Deviations: N/A

Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Parent							
QC Conc. (ng/mL)	30	400	1200					
Inter day Precision (%CV)	7.4	7.3	9.4					
Inter day Accuracy (%)	103	105.5	101.7					
Cal. Standards Conc. (ng/mL)	10	20	80	200	600	1000	1400	1600
Inter day Precision (%CV)	9.5	3.6	6.8	6.7	6.3	5.4	4.9	6.1
Inter day Accuracy (%)	99.0	99.5	99.4	101	102.5	99.7	102.1	96.9
Linearity Range (range of R^2 values)	0.9890 – 0.9996							

Comments on Study Assay Quality Control: N/A

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: N/A

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
Not submitted	Not submitted	Not submitted

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	N/A
Did recalculation of plasma concentrations change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Incomplete. More information is needed –See Deficiency Comments.

c) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ng*hr/ml	18171.3	28.0	16759.8	29.9	1.084219
AUC∞	ng*hr/ml	18827.7	28.9	17373.5	30.3	1.083702
Cmax	ng/ml	629.77	24.1	567.13	24.6	1.110451
Tmax	hr	8.427	88.2	10.239	85.1	0.82303
T1/2	hr	10.716	33.6	10.371	35.3	1.033266
Kel	1/hr	0.07036	26.7	0.07403	30.1	0.950426

Table 9 LS Geometric Means and 90% Confidence Intervals

Parameter	Test		Reference		T/R	90% CI
	Mean	%CV	Mean	% CV		
AUC0-t	17451.99	29.8	15980.90	33.0	1.092053	102.3 – 116.4
AUC∞	18033.87	30.8	16545.32	33.4	1.089968	102.2 – 116.1
Cmax	613.198	23.4	550.438	25.2	1.114018	105.6 – 117.9

Table 10 Additional Study Information

Root mean square error, AUC0-t	0.196445
Root mean square error, AUC∞	0.194635
Root mean square error, Cmax	0.167706
Kel and AUC∞ determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

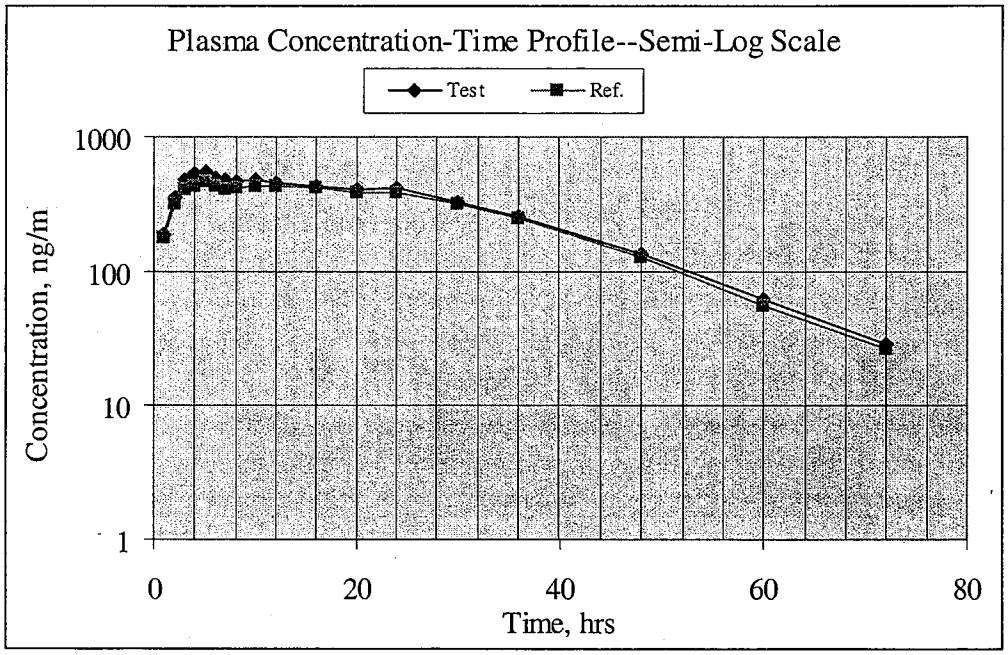
Comments on Pharmacokinetic and Statistical Analysis: OK

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: Incomplete due to analytical deficiencies.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time, hrs	Test (n=52)		Reference (n=52)		T/R
	Mean Conc.(ng/ml)	%CV	Mean Conc.(ng/ml)	%CV	
0	0	---	0	---	0
1	185.43	53.4	176.52	52.8	1.050476
2	347.73	43.9	316.17	45.0	1.09982
3	480.21	34.3	400.13	37.6	1.200135
4	526.00	30.5	427.62	32.7	1.230064
5	539.27	28.2	464.02	34.3	1.16217
6	489.50	27.1	428.31	32.6	1.142864
7	478.00	27.8	407.38	31.2	1.173352
8	467.71	31.5	409.25	32.5	1.142847
10	470.67	26.8	424.65	31.2	1.108372
12	455.96	28.7	421.71	34.3	1.081217
16	430.56	25.6	412.48	29.6	1.043832
20	398.37	29.5	377.88	31.1	1.054224
24	411.06	33.3	379.72	34.2	1.082534
30	325.81	35.6	312.77	39.5	1.041692
36	252.79	46.1	246.34	49.8	1.026183
48	135.33	60.7	126.22	67.6	1.072176
60	62.47	78.7	55.84	83.6	1.118732
72	28.43	102.7	26.45	106.2	1.074858

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a. Study Design

Study Information	
Study Number	AA05458
Study Title	Comparative, Randomized, Single-Dose, 2-way Crossover Bioavailability of Stiefel and Ortho Griseofulvin Microsize Oral Suspension in Healthy Adult Volunteers Following Administration of a 250 mg Dose under Fed Conditions
Clinical Site	[ ]
Principal Investigator	[ ], MD
Study/Dosing Dates	June 20 – July 7, 2003
Analytical Site	[ ]
Analytical Director	[ ]
Analysis Dates	July 16 – July 24, 2003
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	35 days

Treatment ID	Test	Reference
Test or Reference	Test	Reference
Product Name	Griseofulvin Oral Suspension	Grifulvin V
Manufacturer	Stiefel Laboratories	Ortho Dermatological
Batch/Lot No.	L0299	13C973
Manufacture Date	March 2003	N/A
Expiration Date	February 28, 2005	March 2005
Strength	125 mg/5 ml	125 mg/5 ml
Dosage Form	Suspension	Suspension
Batch Size	[ ]	N/A
Potency	103% - 106%	Not reported
Formulation	See Appendix Section B	N/A
Dose Administered	250 mg (10 ml)	250 mg (10 ml)
Route of Administration	Oral	

No. of Sequences	~~2~~
No. of Periods	~~2~~
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 2, 3, 6, 8, 10, 11, 14, 15, 16, 19 BA: 1, 4, 5, 7, 9, 12, 13, 17, 18, 20
Blood Sampling Times (hrs)	0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60, & 72
Blood Volume Collected/Sample	5 ml
Blood Sample Processing/Storage	Stored at -20^0 C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table12
Length of Fasting	10 hrs
Length of Confinement	36 hrs
Safety Monitoring	Yes

Comments on Study Design: Acceptable

b) Clinical Results

Table12 Demographics of Study Subjects

Age (year)		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
Mean	33	Mean	70.4	<18	0%			Caucasian	80%
SD	8	SD	8.8	18-40	75%	Male	80%	Afr. Amer.	15%
Range	18-45	Range	57-87.5	41-64	25%	Female	20%	Hispanic	5%

Table 13 Composition of Meal Used in Fed Bioequivalence Study

Composition of Meal Used in Fed Bioequivalence Study		
Each subject received a standard breakfast consisted of: 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 ml of whole milk.		
Composition	Percent	Kcal
Fat	Not available	Not available
Carbohydrate	Not available	Not available
Protein	Not available	Not available
Total	[redacted]	

Comments on Study Design: Acceptable. The composition of the meal is the same as the FDA standard meal.

Table 14 Dropout Information

Subject No	Reason	Period	Replaced?
9	Personal reasons (found a job)	2	Yes-subject #20 (same sequence)

Table 15 Study Adverse Events

Except for headache or tiredness, no serious adverse events occurred during the conduct of this study.

Adverse Event Description	# in Test Group	# in Ref. Group
N/A		
Total:		

Table 16 Protocol Deviations

Except for some missing samples (late samples) since some subjects did not return for taking samples, no major protocol deviations occurred.

Type	Subject # (Test)	Subject # (Ref.)
N/A		

Comments on Adverse Events/Protocol Deviations: Minor adverse events or protocol deviations did not affect the outcome of the study.

c. Bioanalytical Results

Table 17 Assay Quality Control – Within Study

	Parent							
QC Conc. (ng/mL)	30	400	1200					
Inter day Precision (%CV)	7.0	7.7	7.0					
Inter day Accuracy (%)	108.0	108.3	100.8					
Cal. Standards Conc. (ng/mL)	10	20	80	200	600	1000	1400	1600
Inter day Precision (%CV)	9.6	3.0	9.1	4.6	7.8	5.8	7.0	5.7
Inter day Accuracy (%)	95.8	104	103.8	102	101.3	98.5	99.3	106.0
Linearity Range (range of R^2 values)	0.9899 – 0.9994							

Comments on Study Assay Quality Control: N/A

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: N/A

Table 17 SOP's dealing with analytical repeats

None was submitted

SOP No.	Date of SOP	SOP Title
		Not available

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	N/A
Did recalculation of plasma concentrations change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: Incomplete—See Deficiency Comments.

d. Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 22 and Figure 2

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ng*hr/ml	20388.6	29.7	19496.5	27.8	1.045757
AUC∞	ng*hr/ml	20735.2	31.1	19831.9	29.2	1.045548
Cmax	ng/ml	1310.28	16.4	1253.22	22.4	1.045531
Tmax	hr	4.944	38.3	4.556	21.6	1.085162
T1/2	hr	9.043	27.9	8.873	32.3	1.019159
Kel	1/hr	0.08367	33.1	0.08685	35.5	0.963385

Table 20 LS Geometric Means and 90% Confidence Intervals

Parameter	Test		Reference		T/R	90% CI
	Mean	%CV	Mean	% CV		
AUC0-t	19728.42	25.7	18907.95	25.1	1.043393	99.2 – 109.7
AUC∞	20017.56	26.4	19194.21	25.7	1.042896	99.2 – 109.6
Cmax	1293.525	16.7	1221.575	24.1	1.058899	97.1 – 115.4

Table 21 Additional Study Information

Root mean square error, AUC0-t	0.086081
Root mean square error, AUC∞	0.085990
Root mean square error, Cmax	0.148097
Kel and AUC∞ determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as Cmax	None
Were the subjects dosed as more than one group?	No

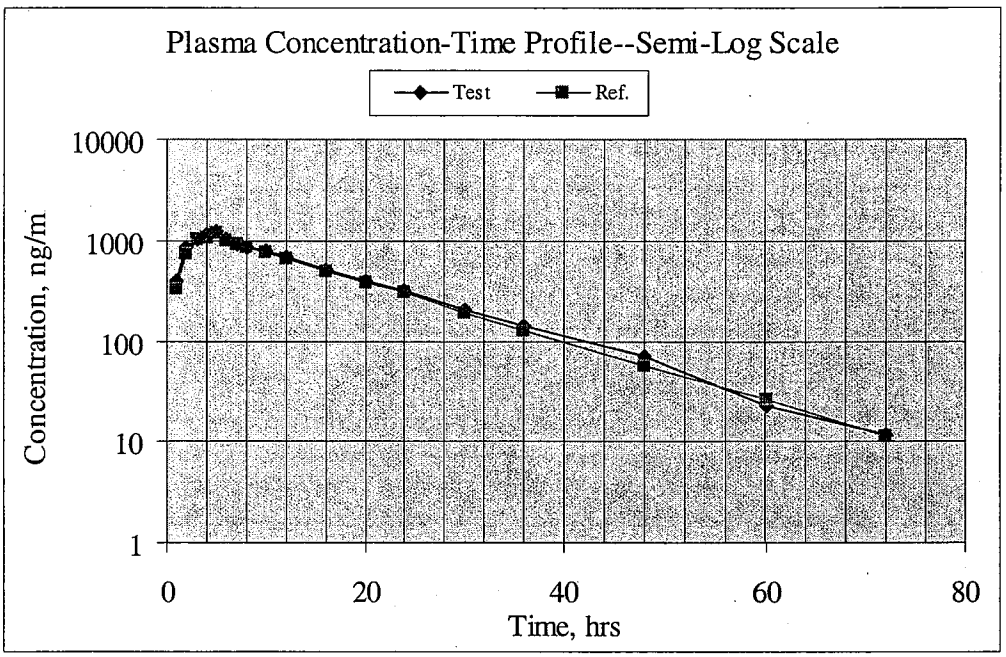
Comments on Pharmacokinetic and Statistical Analysis: N/A

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: Incomplete due to analytical deficiencies.

Table 22 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Time, hrs	Test (n=18)		Reference (n=18)		T/R
	Mean Conc.(ng/ml)	%CV	Mean Conc.(ng/ml)	%CV	
0	0	---	0	---	0
1	393.89	40.8	333.56	39.7	1.180867
2	865.22	28.7	736.44	29.8	1.174868
3	1039.56	24	1009.67	26.9	1.029604
4	1148.94	23.2	1073.56	22.7	1.070215
5	1254.39	18.8	1205.28	21.9	1.040746
6	1032.11	15.5	990.50	25	1.042009
7	918.94	12.6	927.56	19.8	0.990707
8	869.78	12.5	849.78	17	1.023536
10	794.72	18.5	768.89	18.8	1.033594
12	689.94	28.5	668.00	23.7	1.032844
16	510.17	34.5	494.94	28.8	1.030771
20	395.94	40.9	388.17	35	1.020017
24	313.53	56.5	310.00	50.3	1.011387
30	205.58	62.7	190.40	56.5	1.079727
36	139.76	86.3	128.92	74.7	1.084083
48	71.39	113.4	56.71	106.9	1.258861
60	22.34	107.9	26.16	155.7	0.853976
72	11.74	213.1	11.15	192.7	1.052915

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Ingredients	Amount (mg) per 5 ml	%w/w
Griseofulvin, USP Micronized		
Alcohol, USP		
Docusate Sodium, USP		
FD&C Red #40		
FD&C Yellow #6		
Magnesium Aluminum Silicate, NF		
Menthol, USP		
Mehylparaben, NF		
Orange Cream Flavor		
Propylene Glycol, USP		
Propylparaben, NF		
Purified water, USP		
Saccharin Sodium, USP		
Simethicone Emulsion, USP		
Sodium Alginate, NF		
Sucrose, NF		
Total	6150	100

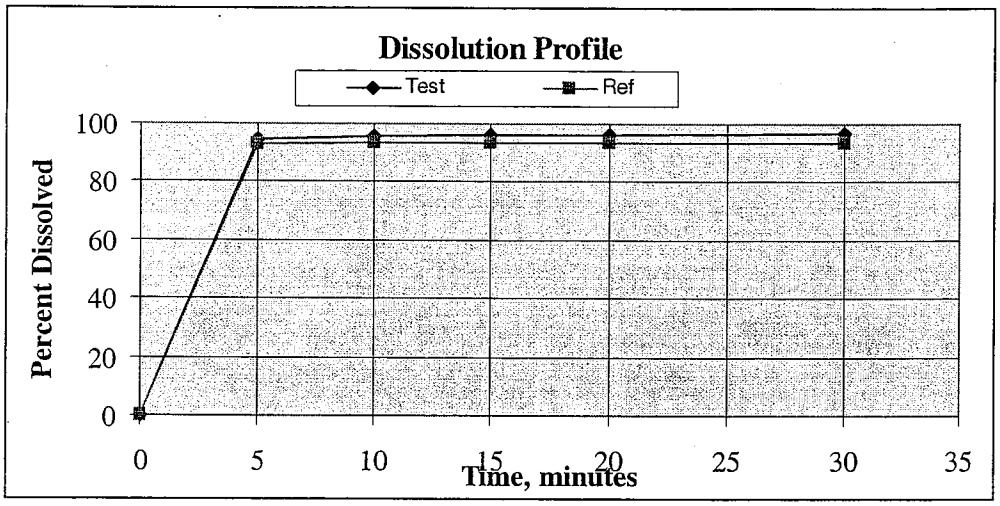
C. Dissolution Data

(Paddle – RPM, 1000 ml water containing 5.4 mg of SLS/ml)

Table 24

Sampling Time (minutes)	Test Product, Strength: 125mg/5ml Lot No. L0299			Ref. Product, Strength:125mg/5ml Lot No. 13C973		
	Mean	%CV	Range	Mean	%CV	Range
5	94.7	0.8		92.6	0.7	
10	95.8	1		93.2	0.4	
15	96.1	0.9		93.3	0.7	
20	96.4	1		93.4	0.7	
30	96.5	0.8		93.5	0.7	

Figure 3 Dissolution Profiles



D. Consult Reviews

None

E. SAS OUTPUT

SAS
FASTSTUDY.TXT

SAS
FEDSTUDY.TXT

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCE DEFICIENCIES

ANDA/AADA: 65-200 APPLICANT: Stiefel

DRUG PRODUCT: Griseofulvin Oral Suspension, 125 mg/5ml

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

1. Please provide a table that identifies every missing sample in the BE studies (fasting and fed). Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis.

2. Please provide the Standard Operating Procedures (SOPs) of the analytical method, the SOP for chromatographic acceptance criteria and verification of chromatograms, and SOPs for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study. Otherwise, the Division of Bioequivalence will not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

3. The dissolution testing is incomplete. You are requested to conduct dissolution testing using the paddle method at 25 RPM in 1000 ml of water containing 5.4 mg of SLS per ml. Suggested sampling times: 10, 20, 30 and 45 minutes and until at least —⅔ of the labeled drug is dissolved.

4. The potency of the reference product used in the studies was not provided.

Sincerely yours,

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

CC: ANDA 65-200
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-658/Reviewer 9-29-04
HFD-658/Bio Team Leader 9/29/2004
HFD-650/Dale Conner 9/29/04

BIOEQUIVALENCE-DEFICIENCIES

Submission Date: 11/24/03

1. **FASTING STUDY** (STF)
Clinical: [ ]
Analytical [ ]

Strength: 125mg/5ml
Outcome: IC

2. **FOOD STUDY** (STP)
Clinical:
Analytical: [ ]

Strength: 125mg/5ml
Outcome: IC

Outcome Decisions:
IC - Incomplete

WinBio Comments

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-200
Drug Product Name	Griseofulvin Oral Suspension, USP
Strength	125 mg/5 ml
Applicant Name	Stiefel Laboratories
Address	Coral Gables, FL
Submission Date(s)	October 22, 2004
Reviewer	Nhan L. Tran
First Generic	Yes
File Location	V:\firmsnz\stiefel\ltrs&rev\65200A1004.DOC

I. Executive Summary

This is a review of a study amendment. Stiefel is referencing Ortho's Grifulvin V® Oral Suspension. The original submission contained the results of a single-dose fasting and a single dose non-fasting bioequivalence study. The studies are incomplete due to analytical method deficiencies. Additionally, dissolution testing data using the firm's method (1000 mL water with 5.4mg/ml SLS, paddle at [redacted] rpm) were found indiscriminating as most of the drug is dissolved within 5 to 10 minutes. The dissolution testing is incomplete.
The original review is in **V:\firmsnz\stiefel\ltrs&rev\65200N1103.DOC**
In this amendment, the firm has satisfactorily addressed all issues of concern. However, the application is incomplete pending the firm's acknowledgement of their acceptance of the FDA recommended dissolution method and specification (1000 mL water with 5.4mg/ml SLS, paddle at 25 rpm with the specification of NLT [redacted]% in 30 minutes).

II. Review of the firm's responses

Deficiency 1. *Please provide a table that identifies every missing sample in the BE studies (fasting and fed). Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis.*

Firm's response: The firm indicated that there were missing samples for two subjects in the non-fasting study (Subject #9 and 19) and two subjects in the fasting study (Subject #21 and 46). Those subjects were dropped from the studies for various reasons; therefore, samples were not analyzed and reported as missing. The firm also provided a table that identified every reassayed sample in the study and the reasons for reassay. There were no reassays in this study due to pharmacokinetic reasons.

DBE Comment: Data presented by the firm indicated that three (3) samples were reassayed for the fed study due to "Above Analytical Range", one (1) sample in the fasting study due to "Unacceptable Chromatography". Two (2) runs were reassayed due to "QCs Unacceptable" and two (2) were reassayed due to "Standard Unacceptable". The response is acceptable.

Deficiency 2. *Please provide the Standard Operating Procedures (SOPs) of the analytical method, the SOP for chromatographic acceptance criteria and verification of chromatograms, and SOPs for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study. Otherwise, the Division of Bioequivalence will not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.*

Firm's response: A copy of the requested SOP was provided in this amendment (SOP# GL-BIO 10603-00). The firm indicated that all reassays done in this study were conducted according to this SOP and this SOP was in place at the start of the study. The firm stated that since no reassays were performed for pharmacokinetic reasons, no further pharmacokinetics or statistical analyses were needed.

DBE Comment: The firm's response is acceptable.

Deficiency 3. *The dissolution testing is incomplete. You are requested to conduct dissolution testing using the paddle method at 25 RPM in 1000 ml of water containing 5.4 mg of SLS per ml. Suggested sampling times: 10, 20, 30 and 45 minutes and until at least — % of the labeled drug is dissolved.*

Firm's response: Dissolution data using the FDA recommended method were provided.

DBE Comment: Data provided by the firm indicated that the test met the specification at S1 level: NLT – % in 30 minutes. Data are provided below:

USP Apparatus II (Paddle), at 25 RPM, medium: water containing 5.4mg of SLS/ml; 1000ml.

Sampling (min.)	Test Product, Lot No. L0299			Reference Product, Lot No. 13C973		
	Mean	%CV	Range	Mean	%CV	Range
10	**94.1**	**4.4**		**91**	**1.0**	
20	**95**	**2.7**		**91.5**	**1.8**	
30	**95.3**	**2.3**		**90.7**	**1.4**	
45	**95.5**	**2**		**91**	**1**	

The response is acceptable.

Deficiency 4. *The potency of the reference product used in the studies was not provided.*

Firm's response: The potency of the reference product is 2.45% w/v.

DBE Comment: The response is acceptable.

III. Recommendations

1. The *in vivo* bioequivalence studies conducted under fasting and non-fasting conditions by Stiefel on its Griseofulvin Oral Suspension USP, 125mg/5ml, lot # L0299, comparing it to the reference product, Grifulvin V® Microsize Suspension, 125mg/5ml, lot #13C973, are acceptable to the Division of Bioequivalence. The studies demonstrate that under fasting and non-fasting conditions, Stiefel's Griseofulvin Oral Suspension, USP, 125mg/5ml, is bioequivalent to the reference product, Grifulvin V® Microsize Suspension, 125mg/5ml, manufactured by Ortho Laboratories.

2. The dissolution testing conducted by Stiefel on its Griseofulvin Oral Suspension USP, 125mg/5ml, is acceptable. The dissolution testing should be conducted in 1000 mL of water containing 5.4mg of SLS per ml using USP Apparatus II (Paddle) at 25 rpm. The test product should meet the following specification: Not less than — % of the labeled amount of griseofulvin in the dosage form is dissolved in 30 minutes.

3. However, the application is incomplete. The firm should be advised to acknowledge acceptance of FDA's recommended dissolution method and specification.

11/22/04

Nhan L. Tran, Reviewer, Branch III, Date signed

11/22/2004

YC Huang, Team Leader, Branch III, Date signed

11/22/04

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCY

ANDA/AADA: 65-200 APPLICANT: Stiefel

DRUG PRODUCT: Griseofulvin Oral Suspension USP, 125 mg/5ml

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

Please acknowledge you have accepted the following FDA recommended dissolution method and specification:

> The dissolution testing should be conducted in 1000 mL of water containing 5.4 mg of SLS per ml using USP apparatus II (Paddle) at 25 rpm. The test product should meet the following specification:
>
> Not less than —% (Q) of the labeled amount of griseofulvin in the dosage form is dissolved in 30 minutes.

Sincerely yours,

Barbara M Davit

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

CC: ANDA 65-200
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-658/N. Tran
HFD-658/Y. Huang 11/22/2004
HFD-650/D. Conner 11/22/04

BIOEQUIVALENCE - Incomplete

Submission date: 10/22/04

(The firm needs to acknowledge acceptance of FDA's recommended dissolution method and specification.)

1. STUDY AMENDMENT (STA) OK

Strength: 125mg/5ml
Outcome: IC

Clinical: [ ]
Analytical [ ]

Outcome Decisions: **IC** - INCOMPLETE

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

GENERIC NAME: **Griseofulvin** ANDA #: 65-200 SPONSOR: Stiefel
DOSAGE FORM: Oral Suspension STRENGTH: 125mg/5ml
TYPES OF STUDIES: Fasting and non-fasting
CLINICAL STUDY SITE: [ ]
ANALYTICAL SITE:

STUDY SUMMARY: Studies acceptable

DISSOLUTION: Acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes___No___
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)
DBE Dissolution Method and Spec acknowledged by firm: Yes ___Amendment Date - 12/02/04
PROJECT MANAGER: Beth F. Fritsch DATE: 12/20/04
Beth Fabian Fritsch, R.Ph., MBA

PRIMARY ~~REVIEWER~~ : Nhan L. Tran, Ph.D. BRANCH: III
INITIAL : NLT DATE : 12-21-04

TEAM LEADER : Y.C. Huang, Ph.D. BRANCH: III
INITIAL : YCH DATE : 12/21/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : DPC DATE : 12/21/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

ADMINISTRATIVE DOCUMENTS

TELEPHONE MEMO

TO: Mary Jane Carr (Stiefel Labs)

REF# ANDA 65-200

FROM: Leo Zadecky

DATE: 12, 13 January 2004

SUBJECT: Griseofulvin Oral Suspension USP 125 mg/5ml

CONTENT:

Ms. Carr was phoned to resolve deficiencies with Stiefel Labs' ANDA 65-200.

1) **The 356h form initially submitted did not include the full name of the drug as it appears in the orange book. Griseofulvin Oral Suspension USP, 125 mg/ 5ml. Ms. Carr has faxed a copy of the changed 356h and has promised to send a signed 356h with the correction.**

2) **A non singed Categorical Exclusion claim was submitted in the application, In addition, on a separate page, Stiefel labs comfirms compliance with federal, state and local environmental laws. The latter page is signed. Ms. Carr has agreed to compile this information onto one page and sign. She has already faxed a copy and will send an original signature with the above revised 356h.**

3) **Additionally, Ms Carr has amended the 356 to include the proper holder of the RLD, J and J.**

OGD APPROVAL ROUTING SUMMARY

ANDA # 65-700 Applicant Stiefel Labs, Inc.

1g Griseofulvin Oral Susp. USP. Strength(s) 125 mg/5 ml

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: DRAFT Package FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 7 JAN 05 Date _____
Initials MMS Initials _____

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)

Pediatric Exclusivity System
RLD = NDA# _____

Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked _____

If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐ Nothing Submitted ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Written request issued ☐
Has case been settled: Yes ☐ No ☐ Study Submitted ☐
Date settled:

Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments: no patents/exclusivities! - eligible for Full Approval

2. Project Manager, RNguyen Team 6
Review Support Branch

Date 1/7/05 Initials (MM) Date 1/21/05 Initials (MM)

Original Rec'd date 11/24/03
Date Acceptable for Filing 11/26/03
Patent Certification (type) 2
Date Patent/Exclus.expires —
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☒ Acceptable ☐ OAI ☐
Date of EER Status 1/6/05
Date of Office Bio Review 12/21/04
Date of Labeling Approv. Sum 12/17/04
Date of Sterility Assur. App. —
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. David Read (PP IVs Only) Pre-MMA Language included ☐ Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials _____
Comments:

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:

1/25/05

Date 2/7/05
Initials _____

cmc satisfactory.

REVIEWER: FINAL ACTION

Frank Holcombe First Generics Only Date 3/2/05
Assoc. Dir. For Chemistry Initials RSA
Comments: (First generic drug review) satisfactory

NDA 62483
RLD = Gastrulin V Oral Suspension 125mg/5mL
Johnson + Johnson Consumer Products, Inc.

6. Vacant Date
Deputy Dir, DLPS Initials

7. Peter Rickman Date 3/2/05
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments:
No Patent or exclusivity issues - eligible for Full approval
Labeling acceptable 12/17/04 per LAS
Office Level Bio acceptable 12/21/04 (Fasting & non-fasting BE studies)
No DSI inspection needed
EES acceptable 1/6/05 No OAI alerts OK for full approval

OR

8. Robert L. West Date
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 1/6/05 (Verified 2/9/05). No O.A.I. alerts
noted -

APPEARS THIS WAY
ON ORIGINAL

9. Gary Buehler Date 3/2/05
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team 6 Date 3/3/05
Review Support Branch Initials AW
_____ Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
4:00 Time notified of approval by phone 4:07 Time approval letter faxed
FDA Notification:
3/3/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/3/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-200

CORRESPONDENCE

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

January 12, 2004

Leo B. Zadecky
Assistant Regulator
Office of Generic Drugs (HFD-615)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

NEW CORRESP (NC)

RE: ANDA 65-200
Griseofulvin Oral Suspension USP, 125 mg/5 mL

Dear Mr. Zadecky:

Reference is made to our Abbreviated New Drug Application, Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL, ANDA 65-200, submitted November 24, 2003.

Reference is also made to FDA's January 12, 2004 telephone request specific to an updated form FDA 356h and an updated claim for categorical exclusion.

We are here providing an updated form FDA 356h, revised to specify the established name, Griseofulvin Oral Suspension USP, 125 mg/5 mL, and an updated claim for categorical exclusion, as requested.

We look forward to your review.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr
Assistant Director
Regulatory Affairs

MJC:lal

RECEIVED
JAN 13 2004
OGD/CDER

2.1

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

January 13, 2004

Leo B. Zadecky, R.Ph.
Regulatory Management Officer
Division of Labeling and Program Support (HFD-615)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

RE: TELEPHONE AMENDMENT
ANDA 65-200
Griseofulvin Oral Suspension USP, 125 mg/5 mL

Dear Mr. Zadecky:

Reference is made to our Abbreviated New Drug Application, Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL, ANDA 65-200, submitted November 24, 2003.

Reference is also made to FDA's January 13, 2004 telephone request specific to an updated form FDA 356h.

We are here providing an updated form FDA 356h revised to specify the reference listed drug holder, J and J, as requested.

We look forward to your review.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr
Assistant Director
Regulatory Affairs

MJC:lal

RECEIVED
JAN 15 2004
OGD/CDER

ANDA 65-200

Stiefel Laboratories, Inc.
Attention: Mary Jane Carr
Route 145
Oak Hill, NY 12460

JAN 22 2004

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversations dated January 12, 2004 and January 13, 2004 and your correspondence dated January 12, 2004 and January 13, 2004.

NAME OF DRUG: Griseofulvin Oral Suspension USP, 125 mg/5 mL

DATE OF APPLICATION: November 24, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 26, 2003

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 65-200

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement:
HFD-615/MShimer, Chief, RSB _____ date 22 JAN 2004
HFD-615/LZadecky, CSO _____ date 1-22-04
Word File V:\FIRMSNZ\LTRS&REV\65200.ACK
F/T 1-21-04
ANDA Acknowledgment Letter!

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

July 1, 2004

Gary J. Buehler
Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

ORIG AMENDMENT
N/AM.

RECEIVED
JUL 0 2 2004
OGD / CDER

RE: **MINOR AMENDMENT**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Mr. Buehler:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL.

Reference is also made to FDA's 8 April 2004 not approvable communication specific to subject application.

We are here responding to FDA's 8 April 2004 communication via this Minor Amendment to the ANDA.

Our response is numerically keyed to FDA's comments for ease of review. Additional supporting data, as referenced by tab and page, is also included in this submission as required.

A. Chemistry Deficiencies:

FDA Comment

1. To facilitate the review, please provide in the Components and Composition section of the submission the function of each inactive ingredient in Griseofulvin Oral Suspension, USP (microsize) as well as a concise tabular list of all in-process controls used during the manufacture of the drug product.

Stiefel Response

Please find enclosed a listing of the functionality for each inactive ingredient of Griseofulvin Oral Suspension, USP (microsize) [see TAB 1].

In-process controls used during the manufacture of the drug product were summarized at p. 2271 (Volume 8 of 20) of the original ANDA. We are here

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7/1/2004 STIEFEL LETTER

Stiefel Response

Please find enclosed available 365 day (12 month) long-term (25°C/60% Relative Humidity) stability data for drug product, Package Lot #L0299 [see Tab 7].

FDA Comment

5. The Drug Substance Drug Master File (DMF # ——— has been reviewed and found inadequate. The DMF holder has been informed of the deficiencies. Please be aware that the application cannot be approved until deficiencies regarding this DMF have been addressed satisfactorily by the holder.

Stiefel Response

We have received notification from the holder of DMF ——————————— that deficiencies for the drug substance, Griseofulvin USP, have been addressed by a complete response on April 15, 2004. [see Tab 8]

We look forward to FDA's timely review of this submission.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Assistant Director
Regulatory Affairs

MJC:lal

Research in Dermatology

ORIG AMENDMENT
N/AA

ORIGINAL

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

September 3, 2004

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: **TELEPHONE AMENDMENT:**
INFORMATION REQUEST
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL.

Reference is also made to FDA's 1 September 2004 telephone request for chemistry related information specific to subject ANDA.

We are here responding to FDA's 1 September request via this Telephone Amendment to the ANDA.

Specific to the process _____ we here confirm that _____
_____.

[redacted] However, results specific to the above have been included under the Remarks section (page 3) of subject COA (see following).

CORPORATE OFFICES: 255 ALHAMBRA CIRCLE, CORAL GABLES, FLORIDA 33134
ATLANTA, GEORGIA • RENO, NEVADA • ROCKVILLE, MARYLAND • BAYAMON, PUERTO RICO • BUENOS AIRES, ARGENTINA • CASTLE HILL, NSW, AUSTRALIA • BRUXELLES, BELGIUM • SAO PAULO, BRAZIL • MONTREAL, CANADA
SANTIAGO, CHILE • BOGOTA, COLOMBIA • CAIRO, EGYPT • PARIS, FRANCE • OFFENBACH/MAIN, GERMANY • ATHENS, GREECE • KOWLOON, HONG KONG • AMSTERDAM, HOLLAND • DUBLIN & SLIGO, IRELAND • MILAN, ITALY
TOKYO, JAPAN • SEOUL, KOREA • MEXICO CITY, MEXICO • CASABLANCA, MOROCCO • LAHORE, PAKISTAN • LIMA, PERU • MANILA, PHILIPPINES • WARSAU, POLAND • AMADORA, PORTUGAL • JURONG, SINGAPORE
JOHANNESBURG, SOUTH AFRICA • MADRID, SPAIN • ZURICH, SWITZERLAND • TAIPEI, TAIWAN • BANGKOK, THAILAND • HIGH WYCOMBE/BUCKS & SLOUGH/BERKS, UK • CARACAS, VENEZUELA

Lastly, we are here providing updated tests and specifications for Griseofulvin, USP which include a reduction in the specification limit for [redacted], from —% to —%, as requested (see attached).

This submission is complete in one (1) volume, not including additional copies which are also provided, as required.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Assistant Director
Regulatory Affairs

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

September 8, 2004

ORIG AMENDMENT

N/AF

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **Final Printed Labeling**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL.

Reference is also made to FDA's 6 August 2004 labeling deficiency communication specific to subject ANDA.

We are here providing final printed labeling, in electronic (PDF) format, as required. Subject labeling is also provided in MS Word format, as requested.

In addition to the above, we are here providing, in electronic (PDF and MS Word) format, a side-by-side comparison of subject labeling to our last submission with all differences annotated and explained.

All of the above referenced files are included on one (1) CDROM (approximately 1420 kilobytes) which has been scanned for viruses by Symantec AntiVirus, Version 8.00.9374, and determined to be virus free.

We recognize the significant rewrite of subject labeling undertaken at FDA, and have revised our labeling to duplicate the FDA rewrite, with the exception of the following:

[ ]

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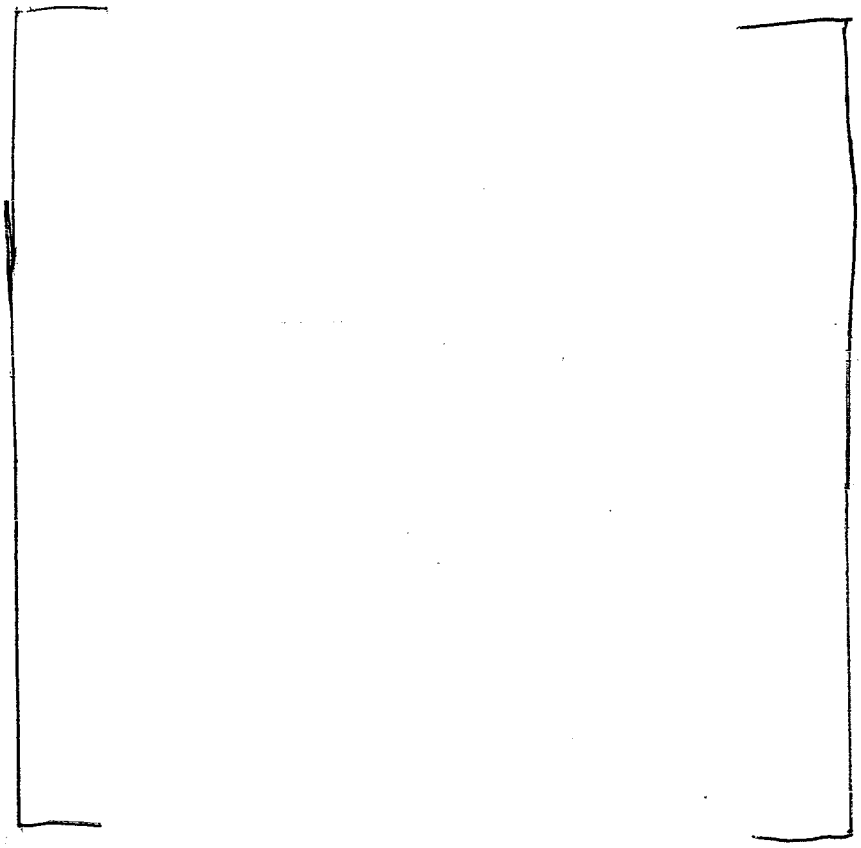
SEP 10 2004
OGD/...



Please direct all communications concerning this submission to:

Mary Jane Carr
Assistant Director
Regulatory Affairs
Stiefel Laboratories, Inc.
Route 145
Oak Hill, New York 12460

We look forward to your timely review.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Assistant Director
Regulatory Affairs

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

September 23, 2004

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AF

RE: **Telephone Amendment**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL and to our 8 September 2004 amendment specific to Final Printed Labeling for subject ANDA.

Reference is also made to FDA's 22 September 2004 telephone request for supporting documentation to justify the change in the presentation of species from that referenced in FDA's 6 August 2004 deficiency communication specific to subject labeling.

[ ]

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SEP 27 2004
OGD/CDER

[redacted]

We look forward to FDA's timely review of this submission.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr
Assistant Director
Regulatory Affairs

ORIGINAL

ORIG AMENDMENT

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

October 8, 2004

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: **TELEPHONE AMENDMENT**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL and to our 8 September 2004 submission specific to Final Printed Labeling for subject ANDA.

Reference is also made to FDA's 6 October 2004 telephone request for electronic labeling in "true size".

We are here responding to FDA's 6 October request via this Telephone Amendment to the ANDA.

Please find enclosed one (1) diskette containing a .pdf file of the product labeling, formatted in "true size", as requested. A hard copy of subject file is also enclosed.

Please note that subject file must be set to landscape for review.

This submission is complete in one (1) volume, not including additional copies which are also provided, as required.

Sincerely,
STIEFEL LABORATORIES, INC.

Maryjane Carr

Mary Jane Carr
Assistant Director
Regulatory Affairs

RECEIVED
OCT 12 2004
OGD/CDER

ORIGINAL

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

October 22, 2004

ORIG AMENDMENT
N/A5

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **Bioequivalency Amendment**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL.

Reference is also made to FDA's 30 September 2004 bioequivalency deficiency communication.

We are here responding to FDA's 30 September deficiency communication via this Bioequivalency Amendment to the ANDA.

Our response is numerically keyed to FDA's comments for ease of review. Additional supporting information, referenced by tab and page, is also included in this submission as required.

FDA Comment

1. Please provide a table that identifies every missing sample in the BE studies (fasting and fed). Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis.

Stiefel Response

In accordance with FDA's request we are here providing information specific to every missing sample in the BE studies (fed and fasting), as well as information specific to every reassayed sample.

At appendix 16.3, section 2.2.3 of the analytical reports (pp. 470 and 1078 of the original ANDA), the following tables were provided to identify every sample, to include every missing sample, in the BE studies.

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10/22/2004 STIEFEL LETTER

Stiefel Response

The reference product, Grifulvin® V (griseofulvin oral suspension), Lot #13C973, used in the BE studies was analyzed during May 2003 and determined to contain 2.45% w/v griseofulvin (please see Tab 5).

We look forward to FDA's timely review of this submission.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Assistant Director
Regulatory Affairs

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

ORIGINAL

October 25, 2004

ORIG AMENDMENT
N/AF

OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
Food and Drug Administration
MPN2, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **Telephone Amendment**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL and to our 8 October 2004 telephone amendment specific to electronic labeling.

Reference is also made to FDA's 22 October 2004 telephone request for electronic labeling, reformatted and with all non-label copy information removed.

We are here responding to FDA's 22 October 2004 request via this Telephone Amendment to the ANDA.

Please find enclosed one (1) diskette containing a .pdf file of the product labeling reformatted, as requested. A hard copy of subject file is also enclosed.

Please note that subject file is contained on two (2) pages. The copy contained on the first page represents the frontside of the onsert, while copy contained on the second page represents the backside of the onsert.

This submission is complete in one (1) volume, not including additional copies which are also provided, as required.

Sincerely,
STIEFEL LABORATORIES, INC.

Maryjane Carr

Mary Jane Carr
Assistant Director
Regulatory Affairs

RECEIVED
OCT 26 2004
OGD / CDER

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

ORIG AMENDMENT
N | AF

November 24, 2004

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: **LABELING AMENDMENT**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL.

Reference is also made to FDA's 15 November 2004 labeling deficiency communication specific to subject ANDA.

We are here responding to FDA's 15 November communication via this Labeling Amendment to the ANDA.

Please find enclosed final printed labeling of the Professional Package Insert (Onsert) revised in accordance with FDA's 15 November recommendations. Subject labeling is provided electronically in PDF format and in MS Word format, as requested. A side-by-side comparison to our November 24, 2003 draft labeling, with all differences annotated and explained, is also provided in PDF format.

One (1) copy of subject diskette is enclosed in the Archival Copy of this submission.

This submission is complete in one (1) volume, not including additional copies which are also provided, as required.

Sincerely,
STIEFEL LABORATORIES, INC.

MaryJane Carr

Mary Jane Carr
Assistant Director
Regulatory Affairs

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ORIG AMENDMENT
N/AB

Research in Dermatology

STIEFEL LABORATORIES, INC., OAK HILL, NY 12460 • TEL. 518-239-6901 • FAX. 518-239-6341

December 2, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **Bioequivalency Amendment**
ANDA 65-200
Griseofulvin Oral Suspension, USP
(microsize) 125 mg/5 mL

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application for Griseofulvin Oral Suspension, USP (microsize) 125 mg/5 mL.

Reference is also made to FDA's 24 November 2004 bioequivalency deficiency communication.

We are here responding to FDA's 24 November deficiency communication via this Bioequivalency Amendment to the ANDA.

Our response is numerically keyed to FDA's comments for ease of review. Additional supporting information, referenced by tab and page, is also included in this submission as required.

FDA Comment

1. Please acknowledge you have accepted the following FDA recommended dissolution method and specification:

   The dissolution testing should be conducted in 1000 mL of water containing 5.4 mg of SLS per ml using USP apparatus II (Paddle) at 25 rpm. The test product should meet the following specification:

   Not less than – % (Q) of the labeled amount of griseofulvin in the dosage form is dissolved in 30 minutes.

Stiefel Response

We here confirm that dissolution testing and release will be conducted in accordance with the FDA recommended dissolution method and specification as stated above.

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OGD / CDER

Griseofulvin-2 test methodology has been revised to incorporate a speed change from — RPM to the FDA recommended speed of 25 RPM. Test methodology has previously incorporated a dissolution medium containing 5.4 mg per mL of SLS in water with the USP apparatus II (Paddle). The percent recovery of Griseofulvin (Q) for each sample is specified at not less than — % in 30 minutes.

Griseofulvin-2 test methodology is attached at Tab 1 for your convenience.

We look forward to FDA's timely review of this submission.

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Vice President