STIEFEL®
Research in Dermatology

FAX MEMORANDUM

Route 145 Oak Hill, NY 12460
Tel (518)239-6901 Fax (518)239-8402

To: Ms. Victoria Lutwak, Project Manager
Division of Dermatologic and Dental Drug Products, CDER, FDA

From: Mary Jane Carr

Pages: 13 pages – Including Cover Sheet

Fax: 301-827-2091

Date: June 14, 2002

Re: NDA 50-741: Clindoxyl Topical Gel (clindamycin-benzoyl peroxide)

cc:

cc:
Wilkin
Lieke
Hueve
Vidra

Dear Ms. Lutwak:

Reference is made to our new drug application for Clindoxyl™ Topical Gel (clindamycin-benzoyl peroxide), NDA 50-741.

Reference is also made to our May 28 and June 4, 2002 telephone discussions specific to the DMETS review of the Clindoxyl tradename.

We have prepared this submission in an effort to assist the Division as it considers the clinical relevance of concerns raised in the Division of Medication Errors and Technical Support re-review of the trademark "Clindoxyl".

Also as discussed, enclosed is a copy of the correspondence provided to Stiefel Laboratories, Inc. from Humberto C. Antunes, President, Galderma Laboratories, LP which we believe should alleviate any concern the Division may have concerning the co-existence in the marketplace of our proposed tradename, Clindoxyl, and the Galderma tradename, Clindagel.

Also as agreed we are providing an alternate tradename, Duac, for review by DMETS, in the event the Clindoxyl tradename is ultimately shown to be unacceptable in regard to public safety.

We here confirm that the enclosed information will be formally submitted via a telephone amendment to the pending NDA.

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Senior Manager
Regulatory Affairs

GALDERMA
USA

GALDERMA
LABORATORIES, L.P.

Humberto C. Antunes
President

14531 N. Freeway
Fort Worth
TEXAS
76177

Tel: (817) 961-5007
Fax: (817) 961-0035

May 29, 2002

Mr. Charles W. Stiefel
Stiefel Laboratories, Inc.
255 Alhambra Circle
Coral Gables, FL 33134

Dear Charlie:

As discussed on the phone, Galderma believes that our trademark Clindagel and Stiefel's trademark Clindoxyl are substantially different phonetically.

Therefore, Galderma believes the trademarks Clindagel and Clindoxyl can coexist in the pharmaceutical marketplace.

Sincerely,

Humberto C. Antunes
President

RECEIVED
JUN - 3 2002

HCA/grp

Cc: Brenda Horn
Laurent Venetz

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE:

To: Mary Jane Cain	**From:** Victoria Lutwak VL
Company: Stiefel	Division of Dermatological and Dental Drug Products
Fax number: 518-239-8402	**Fax number:** 301-827-2075
Phone number: 518-239-6901 X8734	**Phone number:** 301-827-2073
Subject: DRAFT of P.I.	

Total no. of pages including cover:

Comments: We do not have a final decision from DMETS on your tradename/trademark

See following pages.

Document to be mailed: ☐ YES ☒ NO

Number of Pages Redacted 6

❖❖❖

Draft Labeling
(not releasable

Lutwak, Victoria L

Subject:	Clindoxyl Gel
Location:	N225
Start:	Wed 8/7/02 2:30 PM
End:	Wed 8/7/02 3:30 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Lutwak, Victoria L; Luke, Markham C; Huene, Phyllis A; Decamp II, Wilson H; Vidra, James D; Brown, Paul C; Jacobs, Abigail (Abby) C; Wilkin, Jonathan K; CDER 540 Calendar, Shalley, Olsh, Fitch, Lee

T-con with sponsor.
discuss draft labeling
they will send their comments to us today.
VL

APPEARS THIS WAY
ON ORIGINAL

STIEFEL LABORATORIES, INC.
OAK HILL, NY 12460
TEL.: (518)239-6901, FAX: (518)239-8402

* * * FAX * * *

DATE: August 5, 2002

ATTENTION: Ms. Victoria Lutwak – Project Manager

COMPANY: Division of Dermatologic & Dental Drug Products

FAX NO.: 301-827-2075

RE: NDA 50-741: Clindoxyl Topical Gel

FROM: William A. Carr, Jr.

TOTAL PAGES: 2 (including cover sheet)

MESSAGE:

Dear Ms. Lutwak:

Reference is made to our New Drug Application for Clindoxyl Topical Gel (clindamycin, 1% – benzoyl peroxide, 5%), NDA 50-741.

Reference is also made to the Division's July 31, 2002 facsimile transmission containing draft copy for the Clindoxyl package insert.

We wish to address three (3) points concerning the proposed copy.

Point One – Indication

We understand that Clindoxyl Gel is indicated only for the topical treatment of inflammatory acne vulgaris. We further understand that the Division feels that it is necessary to clearly differentiate inflammatory acne vulgaris from the non-inflammatory lesions of acne for which Clindoxyl is not indicated.

We believe that the clear and unequivocal exclusionary references to non-inflammatory lesions at lines 94-95 and 98-100 of the draft package insert make the exclusion absolutely clear.

Point Two – Storage Conditions

Post-dispensing storage is referenced at lines 170-171 and 244-245 of the draft package insert. We believe that adequate stability data is available to support patient storage of the product at room temperature for 60 days post-dispensing. A total of nine (9) lots of finished packaged product have been followed for 21 to 24 months at 6°C followed by 90 days storage at room temperature. All product remained in specification at

1 of 2 cute 8/5

the 90 day room temperature test point.

Point Three – Adverse Reactions

A. We request that the data from all studies be combined. The protocols for all studies included the same procedure for collecting safety data. We believe the combined data will be easier to read.

B. It is important to note that the observed local reactions were generally not severe enough to be considered adverse events by the investigators. And, in fact, the global overall tolerance rating was good to excellent in 99% of patients in the Clindoxyl treatment group. We therefore request that a distinction be made between reported local adverse events and the local tolerance observations. This is accomplished by stating in the text the incidence of all related adverse events in the Clindoxyl Gel group in addition to showing the local reaction data. It is also noted that among these adverse events, no individual adverse event occurred in more than 1% of patients and less than 1% of patients in the Clindoxyl group discontinued the study due to a related adverse event.

C. Patients with a symptom during treatment may have had the same symptom at the same level of severity at baseline. Therefore in order to put the data in proper perspective, we request that the percentage of patients with symptoms at baseline be included in this section.

D. We believe it would be helpful to include the percentage of patients with the symptom at each severity grade.

The proposed text of the Adverse Reactions section is shown below:

ADVERSE REACTIONS

Local Reactions With Use of Clindoxyl Topical Gel % of Patients using Clindoxyl Topical Gel with Symptom Present Combined results from 5 Studies (n = 397)						
	Baseline			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

(Percentages derived by # subjects with symptom score/# enrolled subjects, n =397).

3 of 3 Cuts 8/5

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FILE NO.=961

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-FDA/CDER/DDDDP/HFD540 -

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FACSIMILE TRANSMISSION RECORD

From: Vickey Lutwak VL

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: August 20, 2002

To: Name Mary Jane Cain
Company _____
City _____ State ____
Phone # 518-239-6901-main
direct → 261-8784
FAX # 518-239-8402

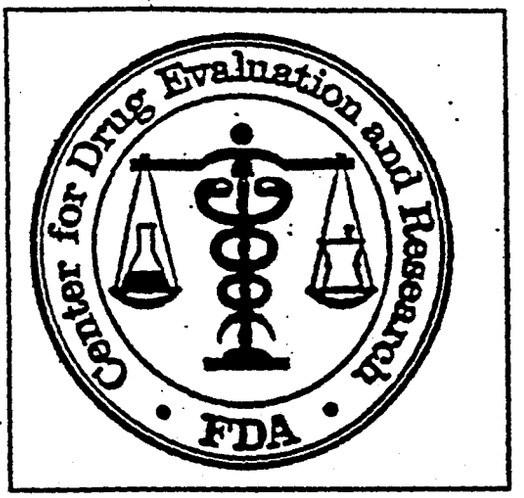
Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

Additional message:

Followup Fax to T-con - 8/20/02

FACSIMILE TRANSMISSION RECORD



From: Vickey Lutwak VL

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: August 20, 2002

To: Name Mary Jane Cain
Company _____
City _____ State ____
Phone # 518-239-6901 - main
direct → 261-8784
FAX # 518-239-8402

Number of Pages (INCLUDING COVER PAGE) 2

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

Additional message:

Followup fax to T-con - 8/20/02

NDA 50-741
August 20, 2002

Recommendation for Nonclinical Studies:

It is recommended that the sponsor conduct a dermal carcinogenicity study and evaluate the effects of the drug on UV-induced skin cancer.

These evaluations may be conducted after NDA approval.

Please provide a written commitment to undertake the above Phase 4 studies.
Please send a letter to the NDA and fax a copy to us.
Thank you.

- Protocol within 4 mo. of letter
- Study start within 6 mo. of approval of the Protocol
- Final Report within 12 months after the Study completion

1-28-02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-741

Stiefel Laboratories, Inc.
Attention: William A. Carr, Jr.
Vice President
Route 145
Oak Hill, NY 12460

Dear Mr. Carr:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clindoxyl™ Gel (clindamycin phosphate 1% and 5% benzoyl peroxide).

I also refer to your letter dated December 15, 2001, received December 18, 2001, containing a request for Formal Dispute Resolution of issues raised in the September 6, 2000, not approvable letter for Clindoxyl™ Gel, the decisions by the Office of Drug Evaluation V and Office of Review Management to uphold that action, and our telephone communication of January 14, 2002.

Your appeal proposed a meeting to bring the unresolved issues to closure or alternatively, a finding by the Division of Dermatologic and Dental Drug Products (the Division) that Clindoxyl™ Gel is safe and effective in the treatment of inflammatory lesions. I have completed the review of your appeal, including the materials submitted and relevant archival documents. Based upon my review, I conclude that the data submitted is insufficient to warrant a reversal of the not approvable letter issued on September 6, 2000.

Pursuant to the regulations regarding dispute resolution, the submission of new information is not allowed (21 CFR 10.75(d)). Therefore, as discussed during our telephone communication on January 14, 2002, the results of a new analysis for Study 150, based on the intent-to-treat population with last observation carried forward, were not considered during this review because they had not yet been submitted to the Division for review.

The major points of your dispute resolution are listed below, followed by my review and conclusions:

A. Fair and Equitable Application of Approval Standards Would Result in Clindoxyl Approval

1. The Endpoint Standard

I acknowledge that our standards regarding demonstration of efficacy for products intended to treat acne (improvement in two of three lesions counts (inflammatory, non-inflammatory and total) and improvement on a global investigator assessment score) have not been promulgated in written guidance to date. However, as stated in our letter of November 20, 2001, the Division has committed to holding an open public meeting on this subject in 2002 to initiate the process of guidance development.

2. The "1 ½ Study" Standard

The approval of products intended to treat acne based on one robust clinical study which met the standard criteria for efficacy, and additional trials which provide supportive evidence, is not

inconsistent with Center standards on establishing evidence for effectiveness. Again, I acknowledge that such a standard has not been promulgated in guidance to date.

3. Discerning Standards and Their Application in Precedents

You provided six examples of reported inconsistency in the application of the above mentioned standards for the approval of related products. It is apparent from your analysis of this information, which spans approximately ten years, that the scientific basis for drug approval has improved over this time period (e.g., pre-specification of primary and secondary endpoints, trial size, populations analyzed). While I agree that consistency in approval standards is important, one cannot ignore advancements in scientific analysis and review. The determination that inadequate information had been submitted to support the efficacy of Clindoxyl was based primarily upon the lack of evidence demonstrating a benefit of the combination product over benzoyl peroxide alone, not on the data submitted for the approval of competitor products.

4. Applying the Divisions Internal Standards to Clindoxyl

As previously stated, the results of a new analysis for Study 150, based on the intent-to-treat population with last observation carried forward, were not considered during this review because they had not yet been submitted to the Division for review. However, I agree that this analysis is important, and therefore recommend that it be submitted to the Division for review.

B. Studies 158 and 150 are Capable of Standing On Their Own

Based upon the presprecified data analyses, neither Study 158 or Study 150 were considered positive for two out of three lesion counts and the global investigator assessment score. However, as discussed above, I feel that the new analysis of Study 150 provides important new data for consideration.

C. Combination Products are Different and There is More than One Way to Arrive at 1 ½ Studies

The determination that insufficient evidence had been submitted to support the efficacy of Clindoxyl was based primarily upon the lack of evidence demonstrating a benefit of the combination product over benzoyl peroxide alone, as discussed earlier. The evidence considered by your expert included analyses not used in this determination (e.g., point estimates of lesion count reduction). I do not consider this sufficient to reverse our earlier decision. Finally, I restate my position regarding the new data analysis for Study 150, and recommend that it be submitted to the Division for review.

In summary, as discussed on January 14, 2002, I find that there is insufficient evidence to reverse the not approvable letter of September 6, 2000. However, I recommend that the results of the new analysis of Study 150 be submitted to the Division for review. In addition, a similar analysis of the global investigator assessment score and revised labeling for an inflammatory lesion (only) indication should be submitted.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. Bernard Schwetz, Acting Principal Deputy Commissioner. The appeal should be sent through the Agency's Chief Mediator and Ombudsman. Any questions concerning this appeal should be addressed via Ms. Kim Colangelo, Dispute Resolution Project Manager, at (301) 594-5413.

Sincerely,

(See appended electronic signature page)

Steven Galson, M.D.
Acting Director
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steven Galson
1/28/02 01:20:56 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Service

Public Health

Food and Drug Administration
Rockville MD
20857

MEMORANDUM OF MEETING MINUTES

Date: August 20, 2002
NDA 50-741
Sponsor: Stiefel Laboratories, Inc.
Type: teleconference
Purpose: A request for post marketing commitments

DRAFT

FDA Attendees:
Paul Brown, Ph.D,
Victoria Lutwak, Project Manager

Stiefel Attendees:
Mary Jane Carr, Regulatory Affairs
William Carr, Vice President
Stiefel's clinical and pre clinical representatives

The t-con was requested by us to ask the sponsor to commit to Phase 4 studies

After a brief introduction to the history and reason for requesting these commitments, the sponsor agreed to the following:

1. The Applicant commits to performing dermal carcinogenicity testing of the combination drug product.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 6 months of the date of the approval of the protocol
Final Report Submission:	Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug products on UV-induced skin cancers.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission:	Within 4 months of the date of this letter

Study Start:	Within 6 months of the date of the approval of the protocol
Final Report Submission:	Within 12 months after the study completion

In addition:

3. The phase 4 agreements were consistent with agreements and recommendations made to other sponsors.

4. The Division might permit some flexibility in the time line for the agreements if the sponsor required more time, for example, to conduct dose range finding studies.

5. We requested that the sponsor send us a letter with the above commitments to the NDA and fax a copy to the Division which they did (see fax correspondence).

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 13, 2001. Number of Pages (including cover sheet) - 2
TO: Mary Jane Carr, Senior Manager, Regulatory Affairs
COMPANY: Stiefel Laboratories, Inc
FAX#: 518-239-8402

MESSAGE: RE: NDA 50-741, Clindoxyl Gel

Labeling comments from the Office of Post-Marketing and Risk Assessment (OPDRA):

Based on the amendment of **March 3, 2000**:

CONTAINER LABEL:

1. We recommend revising the established name and strength to read:

   CLINDOXYL™ GEL
   (clindamycin phosphate 1% and hydrous benzoyl peroxide 5%) Gel

   In addition, we recommend increasing the prominence of the proprietary and established names.

   *Note: The phosphate equivalency will be reflected in the "Each gram contains..." statement.

2. According to the back panel, the product should be stored in a "cold place, preferably in a refrigerator, between 2° and 8° C (36° and 46°F)." However, the next item on the label states, "Store at controlled room temperature between 15° and 30°C (59° and 86°F)" to the pharmacist. These two different storage temperature ranges could be confusing to the user. We recommend revising the label to minimize the confusion.

3. On page 028A, we recommend revising the phrase, [redacted] to read:
   Professional Sample-Not for Sale

CARTON LABELING:

1. On page 030A, the net quantity and the strength are separated by a dash (e.g. 20-5 gram). We recommend revising the labeling so that the strength and the net quantity are separated and easily distinguishable.

2. See comments under CONTAINER LABEL.

Based on amendment dated **July 14, 2000**:

CONTAINER LABEL:

1. We recommend that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10 (g)(2).

2. The proposed container labels for **Clindoxyl Gel** and **Clobevate Gel** (ANDA#: 75-027/S-002) are similar except for the background color and slight adjustment in the location of the two diagonal stripes. Clobevate Gel is also manufactured by Stiefel Laboartories. In order to prevent medication errors due to similar labels of these two **topical** products, we recommend revising Clindoxyl Gel container labels so that it would appear distinctively different (e.g. different design, and colors, boxing, bolding, etc.).

3. The strength of the product is not easily noticeable due to its small font size. We recommend increasing the prominence of the strength.

CARTON LABELING:

1. On the top tuck flap, we recommend adding the established name underneath the proprietary name to be in accordance with 21 CFR 201.10 (g)(1).

2. On the Professional Sample carton, the phrase, " [redacted] ," is confusing in that the carton contains 5 gram tubes. We recognize that Clindoxyl Gel is also available in 45 gram tubes, but it is misleading to place this phrase on the sample carton. We recommend deleting the phrase, " [redacted] ."

3. See comments under CONTAINER LABEL.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

MESSAGE CONFIRMATION

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 13, 2001. Number of Pages (including cover sheet) - 2
TO: Mary Jane Carr, Senior Manager, Regulatory Affairs
COMPANY: Stiefel Laboratories, Inc
FAX#: 518-239-8402

MESSAGE: RE: NDA 50-741, Clindoxyl Gel

Labeling comments from the Office of Post-Marketing and Risk Assessment (OPDRA):

Based on the amendment of **March 3, 2000**:

CONTAINER LABEL:

1. We recommend revising the established name and strength to read:

CLINDOXYL™ GEL
(clindamycin phosphate 1% and hydrous benzoyl peroxide 5%) Gel

In addition, we recommend increasing the prominence of the proprietary and established

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 25, 2000. Number of Pages (including cover sheet) - 4
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find clinical and statistical comments on resubmission dated March 3, 2000.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc: NDA 50-741
HFD-546/D.V FILES

NDA 50-741
Clindoxyl Gel

CLINICAL:

Summary and evaluation: This resubmission of NDA 50-741 for Clindoxyl Gel provides two clinical safety and efficacy studies, and a study on sensitization potential, in response to the non-approvable letter of 5/14/97.

It is felt that the sensitization study is adequate to determine the sensitization potential of Clindoxyl gel.

The non-approvable letter stated that an additional clinical trial is recommended to establish the clinical superiority of Clindoxyl Gel over benzoyl peroxide gel in the treatment of acne. The new studies in the resubmission, Studies 156 and 158, are intended to demonstrate the superiority of Clindoxyl Gel over its components, benzoyl peroxide and clindamycin. Both studies were double blind controlled, multicenter comparisons, with applications once daily for 11 weeks. Study 156 compared Clindoxyl Gel to clindamycin gel and benzoyl peroxide gel; Study 158 had the same treatment arms, with also a vehicle gel arm. The effectiveness parameters were the same in both studies, consisting of lesion counts and an investigator's global evaluation of the percentage of improvement from baseline.

This reviewer's evaluation of these studies was in accordance with current policy that the requirements for a demonstration of effectiveness for a combination product in acne are that the product must demonstrate superiority over each of its components in the percent reduction from baseline of two of the three categories of lesions (inflammatory, non-inflammatory, and total counts) and in the dichotomized investigator's global evaluation, in the ITT population.

Study 156: The results of this study do not demonstrate the effectiveness of the combination product, because the superiority of the combination over benzoyl peroxide has not been shown. Clindoxyl Gel was superior to clindamycin in the percent reduction of the three categories of lesion counts, and was superior to benzoyl peroxide in the percent reduction of non-inflammatory lesions, but was not superior to benzoyl peroxide in the percent reduction of inflammatory lesions or total lesion counts. Clindoxyl Gel was not superior to either benzoyl peroxide or clindamycin in the 'Success Rate', defined as 51% or greater improvement from baseline in the investigator's global evaluation.

Study 158: The results of this study do not demonstrate the effectiveness of the combination product, because the superiority of the combination over benzoyl peroxide has not been shown. Clindoxyl Gel was superior to clindamycin in the percent reduction of inflammatory and total lesion counts, and was superior to benzoyl peroxide in the percent reduction of inflammatory lesions, but was not superior to benzoyl peroxide in the percent reduction of non-inflammatory lesions or total lesion counts. Clindoxyl Gel was superior to clindamycin and to benzoyl

peroxide in the 'Success Rate', defined as 51% or greater improvement from baseline in the investigator's global evaluation.

Conclusions: It is felt that the studies submitted do not demonstrate that Clindoxyl Gel is superior in effectiveness to its component benzoyl peroxide.

Additional comment:

The objective enumeration in Studies 156 and 158 of lesion counts showed significant differences in one category only which were not consistent between the two studies, viz., Study 156 found the combination superior to benzoyl peroxide in non inflammatory lesions only, while Study 158 found the combination to be superior to benzoyl peroxide in inflammatory lesions only. It is plausible that these studies were unsuccessful overall because of under powering.

BIOSTATISTICS:

The objective of this Amendment was to address the deficiencies stated in the 1997 NA Letter and to demonstrate that Clindamycin contributes to the efficacy of the combination. In the statistical review of the Amendment, primary efficacy analysis was based on the ITT population.

Study 156 failed to demonstrate that Clindamycin contributes to the efficacy of the combination. There was no statistically significant difference between Clindoxyl and Benzoyl Peroxide relative to the percent reduction or actual reduction in inflammatory lesions ($p \geq 0.764$), total lesions ($p \geq 0.08$), and proportion of subjects with good to excellent improvement in the Investigator's Global Assessment at endpoint ($p=0.213$).

In Study 158, there was a statistically significant difference between Clindoxyl and Benzoyl groups relative to the percent reduction in inflammatory lesions ($p=0.008$). However, Study 158 failed to show that Clindoxyl is statistically significantly better than Benzoyl Peroxide relative to two of the three categories of lesion counts: there was no statistically significant difference between Clindoxyl and Benzoyl Peroxide relative to the percent reduction of total lesion counts ($p=0.109$) and non-inflammatory lesion counts ($p=0.633$).

In Study 158, for the difference between Clindoxyl and Benzoyl relative to the proportion of patients with good to excellent grades in the Global Improvement, the p-value was close to the nominal (49% vs. 36%, $p=0.042$). In the Per Protocol population, the difference between Clindoxyl and Benzoyl was not statistically significant ($p=0.059$).

Study 158 failed to demonstrate that Benzoyl contributes to the efficacy of the combination. In this study, there was no statistically significant difference between Clindoxyl and Clindamycin relative to the percent reduction of non-inflammatory lesions ($p=0.316$). Results in the Per Protocol population were similar to the results in the ITT population ($p=0.204$).

Internal validity was not shown in Study 158. There was no statistically significant difference between Clindamycin and Vehicle relative to the percent reduction of the inflammatory and total lesion counts ($p=0.487$ and $p=0.108$, respectively) and actual reduction of the inflammatory and total lesion counts, ($p=0.502$ and $p=0.114$, respectively).

MESSAGE CONFIRMATION

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
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9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 25, 2000. Number of Pages (including cover sheet) - 4
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find clinical and statistical comments on resubmission dated March 3, 2000.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 6, 2000. Number of Pages (including cover sheet) - 4
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find action letter for NDA 50-741.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc: Original NDA 50-741
HFD-540 / Div Files

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 50-741

SEP - 6 2000

Stiefel Laboratories, Inc.
Attention: Mr. William A. Carr, Jr.
Route 145
Oak Hill, NY 12460

Dear Mr. Carr:

Please refer to your new drug application (NDA) dated May 3, 1996, received May 14, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clindoxyl (clindamycin phosphate equivalent to 1% clindamycin and 5% benzoyl peroxide) Gel.

We acknowledge receipt of your submissions dated April 4 and 13, May 1 and 2, June 20 and 29; July 14 (two), and August 8, 2000. Your submission of March 3, 2000, constituted a complete response to our May 14, 1997, and January 30, 1998, action letters.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

A. Chemistry:

1. There is an absence of comparative data that indicate equivalence between the [redacted] clindamycin phosphates. These data should include comparisons of: chemical/physical properties, specifications, impurity profiles and stability data for both drug substances and when each is formulated into Clindoxyl Gel.

2. A minimum 12 months stability data of the Clindoxyl Gel formulated with the [redacted] lindamycin phosphate and aged in the commercial package was not submitted. The ICH-Q1A on Stability Guideline should be followed for the recommended batch sizes on three individual stability batches.

B. Clinical:

The clinical studies submitted (Studies 156 and 158) did not demonstrate that Clindoxyl Gel is superior in effectiveness to the benzoyl peroxide gel alone. We recommend an adequate and well-controlled, additional clinical trial evaluating the safety and efficacy of Clindoxyl Gel versus benzoyl peroxide gel in the treatment of acne vulgaris. Such a study would have to demonstrate clinical superiority of the Clindoxyl Gel over the benzoyl peroxide gel alone.

Although not the basis for the Not Approvable action for this application, the following issues should be addressed in the resubmission:

A. Chemistry:

1. Please submit the justification for the hydrous benzoyl peroxide related substance, specifications since none is included in the USP monograph for this bulk drug.

2. Please provide a post-approval commitment statement to determine the viscosity at release and at each stability time point for the first five production batches.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Olga I. Cintron, R.Ph., Project Manager, at (301) 827-2020.

Sincerely,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

09/06/00 14:01

NO.	MODE	BOX	GROUP
829	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.COD
09/06 14:00	01'02"	518 239 6341	004/004	OK		0000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 6, 2000. Number of Pages (including cover sheet) - 4
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find action letter for NDA 50-741.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 6, 2000. Number of Pages (including cover sheet) - 2
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find comments from Biopharmaceutics regarding the March 3, 2000, submission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc: Original NDA 50-741
HFD-540/DIV FILES

NDA 50-741
Clindoxyl Gel

Comments from Biopharmaceutics. These comments are being provided to the Sponsor for future reference:

1. Because of the importance of validation of the integrity of the skin samples in the Franz cell apparatus, the Sponsor should include in their report all of the results of sample integrity testing, i.e., individual TEWL values.

2. Because of the noted analytical problems cited in this study the Sponsor is reminded that demonstration of adequate analytical validation is crucial to the acceptance of the data presented. In their future NDA submissions the Sponsor should provide the necessary analytical validation data needed to validate the methods used in support of both in vivo and in vitro studies.

MESSAGE CONFIRMATION

09/06/00 14:08

NO.	MODE	BOX	GROUP
831	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 6, 2000. Number of Pages (including cover sheet) - 2
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find comments from Biopharmaceutics regarding the March 3, 2000, submission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

MEMORANDUM OF TELEPHONE CONVERSATION

SEP 5 2000

Date: August 22, 2000.

Drug: Clindoxyl Gel

NDA: 50-741

Sponsor: Ms. Mary Jane Carr, Regulatory Affairs
Stiefel Laboratories

FDA: Dr. Jonathan Wilkin, Director, DDDDP, HFD-540
Olga Cintron, Project Manager, DDDDP, HFD-540

Subject: Action Letter for NDA 50-741

The Sponsor was informed that based on the review of the clinical studies submitted the Agency will be issuing a not approvable letter for this NDA. The Agency recommended that the Sponsor wait for the letter, which will detail all the relevant issues. The Sponsor was encouraged to request a meeting to discuss the not approvable issues that will be specified in the action letter.

Conversation ended cordially.

/S/

Signature, minutes preparer

/S/

Concurrence Chair

cc:

NDA 50-741
HFD-540/Div Files
HFD-540/Cintron

HFD 540
CINTRON

MEMORANDUM OF TELEPHONE CONVERSATION

Date: June 12, 2000.

NDA: 50-741

JUN 19 2000

Drug: Clindoxyl Gel

Sponsor attendees:
Mary Jane Carr, Regulatory Affairs, Stiefel Laboratories

FDA attendees:
Jim Vidra, Ph.D., Chemistry Reviewer, HFD-540
Olga Cintron, Regulatory Project Manager, HFD-540

Background information:

- The CLINDOXYL GEL containing [redacted] clindamycin phosphate (CP) was used in all pivitol trials and will be replaced by [redacted]
- That Stiefel has 18 months of stability data on the [redacted] material and 1 month on the [redacted] material as of 3/00.
- That there is sufficient [redacted] for [redacted] production batches of CLINDOXYL GEL for validation purposes.

Discussion points:

Agency comments and highlights of the conversation:

- Is there sufficient [redacted] to allow for the introduction of CLINDOXYL GEL into the marketplace to allow for additional stability data to be generated on the [redacted] ? If so, how much?
  Sponsor's response: We have supply of [redacted]
- Stiefel should generate 6-9 additional months of stability data on the [redacted] material before converting to the [redacted]
- It was initially recommended by the Agency that Stiefel remove mention of the [redacted] material from their resubmission and, upon eventual NDA Approval with the [redacted] material, submit the new [redacted] supplier with supporting data as an NDA Supplement. The supplement should contain [redacted] name, address, contacts, data comparing the [redacted] material and comparative stability data. However, Stiefel later suggested they would submit

six month accelerated and long-term stability data in July 2000, thus allowing the use of the —— clindamycin phosphate for NDA approval.

- The minimal stability data should include: 6 months accelerated stability + 6-12 months long-term stability (25°C/60%RH)

The Agency would "consider" a '—— . expiry date for the Abbott material based on this stability data.

Action Item:

- Stiefel to submit a minimum of 6 months accelerated and long-term stability data to the Agency in July 2000 or as soon as this stability data becomes available. This data is needed for approval of both CP. If this data is not received at that time, only the material will be approved.

Signature, minutes preparer: /S/

Concurrence, Chair

/S/

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 50-741
HFD-540/Div File
HFD-540/DeCamp
HFD-540/Vidra
HFD-540/Cintron

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 27, 2000. Number of Pages (including cover sheet) - 2
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Steifel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find request for information from the chemist.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc: NDA 50-741
HFD-540/DIV FILES
HFD-540/Vidra

NDA 50-741
Clindoxyl Gel

1. It is unclear in the submitted CMC documents whether [redacted] clindamycin phosphate was the only clindamycin phosphate used in all Phase III pivotal clinical trials and preclinical studies. Please provide a summary table listing which clinical trials and preclinical studies used either the [redacted] or [redacted] clindamycin phosphates by lot or batch numbers and by formulation numbers.

2. An explanation why [redacted] the primary clindamycin phosphate supplier, is being replaced with the [redacted] material.

3. A table listing [redacted] clindamycin phosphate specifications which include specific impurity limits. These data appeared scattered throughout the submission and difficult to identify.

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

04/27/00 18:18

NO.	MODE	BOX	GROUP
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04/27 18:17	00'28"	518 239 6341	002/002	OK		0000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 27, 2000. Number of Pages (including cover sheet) - 2
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Steifel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find request for information from the chemist.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 26, 2000. Number of Pages (including cover sheet) - 1
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find request for information from Biostatistics.

1. Statistical Reports of Studies 156 and 158 in electronic format (on diskette)
2. SAS data sets, data dictionary, and programs for the primary efficacy analysis in Studies 156 and 158 (in SAS, version 6.12).

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc: NDA 50-741
HFD-540/Freidlin
HFD-540/Cintron

MESSAGE CONFIRMATION

04/26/00 13:32

NO.	MODE	BOX	GROUP
005	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
04/26 13:32	00'20"	518 239 6341	001/001	OK		0000

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 26, 2000. Number of Pages (including cover sheet) - 1
TO: Ms. Mary Jane Carr, Regulatory Affairs
COMPANY: Stiefel Labs.
FAX #: 518-239-6341

MESSAGE: Re: NDA 50-741 Clindoxyl Gel

Please find request for information from Biostatistics.

1. Statistical Reports of Studies 156 and 158 in electronic format (on diskette)
2. SAS data sets, data dictionary, and programs for the primary efficacy analysis in Studies 156 and 158 (in SAS, version 6.12).

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager

MEMORANDUM OF TELEPHONE CONVERSATION

Date: February 25, 1997

To: William A. Carr, Jr.
Vice President, Regulatory Affairs
Stiefel Laboratories. Inc.
(518) 239-6901

From: Kevin Darryl White, M.B.A.
Project Manager, HFD-540

Subject: NDA 50-741 Re: Quality Review of Clindamycin Phosphate supplied by

Mr. White inquired about current CMC developments with respect to the quality of Clindamycin Phosphate supplied by for NDA 50-741 Clindoxyl Gel. Mr. Carr indicated that a FDA inspection of bulk clindamycin phosphate shipped from facility was recently completed. He stated that the quality of the clindamycin phosphate was judged to be "satisfactory." The investigator issued a FDA-483 with a single observation specific to an incorrect moisture calculation performed at Stiefel Research. He added that the incorrect calculation in no way impacted the satisfactory quality of clindamycin phosphate.

Mr. Carr also indicated that Stiefel has produced a pilot batch of Clindoxyl using clindamycin phosphate produced by the . He asserted that stability results should be equivalent to that obtained with material.

cc:
Orig NDA 50-741
HFD-540
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Mokhtari-Rejali
HFD-540/SUPV PROJ MGR/Kozma-Fornaro
HFD-540/PROJ MGR/White

ATTACHMENTS

TELEPHONE MEMO

STIEFEL LABORATORIES, INC.
OAK HILL, NY 12460
TEL.: (518)239-6901, FAX: (518)239-8402

*** FAX ***

DATE: February 25, 1997

ATTENTION: Mr. Kevin Darryl White, MBA

COMPANY: Food and Drug Administration

FAX NO.: 301-827-2075

FROM: William A. Carr, Jr.
Vice President

TOTAL PAGES:

Dear Mr. White:

I am writing to briefly and informally summarize our recent discussion concerning Clindamycin Phosphate, USP produced by the —

As discussed, we have just completed a lengthy and exhaustive FDA inspection of the several lots of Clindamycin Phosphate shipped to us from — facility.

At the conclusion of the inspection the FDA inspector issued a FD-483 with a single observation specific to an incorrect moisture calculation performed at Stiefel Research. The incorrect calculation in no way impacted the satisfactory quality of Clindamycin Phosphate.

We understand that FDA is evaluating several of the antibiotics produced at including of course Clindamycin Phosphate. We further understand that our entirely satisfactory Clindamycin Phosphate test results are typical of the results that FDA has encountered nationwide.

It may also be worth noting that a significant body of Clindoxyl data (tox, clinical, stability) submitted to FDA was developed with active ingredient produced at — Plant - a facility that was apparently satisfactory in all respects.

Please also note that we have just produced a substantial pilot batch of Clindoxyl using Clindamycin Phosphate produced by the — We anticipate that stability results for subject product (recognizing that Clindamycin Phosphate is fully solubilized) will be equivalent to that obtained with — material.

Please feel free to call at any time.

Best Regards,

Stiefel Laboratories, Inc.
Oak Hill, NY 12460
Tel.: (518)239-6901, FAX: (518)239-8402

* * * FAX * * *

February 27, 1997

Attention: Mr. Kevin Darryl White, M.B.A.
Company: U.S. Food and Drug Administration
FAX No.: 301-827-2075

From: William A. Carr, Jr.
Vice President

Total Pages: 4 - including cover

Message:

As requested, please find following form FDA 483 issued by FDA Investigator Nancy Saxenian on February 19, 1997. Referenced inspection is specific to FDA's quality review of Clindamycin Phosphate, USP supplied by [redacted], a wholly owned subsidiary of [redacted].

Also following, please find our response, dated February 25, 1997, to referenced form FDA 483.

If additional information is required, please contact me at (518) 239-6901.

Sincerely,

Research in Dermatology

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

February 25, 1997

Acting Director
U.S. Food and Drug Administration
599 Delaware Avenue
Buffalo, NY 14202

Dear Sir:

U.S Food and Drug Administration Investigator Nancy A. Saxenian audited the Oak Hill, New York facilities of Stiefel Laboratories, Inc. from 7 February to 19 February 1997.

Subject audit was directly associated with the active raw material Clindamycin Phosphate manufactured by [redacted]

At the conclusion of the inspection FDA issued Form FDA 483 with one (1) observation.

Our response follows.

FDA Observation

1. Failure to perform an adequate review of analytical batch records for accuracy on the active raw material, Clindamycin Phosphate.

   For example - In 8 out 10 records reviewed, the value for Assay % (Anhydrous Basis) was incorrectly calculated and incorrectly documented on the Certificate of Analysis.

   The calculation was based on the Loss on Drying value, but should have been based on the % water value.

Batch records reviewed cover Raw Material Lot #s B0048R, B0065R, B0294R, & B0147R.

CORPORATE OFFICES 255 ALHAMBRA CIRCLE, SUITE 1000, CORAL GABLES, FLORIDA 33134
ATLANTA, GEORGIA • RENO, NEVADA • BUENOS AIRES, ARGENTINA • EPPING, AUSTRALIA • BRUXELLES, BELGIUM • [illegible]

Stiefel Response

The observation is correct. We have discussed and investigated the oversight with appropriate personnel in detail.

The error has been linked to one specific technician in our Quality Control Laboratory (the individual performing the % water testing) inadvertently reporting to the technician in our Analytical Laboratory [the individual performing the Assay % (as is basis) and calculating the Assay % (anhydrous basis)] "Dec LOD" values instead of "% Water" values.

In order to prevent similar occurrences in the immediate future, an internal memorandum has been distributed instructing laboratory personnel to utilize only the approved results residing in the LIMS. For the longer term an updated version of the appropriate SOP is under committee review. This SOP will instruct technicians to obtain laboratory results needed from other individuals or departments via the LIMS. Only values that have gone through our normal review and approval procedures can be accessed as results on the LIMS. The updated SOP should be issued within a month.

We have corrected all those Certificates of Analysis and supportive laboratory data related to this observation. FDA investigator Nancy A. Saxenian was supplied copies of corrected Certificates of Analysis relative to the inspection prior to the conclusion of the audit.

It should be noted that in all cases where this situation needed to be corrected, the corrected results actually yielded results that demonstrated the materials to be of even higher quality.

Sincerely,
STIEFEL LABORATORIES, Inc.

Randall S. Hayward

Randall S. Hayward
Assistant Director
Regulatory Affairs and
Quality Assurance

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 599 Delaware Ave. Buffalo, NY 14202 (716) 551-4461	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: William A. Carr, Jr.	PERIOD OF INSPECTION 2-7-19-97	C. F. NUMBER 1314819
TITLE OF INDIVIDUAL Vice President	TYPE ESTABLISHMENT INSPECTED Drug Mfr.	
FIRM NAME Stiefel Laboratories Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS ~~Hwy~~ Route 145	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Oak Hill, NY 12460	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM (I) ~~(WE)~~ OBSERVED:

(1.) Failure to perform an adequate review of analytical batch records for accuracy on the active raw material, Clindamycin Phosphate.

For example - In * 8 out 10 records reviewed, the value for Assay % (Anhydrous Basis) was incorrectly calculated and incorrectly documented on the Certificate of Analysis.
The calculation was based on the Loss on Drying value, but should have been based on the % Water value.

* Batch records reviewed cover Raw Material Lot #s B0048R, B0065R, B0294R + B0147R.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	EMPLOYEE(S) NAME AND TITLE (Print or Type) Investigator Nancy A. Sikeman	DATE ISSUED 2/19/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: February 28, 1997

To: NDA 50-741 file

From: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540 /S/

Subject: [redacted], as a supplier of clindamycin phosphate, USP

Through: Jonathan Wilkin, M.D.
Director, DTDP, HFD-540 /S/ 2/28/97

I called the applicant, Stiefel Laboratories, Inc. (NDA 50-741) (along with K. D. White) on February 4, 1997, and spoke to Bill Carr, Vice-President. Our purpose was to advise that they should discuss Janet Woodcock's letter of December 12, 1996, with their contact at [redacted] This letter raises regulatory problems that may affect this firm's acceptability as a supplier of clindamycin phosphate. We suggested that they may want to consider the possibility of withdrawing their application (NDA 50-741) pending resolution of [redacted] problems and/or identifying a new supplier. We also advised Mr. Carr that problems at [redacted] are sufficiently severe that the validity of the clinical trials for Clindoxyl may be uncertain; our review is continuing at present, pending further discussions with the Office of Compliance.

cc: Orig: NDA 50-741
HFD-540
HFD-540/Wilkin
HFD-540/Rejali
HFD-540/White
HFD-540/Fornaro
HFD-540/Cook

MEMORANDUM OF A TELEPHONE CONVERSATION

April 8, 1997

Between: William A. Carr, Regulatory Affairs
Mary Jean Pravera &
Randy Hayward
(518)-239-6901 x309

And: Nahid Mokhtari-Rejali, Ph.D.
HFD-560

Subject: Clarification on the clindamycin phosphate used in the clinical trials

I called Bill, Regulatory Affairs, to clarify the lots numbers used in the clinical trails. Bill was transferred my call to talk to Randy Hayward and Mary Jean Praver, Regulatory Affairs. I told them that per February 25, 1997, Stiefel has noted "Significant data (tox, clinical, stability) submitted to FDA was developed with Clindamycin produced at —— plant - a facility that was apparently satisfactory." This statement is very confusing, and the —— facility was not identified in the original NDA. In addition, according to the recent inspection of February 1997, the lots reviewed for quality review of clindamycin were different from the lots used in the clinical trial.

During this conversation, Mary Jean said that the BUF-DO inspection of February 1997, only focused on the quality of recent lots of clindamycin manufactured (1995) at the switched facility of —— facility with GMP problems. The clindamycin phosphate (lots 94192 & 91779) used in the clinical batches were produced at —— facility on 1991 & 1994, respectively. This facility, —— has been found to satisfactory from GMP stand point during the previous inspection.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: May 12, 1997

To: Jonathan Wilkin, M[illegible] /s/
Director, DDDDP, H[illegible]-540

From: Wilson H. De Camp, Ph.D.
Chemistry Team Leader, HFD-830 WDS 5/12/97

Subject: NDA 50-741, Clindoxyl Gel, Stiefel Laboratories: other recalls of clindamycin phosphate products

Through: Chi-Wan Chen, Ph.D.
Director, Division of New Drug Chemistry III CWC 5/12/97

Please note the attached fax transmissions from Nick Buhay, HFD-325. The 5/1 transmission is a review by Mary Fanning, M.D., dated January 23, 1997, of the health hazards associated with bulk drugs manufactured by ———. This review recommends a class II recall, even though no serious consequences have been detected. The second fax, initially dated 5/2, and resent with additions on 5/12, presents the status of all the dosage form recalls related to the ——— bulk drug recall.

It is clear that all firms with marketed clindamycin phosphate products manufactured from ——— bulk were subject to recall. Therefore, the quality of the investigational batches of Stiefel's Clindoxyl Gel is equally suspect.

This conclusion adds support to the chemistry recommendation of a non-approval action for this application, as stated in Dr. Rejali's review that I concurred with on May 9, 1997.

Attachments (2)
cc: orig: NDA 50-741
HFD-540/NDA 50-741
HFD-540/Walker
HFD-540/White
HFD-560/Mokhtari-Rejali
HFD-830/Chen

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: May 12, 1997

To: Jonathan Wilkin, M.D.
Director, DDDDP, HFD-540

From: Wilson H. De Camp, Ph.D.
Chemistry Team Leader, HFD-830 WDC 5/12/97

Subject: NDA 50-741, Clindoxyl Gel, Stiefel Laboratories: other recalls of clindamycin phosphate products

Through: Chi-Wan Chen, Ph.D.
Director, Division of New Drug Chemistry III CWC 5/12/97

Please note the attached fax transmissions from Nick Buhay, HFD-325. The 5/1 transmission is a review by Mary Fanning, M.D., dated January 23, 1997, of the health hazards associated with bulk drugs manufactured by [redacted] This review recommends a class II recall, even though no serious consequences have been detected. The second fax, initially dated 5/2, and resent with additions on 5/12, presents the status of all the dosage form recalls related to the [redacted] bulk drug recall.

It is clear that all firms with marketed clindamycin phosphate products manufactured from [redacted] bulk were subject to recall. Therefore, the quality of the investigational batches of Stiefel's Clindoxyl Gel is equally suspect.

This conclusion adds support to the chemistry recommendation of a non-approval action for this application, as stated in Dr. Rejali's review that I concurred with on May 9, 1997.

Attachments (2)
cc: orig: NDA 50-741
HFD-540/NDA 50-741
HFD-540/Walker
HFD-540/White
HFD-560/Mokhtari-Rejali
HFD-830/Chen

FAX TRANSMISSION

DIVISION OF MANUFACTURING AND PRODUCT QUALITY

TO: Tony DeCamp DATE: 5/1

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MEMORANDUM

Date: January 23, 1997

To: Doug Ellsworth
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Through: Doug Sporn /S/ 1/23/97
Director, Office of Generic Drugs
HFD-600

From: Mary Fanning, MD, PhD /S/ 1/23/97
Associate Director for Medical Affairs
Office of Generic Drugs

Subject: Health hazard evaluation, ———

I was asked to do a Health hazard evaluation for three generic antibiotic products which received their bulk drug substance from ——. I have reviewed all the relevant information provided and my Health hazard evaluation report is attached.

APPEARS THIS WAY
ON ORIGINAL

HEALTH HAZARD EVALUATION

Generic Cefaclor, Clindamycin and Minocycline Bulk Drug Substance

Statement of Problem: Bulk drug preparation for generic Cefaclor (Lederle, Zenith), Clindamycin Phosphate (Biocraft, Danbury), and Minocycline (Biocraft, Danbury) has been carried out by [redacted] using a manufacturing process which differs from the approved process. Production of new bulk substance by [redacted] has been halted.

An evaluation of the need to withdraw all existing and affected drug from the marketplace has been requested by the Office of Compliance. In reaching a decision, the primary concern is that the faulty manufacturing process used by [redacted] to prepare the three bulk drug substances might have led to impurities or differences (major or minor) in the metabolites, which might represent an important safety or efficacy risk.

This Hazard Evaluation will address this issue and reach a conclusion. Rationale for such a decision will be based on the potential "hazard" to the public health of the American population. This will be estimated by reviewing information available to CDER from prior exposure to each of these generic medications and the Reference Listed Drug (RLD), as well as evaluation of documentation provided by [redacted] obtained in the course of their investigation of [redacted] manufacturing process. This "hazard" would occur from further exposure to the products currently on the market, and would manifest as decreased efficacy/potency or increased adverse events due to potential impurites in the products.

The hazard evaluation has been done by analysis of relevant information in the following three categories:

1. Alteration of chemical composition of the bulk drug substance.

2. Assessment of potential harm due to altered drug effect (efficacy risk).

3. Assessment of safety (both theoretical and observed).

I. Assessment of alterations in bulk substance due to altered manufacturing processes.

On review of the chemistry information provided, there is no evidence of additional impurities in the bulk drug substance processed by ——— . This is based on comparisons of multiple batches of drug substance, prepared between 1992 and 1996, to the batches prepared using the approved manufacturing process under the careful scrutiny of ——— 1 mechanical engineers. During their investigation, ——— identified several to numerous areas of manufacturing process discrepancy from the approved process for each drug substance under scrutiny in this report. The faulty manufacturing procedures, although in urgent need of correction, have not, to date, led to an observed basis for risk of unusual adverse events. However, since we cannot confirm the actual synthetic route and methods of manufacture employed by ——— , the tests and specifications for trace impurities, for example, may be inadequate. This information has also been reviewed in detail by the Chemistry division and they concur with this conclusion.

II. Assessment of potential harm due to altered drug effect (efficacy risk).

This type of assessment cannot be made in a passive reporting system which is the majority of the post-marketing information available. Although there are no reports of drug failure in a setting where the drug should work (appropiate clinical and microbiologic setting), these events would be rare even if it was occuring and should be predicted by the results of microbiology testing to identify the causative agent and its susceptiblity profile. This is a standard way of monitoring treatment of infections. In addition, susceptibility testing of organisms as well as the listing of organisms which are susceptible to the drug are routinely inserted into the drug labelling and can be found in the Physician's Desk Reference (PDR).

If efficacy were indeed affected, an analysis of the potential risk would be best carried out by evaluating the potential impact of drug failure on the individuals treated for the approved indications. This would be dependent on the severity of illness and the availability of alternative therapy should the patient fail to respond to one of these medications.

A. CEFACLOR

Indications (as listed in the Physician's Desk Reference [PDR]):

Otitis Media caused by *S. pneumonia, Staphylocci and* S. *pyogenes.*

Lower respiratory tract infections including pneumonia caused by *S. pneumonia, H. influenza, and S.pyogenes.*

Upper respiratory tract infections including tonsillitis and pharyngitis caused by *S. Pyogenes.*

Urinary tract infection including pyelonephritis and cystitis caused by *E. Coli, P. mirabilis, Klebsiella sp.* and coagulase-negative staphylococci.

Skin and skin structures infections caused by *Staphylococcus aureus* and *S. pyogenes.*

B. CLINDAMYCIN

Indications (PDR):

"Clindamycin is indicated in the treatment of serious infections caused by anaerobic bacteria. Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci and staphylococci. It should be reserved for penicillin-allergic patients or other patients for whom, in the judgement of the physician, a penicillin is inappropriate."

C. MINOCYCLINE

Indications:

Treatment of infections due to Rickettsia, Mycoplasma, agents of Psittacosis, Ornithosis, Lymphogranuloma venerium, Granuloma inguinale, and *Borrelia recurrentis* (which causes relapsing fever), and those due to the following gram-negative microorganisms: *Haemophilus ducreyi,*

Yersinia pestis, Francisella tularensis, Bartonella bacilliformis, Bacteroides species, Vibrio comma, Vibrio fetus and *Brucella species.*

This drug can be used in the treatment of a variety of additional infections, but susceptibility testing is recommended to ensure that the organism will respond to the treatment. (Synthesis of PDR listing)

All of the medications under consideration are orally administered. Therefore, the patients receiving these treatments are not acutely ill, but have mild to moderate infections. This allows for the time required to get a culture, confirming the organism causing the infection, and obtain culture and sensitivity results which predict clinical outcome in most of the patients treated for approved indications.

Although Minocycline is used in the treatment of a variety of rare illnesses, as listed above in section C, alternative medication is available for these indications. In fact, there are alternative treatments, if the patient is not responding, for the listed indications of the three drugs; Cefaclor, Clindamycin and Minocycline.

III. Assessment of safety

A. Process used for safety/hazard evaluation

A safety assessment was done by evaluating the observed risk of adverse events due to impurities which might be present in the products which received their bulk drug substance from [redacted]. As indicated under section I, there were no observed new chemical components in the bulk drug substance(s) of the products currently on the market which differed from the batches prepared under the direction of [redacted] personnel using the approved manufacturing process (tested concurrently) for each medication. If these were present, there would be a reasonable concern that toxicities might occur, which would either be unexpected adverse reactions or present as an increase in the allergic/anaphylactic/serum-sickness reactions which occur with the reference listed drugs for all the anti-infectives under consideration.

Despite lack of evidence (chemistry) that there might be a safety risk associated with leaving these drugs on the market, a review of the clinical information available will allow a more comprehensive evaluation of the potential hazard. This would be based on the possibility that other events may have occured during the manufacturing process which have produced components that are undetectable by the testing carried out thus far but are clinically important.

In order to evaluate the safety risk, the Spontaneous Reporting System (SRS) was used to look at comparative safety profiles of the reference listed drugs and the generic drugs in question. This passive reporting system is an imperfect tool to establish the true event rate. However, the information obtained through this system allows comparison among all the drugs in question, because the methodology used to collect the information should have no reporting bias in favor of one drug versus another.

A hazard evaluation in this context will not depend on incidence of the events (a figure difficult to obtain because of lack of the denominator, ie. the number of courses of medication prescribed). Instead, it is the overall population burden of these events and the appearance of adverse drug effect (ADE)patterns, including changing trends, that do not match the innovator drug that needs to be considered. While the passive reporting system for adverse drug events underestimates the true number of events, it provides a comparison between drugs (RLD vs. Generic) allowing an analysis of relative safety and risk.

B. Information used in completing the hazard evaluation

1. Observed population burden of ADEs

The overall number of serious ADEs, the number of these that led to death, and the number of years of reporting were obtained for the RLD and generic versions of Cefaclor, Clindamycin and Minocycline. The duration (and extent)of exposure to each drug in the market place is linked to the overall significance of the gross numbers received. The following table identifies, for each of the drugs in question, the approval dates by month and year, the duration of passive reporting and the numbers of serious ADEs and deaths.

TABLE 1

Approval dates, Duration of ADE reporting, Serious ADEs and Deaths reported

CEFACLOR	Approval Date	Number of Years of Reporting	Serious ADEs	Deaths
Lilly	- - -	18 years	2205	126
Lederle	4/95	1.5 years	0	0
Zenith	4/95	1.67 years	2	1
CLINDAMYCIN				
Upjohn	4/88	27 years	347	174
Biocraft	9/89	7.25 years	2	0
Danbury	7/91	5.5 years	0	0
	Approval Date	Number of Years of Reporting	Number of Serious ADEs	Number of Deaths
MINOCYCLINE				
Lederle	---	24 years	232	17
Biocraft	3/92/	4.75 years	1	0
Danbury	12/92	4 years	2	0

2. Major Adverse Drug Reactions listed in the PDR

a. Cefaclor

Hypersensitivity reactions (1.5%), skin rash (1%), pruritis, urticaria (< 0.05%), anaphylaxis, Stevens-Johnson syndrome, rarely. Anaphylaxis more common in individuals with a history of penicillin allergy.

Serum-sickness like reactions, probably due to

hypersensitivity, are most often associated with a repeat course of cefaclor. Incidence in clinical trials ranged from 0.024% to 0.5% in adults and 0.055% in children. The label also lists a rate of 0.003% in spontaneous event reports, presumably, post-marketing.

Gastrointestinal symptons (2.5%).

Other - miscellaneous.

b. Clindamycin

Gastrointestinal, including diarrhea, colitis and pseudo-membranous colitis.

Hypersensitivity reactions, including rashes (common), erythema multiforme and Stevens-Johnson syndrome rarely, and a few reported cases of anaphylactoid reactions.

Other - miscellaneous.

c. Minocycline

Gastrointestinal.

Rash, photosensitivity, erythema multiforme and rarely Stevens-Johnson syndrome.

Hypersensitivity reactions including urticaria, anaphylaxis, and anaphylactoid reactions.

Other - miscellaneous.

3. Most frequent ADEs/death observed in the Spontaneous Reporting System for the innovator drug during the reporting period.

a. Cefaclor:

Rash/death (491/12)
Serum-sickness/death (463/1)
Urticaria/death (362/1)
Anaphylaxis/death (308/13)

b. Clindamycin:

Colitis/death (124/82)

c. Minocycline:

Fever/death (23/1)
Rash/death (17/2)

4. Serious ADEs and associated deaths during reporting period

a. Cefaclor - Reporting period for innovator drug beginning 1979

Table 2a

Cefaclor	Lilly	Lederle	Zenith
# serious ADEs reported	2205	0	2
# associated deaths	126	0	1

b. Clindamycin - reporting period for innovator drug beginning 1970

Table 2b

Clindamycin	Upjohn	Biocraft	Danbury
# serious ADEs reported	347	2	0
# associated deaths	174	0	0

c. Minocycline - reporting period for innovator beginning 1972

Table 2c

Minocycline	Lederle	Biocraft	Danbury
# serious ADEs	232	1	2
# associated deaths	17	0	0

5. Most frequent ADEs and associated deaths reported

a. Cefaclor

Cefaclor	Lilly	Lederle	Zenith
Total serious ADEs/deaths since approval	2205/126	0	2/1
Allergic reaction	105/11	0	0
Anaphylaxis	308/13	0	1/1
Facial edema	112/0	0	0
Serious serum sickness	463/1	0/0	1/1
Dyspnea	172/5	0	0
Edema, larynx	27/2	0	0
Edema, lung	6/3	0	0
Stridor	5/1	0	0
Pruritis	97/0	0	0
Rash	491/12	0	0
Urticaria	362/1	0	0

b. Clindamycin

Clindamycin	Upjohn	Biocraft	Danbury
Total serious ADEs/deaths since approval	347/174	2/0	0
Allergic reaction	4/0	1/0	0
Anaphylaxis	4/1	1/0	0
Facial edema	2/0	0	0
Serious serum sickness	1/1	0	0
Dyspnea	3/0	0	0
Edema, larynx	0/0	0	0
Edema, lung	1/0	0	0
Stridor	0	0	0
Pruritis	7/2	0	0
Rash	29/5	0	0
Urticaria	3/1	0	0
Colitis	124/82	0	0
Diarrhea	44/11	0	0

c. Minbcycline

Minocycline	Lederle	Biocraft	Danbury
Total serious ADEs/deaths since approval	232/17	0	0
Allergic reaction	11/0	0	0

Anaphylaxis	13/0	0	0
Facial edema	1/0	0	0
Serious serum sickness	9/0	0	0
Dyspnea	11/1	0	0
Edema, larynx	1/0	0	0
Edema, lung	2/0	0	0
Stridor	1/0	0	0
Pruritis	12/0	0	0
Rash	17/2	1/0	0
Somnolence	1/0	0	1*
Confusion	2/0	0	*
Dizziness	2/0	0	*
Urticaria	16/0	0	0
Fever	23/1	0	0
Other: CVA	0	0	1/0

6. Number of reported innovator ADEs and deaths in the time period the generic product(s) have been on the market

a. Cefaclor

Table 3a

Time period: 1.66 years	Total serious ADEs	Hospitalization	Death
Lilly	236	210	12
Lederle	0	0	0
Zenith	2	0	1

b. Clindamycin

Table 3b

Time period: 7.25 years	Total serious ADEs	Hospitalization	Death
Upjohn	110	83	20
Biocraft	2	1	0
Time period: 5.5 years			
Upjohn	135	103	29
Danbury	0	0	0

c. Minocycline

Table 3c

Time period: 4.75 years	Total serious ADEs	Hospitalization	Death
Lederle	81	65	7
Biocraft	0	0	0
Time period: 4 years			
Lederle	64	50	7
Danbury	2*	1*	0

*1= CVA not attributed to medication

7. Description of ADEs reported for the generic drug(s)

a. Cefaclor - Zenith (2 ADEs reported)

i.Cefaclor, 250 mg. three times daily, was given to a 41 year old man with no known history of allergies, for treatment of upper respiratory infection. Prior treatment with a cephalosporin had been uneventful. Seven days into therapy he experienced itching, followed

shortly by hives and then anaphylaxis. A subsequent diagnosis of serum-sickness, 48 hours later, required ongoing treatment with Prednisone and had not resolved at the time of reporting, 7 days later.

ii.Cefaclor, 250 mg three times a day, was prescribed for treatment of sinusitis for a 36 year old man. He had taken cefaclor 8 months previously and had also taken several of the tablets remaining prior to obtaining the prescription. After the first dose, he developed acute anaphylaxis and died before the ambulance arrived.

b. Clindamycin - Biocraft (2)

i.A 48 year old man received Clindamycin therapy (300mg. Q6H) for a tooth abscess. He had a history of previous allergy to penicillin, atropine and codeine. On the first day of therapy he developed symptoms of anaphylaxis with a skin rash. He required hospitalization.

ii.A 58 year old man developed stomach and chest pain after 2-3 days of Clindamycin 150mg. Q6H treatment for a tooth abscess. EKG was normal and the patient had no history of allergies. He remained in hospital overnight and his symptoms resolved on discontinuing the drug.

c. Minocycline (Biocraft - 1, Danbury - 2)

i.Biocraft -

a. A 16 year old female took one dose of Minocycline, 100mg. prescribed at HS for acne therapy, and developed dyspnea, pharyngitis, rhinitis and rash. She had no history of allergies and her symptoms resolved following hospitalization and discontinuation of Minocycline.

ii.Danbury

a. A 37 year old female who received Minocycline 100mg. for treatment of a skin allergy, developed disabling

symptoms of confusion, somnolence and dizziness after her second dose. These symptoms resolved on discontinuing Minocycline.

b. A 77 year old man developed a stroke 45 minutes after taking one dose of Minocycline 100mg. for treatment of rosacea. No relationship was found between onset of his CVA and Minocycline.

7. Report of a cluster of cases

A report was submitted from the Raleigh, North Carolina FDA field office and received January 13,1997 for incorporation into this evaluation. It describes a cluster of cases of serious allergic response, associated with Zenith Cefaclor, which occured between 4/1/95 and 3/96. These 9 patients were dispensed medication by a pharmacist whose own reaction is listed under the cefaclor case descriptions (p.13). He subsequently phoned all the patients to whom he had dispensed this medication during this interval to find out whether they had had similar reactions.

This pharmacist first ordered Zenith's cefaclor in December,1995 following a promotional campaign in the region and the offer of a very competitive price. Proir to that he had dispensed the Mylan cefaclor product. The cases he summarized for the field office ranged in age from 1 to 89. All patients were given Cefaclor either for upper respiratory infection or ear infection. The symptoms experienced were similar among all the cases and included urticaria, hives, shortness of breath and anaphylaxis. However, not all symptoms were experienced by each individual and there was a range of severity of the symptomatology. Four of these cases had received cefaclor previously and one was allergic to Penicillin. No deaths or hospitalizations occured.

The pharmacist sent a drug sample to the manufacturer who reported that the drug was "pretty much within limits", and would test it further. The manufacturer would not release the analytical report to the pharmacist. The Raleigh office tested the drug samples

they received and concluded that the ID, and potency were within normal limits and that no impurities or trace contaminants were found. The local supplier of this drug also supplied —— other stores and had received no complaints or reports from their other clients.

This cluster is unusual in that pharmacists do not routinely follow-up with their patients in this way. This occured, most likely, because of the pharmacist's own experience and his desire to know if it was an isolated event. Nonetheless, he concluded that the frequency and severity of the adverse events was completely out of keeping with any pattern of adverse events he had seen in his practice and specifically in comparison to the RLD and other generic form of Cefaclor he had dispensed. This observed cluster raises cause for concern that the adverse event rates may be seriously underreported by the passive reporting system discussed previously.

IV. Conclusion

The bulk drug substance supplied by ——— to several generic drug companies has not been found to contain impurities which are not present in the RLD. However, the testing done thus far did not provide full assurance that the potency of the drug was unaffected or that there were no new chemical components which might lead to serious safety concerns.

The way in which these drugs are used in medical practice ensures that there is a timely change in therapy for patients who are not responding to the treatment. Problems in drug potency would, therefore, only lead to temporary morbidity, until a drug that could resolve the symptoms experienced was initiated. The potency of these generic products, which in part determines their bioequivalence to the innovator product, cannot be adequately evaluated through the information available.

The serious adverse event reporting for the generics of all three anti-microbial agents is notably low, both on the face of it and in comparison to innovator drug reports. This is true over their full reporting time as well as over the same reporting period as the generic analog. None of the reported cases of the two generic versions of each product had events which were out of keeping

with the known adverse events previously reported for these agents (RLD). The cluster of cases reported from North Carolina, however, suggests that the true adverse event rates may be much higher than our reporting system has, to date, detected. The greater proportion of serious adverse events, and their consequences, seen with all three innovator products is most likely due to a greater exposure of the public to these agents.

The Food and Drug Administration assesses the production of a pharmaceutical product by examining the results of studies performed on both a demonstration batch of the formulation as well as on production batches. This demonstration batch is termed the bioequivalence batch. The tests applied to the bioquivalence batch include assay, content uniformity, stability, in vitro dissolution and in vivo bioequivalence. Tests on production batches can include all of these, but usually do not include an in vivo assessment of bioequivalnce. Lack of certainty based on misrepresentations and discrepancies relative to data for the production of either the bioequivalence batch or the production batches for a specific drug can lead to a situation in which the quality, purity, potency and consistency of the affectd drug product cannot be assured by the Food and Drug Administration.

Although no serious consequences have been detected in this Health Hazard Evaluation, the quality, purity, potency and consistency of the generic products which are under scrutiny due to the provision of their bulk drug substance by ——— and which remain on the market, cannot be assured by the Food and Drug Administration. Therefore a Class II recall is recommended.

/S/ 1/23/97

Mary M. Fanning
Associate Director of Medical Affairs
Office of Generic Drug Products

APPEARS THIS WAY
ON ORIGINAL

cc. Janet Woodcock
Stephanie Gray
Roger Williams
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HFD-600