Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 10, 2002

NDA # 50-741

NAME OF DRUG: Clindoxyl Gel
(Clindamycin Phosphate 1% and Benzoyl Peroxide 5% Gel)

NDA HOLDER: Stiefel Laboratories, Inc

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540), for a re-review of the proprietary name "Clindoxyl," regarding potential name confusion with other proprietary drug names. This name was reviewed in April 2000 (OPDRA consult # 00-0123) and was found acceptable. The container labels, carton labeling, and package insert labeling were also reviewed in the April 2000 consult and DMETS provided labeling comments. Container labels, carton labeling, and package insert labeling were also submitted for re-review and comment at this time.

PRODUCT INFORMATION

Clindoxyl is a topical gel containing clindamycin 1% as the phosphate and benzoyl peroxide 5%. Clindamycin is an antibiotic and benzoyl peroxide is an antibacterial and keratolytic agent. Clindoxyl Gel is indicated for the topical treatment of inflammatory lesions of acne vulgaris. The usual dosage is one application in the evening or as directed by a physician to affected areas. Clindoxyl Gel is supplied in a 45-gram tube.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Clindoxyl" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[4] The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. Prescription analysis studies were conducted during the previous OPDRA consult and were not repeated for this review.

A. EXPERT PANEL DISCUSSION AND REFERENCE SEARCH

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Clindoxyl." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. It should be noted that in the past DMETS did not have the databases needed to search for distributor sound-alike and/or look-alike names. Since these names do not have to be approved by the FDA prior to their use, generally they cannot be identified in searches of the standard databases (e.g., Orange Book, COMIS, Facts and Comparison, etc). DMETS recently obtained access to the Saegis Pharma In-Use database. Thus, DMETS now has access to data pertaining to sound-alike/look-alike names from distributors. The Saegis Pharma In-Use database also aids in the detection of phonetic similarities between names and unapproved drug products. Using this database, the Expert Panel identified three proprietary names that were not identified in the first review conducted by DMETS. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns about the name Clindoxyl Topical Gel with regard to promotional claims.

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Clindoxyl	**Clindamycin 1% and Benzoyl Peroxide 5% Topical Gel**	**One application at bedtime**	**N/A**
Clindagel	Clindamycin Phosphate Gel 1%	One application daily	LA/SA
Doxil	Doxorubicin HCl Lipsome Injection	50 mg/m ^{2} (doxorubicin HCl equivalent) intravenously at rate of 1 mg/min	SA
Levoxyl	Levothyroxine Sodium Tablets 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg	Individualized based on the patient's age, body weight, cardiovascular status, concomitant medical conditions and medications, and the specific nature of the condition being treated	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name *Clindoxyl*, the primary concerns raised were related to three sound-alike and/or look-alike names: *Clindagel, Doxil* and *Levoxyl*. Of the three products identified, the Expert Panel felt that *Clindagel* had the greatest potential for confusion with Clindoxyl.

Clindagel was identified as a potential look- and sound-alike product that may have potential for confusion with *Clindoxyl*. The names begin with the same prefix "Clind." Additionally, following the prefix each have letters that are similar when scripted 'a' vs 'o' and 'gel' vs 'yl.' When scripted both names look very similar. Moreover, both products contain clindamycin 1% as an active ingredient and are formulated as a gel. They share the same indication of use—the treatment of acne vulgaris. Neither product will require a dosage strength when prescribed because they are only available in a single strength. Furthermore the directions for use may be the same (e.g., Apply once daily to affected areas), although the proposed labeling for *Clindagel* indicates that it should be administered in the evening. *Clindagel* is available in two different size bottles (77 grams and 42 grams) whereas *Clindoxyl* will be dispensed as a 45-gram tube. This difference will not be significant enough to prevent the potential for medication errors because most healthcare providers will prescribe a tube or bottle quantity instead of the appropriate grams. Moreover, it is likely that these products will be stored in close proximity to each other in pharmacy departments. These similarities increase the risk that these products may have an increased potential for confusion.

Clindoxyl Clindagel

Patients who mistakenly receive *Clindagel* instead of *Clindoxyl* should not experience major adverse events since clindamycin is the only active ingredient in *Clindagel* and is also one of the two *Clindoxyl* active ingredients. However, these patients would not have the added benefit of receiving the benzoyl peroxide component of *Clindoxyl*. Although the same experience may be expected from patients who receive *Clindoxyl* instead of *Clindagel*, if a patient is allergic or sensitive to benzoyl peroxide they may experience an adverse event.

Doxil may sound like *Clindoxyl* when presented as a verbal prescription. However, there are several distinguishing factors between *Clindoxyl* and *Doxil* that may decrease the potential risk of medication errors. *Doxil* is a chemotherapeutic agent administered intravenously whereas *Clindoxyl* is topical agent. Prescriptions for *Doxil* will require a dosage amount while prescriptions for *Clindoxyl* will not. Although *Clindoxyl* may be ordered on an inpatient and outpatient basis it is unlikely that *Doxil* will be ordered in a retail setting. Additionally, *Doxil* will usually be prescribed concomitantly with other agents (e.g., corticosteroids, anti-emetics, or other chemotherapeutic agents) which may help to decrease the potential risk of a medication error.

Levoxyl and *Clindoxyl* may look alike when scripted. If the 'c' in *Clindoxyl* is not clearly scripted, then the 'c' may appear to be a part of the beginning tail of the 'l' and thus the name would begin with 'l.' However, there are distinguishing factors between *Clindoxyl* and *Levoxyl* that may decrease the potential risk of medication errors. *Levoxyl* is an oral tablet and *Clindoxyl* is a topical gel. These two products have very different indications of use. *Levoxyl* is indicated for hypothyroidism and pituitary TSH suppression, whereas *Clindoxyl* is indicated for the treatment of acne. The dosages for *Levoxyl* range between 25 mcg and 300 mcg. Whereas, *Clindoxyl* is a combination product with only one proposed dose. As noted above, prescriptions for *Levoxyl* will require a strength. The differences such as dosage, dosage forms, indication, and directions of use between *Levoxyl* and *Clindoxyl* would decrease the potential risk of medication errors.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Clindoxyl, DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified areas of possible improvement, which might minimize potential user error.

GENERAL COMMENTS

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

   CLINDOXYL™ GEL
   (Clindamycin 1% and Benzoyl Peroxide 5% Gel)

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

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

2. A statement on the back panel indicates that patients should "Store in a cold place, preferably in a refrigerator between 2° and 8° (36 ° and 86 °F). However, the next statement on the label states, "Dispense with a 60 day expiration date and specify "Store at controlled room temperature between 15° and 30° C (59° and 86° F). These two different storage temperature ranges could be confusing to the user. We recommend revising the label and labeling to minimize confusion.

IV. RECOMMENDATIONS:

DMETS does not recommend use of the proprietary name Clindoxyl Topical Gel.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
5/10/02 11:17:33 AM
PHARMACIST

Carol Holquist
5/10/02 01:11:38 PM
PHARMACIST

Jerry Phillips
5/13/02 09:31:50 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: March 21, 2002	**DUE DATE:** May 21, 2002	**ODS CONSULT #:** 00-0123-01

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Vickey Lutwak
Project Manager
HFD-540

PRODUCT NAME: **Clindoxyl Topical Gel** (Clindamycin 1% and Benzoyl Peroxide 5% Gel) **NDA:** 50-741	**NDA SPONSOR:** Stiefel Laboratories

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proprietary name Clindoxyl Topical Gel. The proprietary name was reviewed and found acceptable in June 2000 (OPDRA consult # 00-0123).

DMETS RECOMMENDATION: Upon further review, DMETS reverses its initial decision and does not recommend the use of the proprietary name "Clindoxyl Topical Gel."

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-420)

DATE RECEIVED: June 17, 2002	**DUE DATE:** August 15, 2002	**ODS CONSULT #:** 00-0123-02

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Vickey Lutwak
Project Manager
HFD-540

PRODUCT NAME: **Clindoxyl Topical Gel** (Clindamycin 1% and Benzoyl Peroxide 5% Gel) **NDA:** 50-741	**NDA SPONSOR:** Stiefel Laboratories

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: The Division of Dermatologic and Dental Drug Products (HFD-540) requested a review of the proprietary name Clindoxyl Topical Gel on April 1, 2000. During that review, the Division of Medication Errors and Technical Support (DMETS) found no objections to the proposed proprietary name. However, during the final review conducted on May 10, 2002, DMETS reversed the initial decision and did not recommend use of the proprietary name Clindoxyl. This decision was based on the potential for name confusion between the currently marketed product Clindagel and Clindoxyl. Clindagel was not identified during the initial review because DMETS did not have access to the Saegis Pharma In-Use database which, contains data pertaining to sound-alike or look-alike names from distributors and aids in the detection of phonetic similarities between names and unapproved drug products. Using this database, DMETS identified Clindagel as a proprietary name that could have the potential for name confusion with Clindoxyl. On June 14, 2002, Stiefel Research submitted a rebuttal to support the proposed name Clindoxyl and requested a reconsideration of the acceptability of the proposed proprietary name. Additionally, Stiefel Research submitted Duac as an alternate name for review, if DMETs did not agree with information provided in the rebuttal. This review will address both Stiefel's rebuttal and the proposed alternate name, Duac.

DMETS RECOMMENDATION: After review of the information submitted by the sponsor, the Division of Medication Errors and Technical Support (DMETS), does not recommend the use of the name "Clindoxyl." However, DMETS has no objections to the use of the proprietary name, "Duac."

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 13, 2002

NDA # 50-741

NAME OF DRUG: Clindoxyl
(Clindamycin Phosphate 1% and Benzoyl Peroxide 5% Gel)

NDA HOLDER: Stiefel Laboratories, Inc

I. INTRODUCTION:

The Division of Medication Errors and Technical Support (DMETS) previously reviewed the proposed proprietary name, Clindoxyl, on April 1, 2000 (OPDRA consult # 00-0123) and had no objections to the use of the name. However, on May 10, 2002 (ODS consult # 00-0123-1), using data that was unavailable during the initial review, DMETS reversed its initial decision and did not recommend use of the proprietary name Clindoxyl. Stiefel Laboratories, Inc submitted a rebuttal on June 14, 2002 and requested a reconsideration of the acceptability of the proposed proprietary name Clindoxyl. Stiefel Laboratories, Inc also submitted an alternate name for consideration if DMETS did not agree with the rebuttal. Container labels, carton labeling, and package insert labeling were reviewed during the May 10, 2002 review and were not submitted for re-review.

PRODUCT INFORMATION

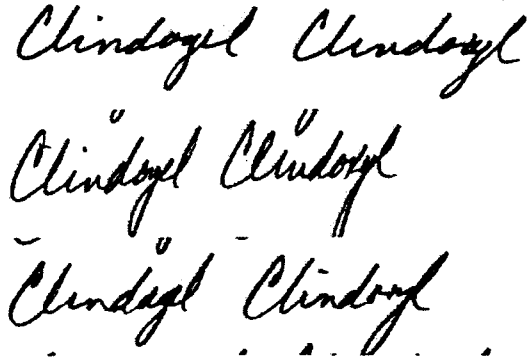
Clindoxyl is a topical gel containing clindamycin 1% as the phosphate and benzoyl peroxide 5%. Clindamycin is an antibiotic and benzoyl peroxide is an antibacterial and keratolytic agent. Clindoxyl Gel is indicated for the topical treatment of inflammatory lesions of acne vulgaris. The usual dosage is one application in the evening or as directed by a physician to affected areas. Clindoxyl Gel is supplied in a 45-gram tube.

II. RISK ASSESSMENT:

A. EVALUATION OF STIEFEL'S RESPONSE

1. CLINDOXYL AND CLINDAGEL

Stiefel notes in their rebuttal that Clindoxyl and Clindagel do not look similar because "Even at a glance, however, the shapes of the two words stand apart; the sharp angles of Clindoxyl's 'x' and 'y' contrast with the rounded curves of Clindagel's 'g' and 'e.'" DMETS disagrees with this statement. The sharp angles and roundness of the 'xy' and the 'ge' may not always be distinctly written. However, the prefix 'Clind' and the last letter 'l' will likely be distinguishable in either name. Additionally, the letters 'a' and 'o' may look very similar when scripted. This combination 'Clinda__l' and 'Clindo__l' contributes to the look-alike characteristics of these two names. Moreover, when scripted (see below) both names look very similar.



DMETS agrees with the sponsor's conclusion that the potential for name confusion due to the sound-alike characteristics is minimal.

Stiefel indicates that both Clindagel and Clindoxyl are both acne medications and " there is no risk that a patient will go completely without therapy if Clindagel is inadvertently prescribed when Clindoxyl was intended." DMETS agrees with this statement. Stiefel also indicates that the "presence of a second active ingredient (benzoyl peroxide) in Clindoxyl may generally provide enhanced efficacy" while presenting "little risk of harm to an acne patient for whom Clindoxyl is inadvertently prescribed instead of Clindagel." DMETS agrees with the conclusion that most patients who receive Clindoxyl instead of Clindagel will have minimal adverse effects. However, some patients may have a hypersensitivity to benzoyl peroxide and the resultant name confusion could result in severe adverse effects for these patients. Additionally, these patients may be aware of their hypersensitivity but may not notice the differences in the two products because the names look similar. The risk of confusing Clindoxyl and Clindagel will probably not result in death or hospitalization; however, the seriousness of the adverse event to the patient is still of concern. Especially, if the medication error is due to name confusion between the two products and if this error was preventable.

Stiefel indicated that they would be willing to "change the design of the brandname 'Clindoxyl' could be changed to read 'ClindOxyl.' Such a change would be consistent with the Center for Drug Evaluation and Research's (CDER's) finding (through the Office of Generic Drugs) that use of upper-case letters in a segment of certain generic names can effectively distinguish them from otherwise similar names in the marketplace." DMETS agrees that changing the design of the proprietary name on packaging would help to decrease 'picking' or 'dispensing' medication errors (i.e., the prescription is interpreted correctly but Clindagel is dispensed instead of Clindoxyl and vice versa). However, medication errors due to sound-alike or look-alike name confusion also occur upon initial receipt of the prescription. Practitioners cognitively misinterpret the drug product then proceed to dispense, transcribe, or administer the incorrect product because this is what they thought was intended to be ordered. If the prescription has been cognitively misinterpreted differences in physical characteristics of the carton or container would not prompt the practitioner that an error has occurred.

2. CLINDOXYL AND DOXIL

As noted in the June 14, 2002 DMETS' review, we feel that the potential for name confusion between Clindoxyl and Doxil is minimal due to several distinguishing factors between the two products. Doxil is an intravenous chemotherapeutic agent that will usually be prescribed concomitantly with other agents (e.g., corticosteroids, anti-emetics, or other chemotherapeutic agents) in an inpatient setting. Clindoxyl, on the other hand, is a topical agent for acne that will usually be dispensed in an outpatient setting. DMETS agrees with the sponsor's conclusion that the risk of medication errors due to name confusion between Clindoxyl and Doxil is minimal.

3. CLINDOXYL AND LEVOXYL

As noted in the DMETS' June 14, 2002 review, we feel that the potential for name confusion between Clindoxyl and Levoxyl is minimal even though the products have the same endings 'oxyl.' These two products are also differentiated by the formulations (cream vs. tablet) and routes of administration (topical vs. oral). Additionally, as noted above, prescriptions for Clindoxyl do not require that a strength be indicated. However, Levoxyl prescriptions require a strength prior to dispensing. Thus, DMETS agrees with the sponsors' conclusion that the risk of medication errors due to name confusion between Clindoxyl and Levoxyl is minimal.

B. DUAC NAME ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

sound-alike or look-alike to "Duac" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[4] The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

1. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Duac." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

a. The Expert Panel identified Ziac, Duract, and Durrax as having the potential for confusion with "Duac." These products are listed in Table 1 (see page 6), along with the dosage forms available and usual dosage.

b. DDMAC did not have concerns about the name Duac Topical Gel with regard to promotional claims.

Table 1
Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Duac	Clindamycin 1% and Benzoyl Peroxide 5% Topical Gel	One application at bedtime	N/A
Ziac	Bisoprolol Fumarate and Hydrochlorothiazide 2.5 mg/6.25 mg, 5 mg/6.25 mg or 10 mg/6.25 mg Tablets respectively	One tablet a day up to a maximum of Bisoprolol Fumarate 20 mg and Hydrochlorothiazide 12.5 mg	SA/LA
Duract	Bromfenac Sodium 25 mg Capsules	25 mg to 50 mg every six to eight hours, maximum 150 mg per day	SA
Durrax	Hydroxyzine 10 mg, 25 mg, or 50 mg Tablets	50 mg to 100 mg up to four times a day	SA

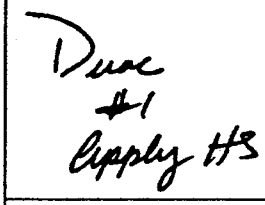
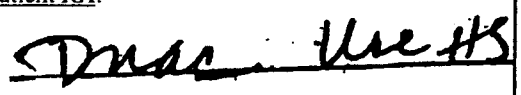
*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

2. PRESCRIPTION ANALYSIS STUDIES

a. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Duac with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 108 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Duac (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

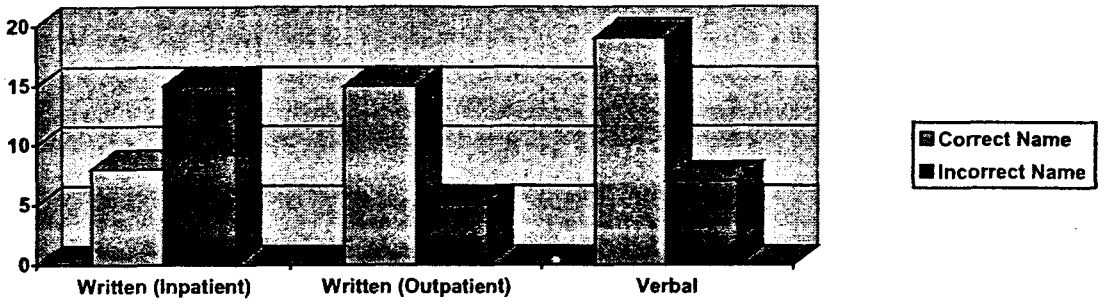
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	The third prescription is Duac. Apply at bedtime. Dispense # 1.
Inpatient RX: 	

b. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	37	23 (62%)	8 (35%)	15 (65%)
Written Outpatient	32	20 (63%)	15 (75%)	5 (25%)
Verbal	39	26 (67%)	19 (73%)	7 (27%)
Total	108	69 (64%)	42 (61%)	27 (39%)



In the verbal study 7 of 26 (27%) participants interpreted "Duac" incorrectly. All of the incorrect name interpretations were phonetic variations of "Duac." These include Duact (1), Duak (1), Duoac (1) Duwac (1), Duwak (1), Dewak (1), and Dulac (1). None of the misinterpreted names were similar to an approved product, although Duact is phonetically similar to Duract, which was withdrawn from the market in 1998.

Among the two written studies, 20 of 43 (47%) participants interpreted the name incorrectly. Twelve respondents misinterpreted the name as Dnac. The remaining single misinterpretations were Derac, Duae, Duak, Dune, Duoc, Dmac, Drac, and Driac. None of the misinterpreted names were similar to an approved product.

3. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Duac, the primary concerns raised were related to three sound-alike and/or look-alike names: Ziac, Duract, and Durrax.

Ziac was identified as a potential look- and sound-alike product that may have potential for confusion with Duac. Ziac is indicated for the treatment of hypertension. Duac and Ziac have the same ending 'ac' which contributes to the look and sound-alike characteristics. However, the beginnings of both names are different 'Zi' vs. 'Du.' The differences in the beginnings should help to distinguish the two products. Additionally, Duac and Ziac are available in different formulations (cream vs. tablet) and routes of administration (topical vs. oral). Although Duac is a combination product, it is only available in one strength, whereas Ziac is available in three different strengths (2.5 mg/6.25 mg, 5 mg/6.25 mg, and 10 mg/6.25 mg). Therefore, Duac may be ordered without indicating a strength while Ziac will require that a strength be noted prior to dispensing. Moreover, the strengths of the two products do not overlap. The differences in the first syllable and the other differences may decrease the potential for name confusion between Duac and Ziac.

Duract is a nonsteroidal anti-inflammatory drug that is indicated for the short-term (i.e., less than 10 days) management of acute pain. Durract is available as 25 mg capsules. Duract was approved in July 1997 and withdrawn from the market in 1998 due to rare but serious reports of liver events associated with long term use (i.e., greater than ten days of treatment). Duac and Duract may sound alike when pronounced. However, the risk of medication errors due to name confusion between the two products is minimal since Duract is no longer marketed and the strengths are different.

Durrax is listed in several electronic references (e.g., http://csi.micromedex.com and www.library.duq.edu/eresources/clinref/datasets/gdh_f/html/chapter/chap1.htm) as a proprietary name for hydroxyzine hydrochloride. Although Durrax and Duac sound similar, DMETS feels that the potential for name confusion is limited due to the differences in formulation (tablet vs. cream), route of administration (topical vs. oral), and marketed strengths (10 mg, 25 mg, and 50 mg vs. combination strength of 1%/5%). Duac may be ordered without a strength whereas prescriptions for Durrax will require that a strength be noted. Additionally, limited data is available on the distribution of Durrax. The product cannot be found in the most commonly used reference resources. For example, the 2001 Drug Topics Red Book which contains a very comprehensive listing of both OTC and prescription products does not list Durrax. The U.S. Patent and Trademark Office's Text and Image Database list the owner of the trademark as Dermik Laboratories but the trademark is listed as cancelled as of February 1, 1993. Moreover, drug information representatives of Aventis Pharmaceuticals (Dermik is a component of Aventis Worldwide) indicated that Durrax is not listed as a Dermik product and that their database does not contain any information about Durrax.

III. RECOMMENDATIONS:

DMETS does not recommend use of the proprietary name Clindoxyl Topical Gel. However, DMETS has no objection to the use of the proprietary name Duac Topical Gel.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Denise Toyer
8/13/02 01:28:08 PM
PHARMACIST

Jerry Phillips
8/14/02 08:42:29 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM: HFD-540 Vickey Lutwak	
OPDRA				
June 17, 2002	IND NO.	NDA NO. NDA 50-741	TYPE OF DOCUMENT Resubmission. Response to NA Letter	DATE OF DOCUMENT June 14, 2002
NAME OF DRUG Clindoxyl Gel	PRIORITY CONSIDERATION 6 month PDUFA due 8-26-02		CLASSIFICATION OF DRUG 4 S	DESIRED COMPLETION DATE

NAME OF FIRM: Stiefel Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

1. Tradename review: In response to the outcome of consult #1 (00-0123-01), the sponsor submitted the following to DMETS for consideration: **DUAC** We have only the name at this time.

2. Stiefel's written response to DMETS and the Division's recommendation that the proprietary name "Clindoxly Topical Gel" is not advised for the reasons stated in the consultation response. Will be sent via interoffice mail. Thank you.

Vickey Lutwak

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)

Vickey Lutwak, PM, HFD 540 7-2073	☐ MAIL	☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER	

APPEARS THIS WAY
ON ORIGINAL

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

Fax: 301-827-2091

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

From: Mary Jane Carr

Pages: 13 pages – Including Cover Sheet

Date: June 14, 2002

cc:

CC:
Wilkin
Luke
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.

2nd Preference

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

Consult Use

Sincerely,
STIEFEL LABORATORIES, INC.

Mary Jane Carr

Mary Jane Carr
Senior Manager
Regulatory Affairs

Research in Dermatology

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

June 14, 2002

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Corporate 2, N214
9201 Corporate Blvd.
Rockville, Maryland 20850

Re: NDA 50-741
TELEPHONE AMENDMENT
Clindoxyl™ Topical Gel (clindamycin – benzoyl peroxide)

Dear Dr. Wilkin:

Reference is made to our New Drug Application, NDA 50-741, for Clindoxyl™ Topical Gel (clindamycin–benzoyl peroxide) submitted on May 13, 1996.

Reference is also made to our Major Amendment to NDA 50-741 submitted on February 22, 2002 and to our May 28, 2002 teleconference with the Division of Dermatologic and Dental Drug Products (the Division). During that teleconference, the Division informed Stiefel of concerns raised in the Division of Medication Errors and Technical Support's (DMETS's) re-review of the trademark "Clindoxyl." We have prepared this submission in an effort to assist the Division as it considers the clinical relevance of these concerns.

Background

Stiefel included "Clindoxyl" as the brandname for its clindamycin phosphate – benzoyl peroxide topical gel in its initial NDA submission (May 1996). In June 2000, the Division informed Stiefel that the brandname had been tentatively accepted by the Office of Post-Marketing Drug Risk Assessment (OPDRA), the predecessor of DMETS. A recent follow-up review by DMETS, however, raised concerns regarding the potential confusion over the similarity in sound or appearance of the name "Clindoxyl" and the brandnames of three other drugs: "Doxil", "Levoxyl", and, most significantly, "Clindagel." Stiefel does not believe that any of these names are sufficiently similar to "Clindoxyl" to cause prescribing confusion and patient harm due to resultant medication errors.

Clindagel

During our May 28, 2002 teleconference, the Division emphasized that "Clindagel" is the name which DMETS believes has the greatest potential for confusion, primarily noting the appearance of the two names when written in long hand.

Stiefel believes that the potential for look-alike confusion of these two names is not great. The two names appear similar to the extent that they share the same first syllable. In that sense they are as mistakable as 'toothpaste' is for 'toothbrush.' Even at a glance, however, the shapes of the two words stand apart; the sharp angles of Clindoxyl's 'x' and 'y' contrast with the rounded curves of Clindagel's 'g' and 'e.' If DMETS or the Division feels strongly that confusion between these two names might exist, the design of the written brandname "Clindoxyl" could be changed to read "ClindOxyl" Such a change would be consistent with the Center for Drug Evaluation and Research's (CDER's) finding (through the Office of Generic Drugs) that use of upper-case letters in a segment of certain generic names can effectively distinguish them from otherwise similar names in the marketplace. For instance, changing the names "acetahexamide" to

"acetaHEXAMIDE" and "tolazamide" to "TOLAZamide" was deemed sufficient to alleviate confusion of these generic names with other names. This is also consistent with the remarks of Janet Woodcock, M.D., Director of CDER, at a National Institute of Health conference entitled "Minimizing Medical Product Errors" held in 1998 where she noted that changes in design of names can prevent medication errors.

Stiefel believes it is important to note that the potential for sound-alike confusion between "Clindoxyl" and "Clindagel" is even more remote. Although the first syllable of the two names is identical in spelling, the pronunciation of the names varies substantially. "Clindagel" is pronounced with inflection on the first syllable—'CLIN-da-gel,' whereas "Clindoxyl" is pronounced with inflection on the middle syllable—'Clin-DOX-yl.' The last syllables of the two words bear little if any similarity; "Clindoxyl" ends with a velarized or hard consonant, as in the word "oxygen," while "Clindagel" ends with a palatalized or soft consonant, as in the word "jealousy."

In sum, the possibility of confusion between these two brandnames is remote. Perhaps equally important, however, Stiefel believes that the potential for harm to patients is slight even if a medication error involving these two drugs does, in fact, occur. Clindagel and Clindoxyl are both acne medicines, one intended to treat acne vulgaris and the other to treat inflammatory lesions associated with acne vulgaris. Thus, both drugs are appropriate for this patient population. Moreover, both drugs are topical preparations of the same active ingredient, clindamycin phosphate, at the same strength, 1%. While the presence of a second active ingredient (benzoyl peroxide) in Clindoxyl may generally provide enhanced efficacy, there is no risk that a patient will go completely without therapy if Clindagel is inadvertently prescribed when Clindoxyl was intended. Similarly, because of the low toxicity profile of topical benzoyl peroxide, its presence in Clindoxyl presents little risk of harm to an acne patient for whom Clindoxyl is inadvertently prescribed instead of Clindagel.

FDA has previously noted that preventing harm to patients, and ensuring proper treatment for patients are major factors in determining the permissibility of a drug name that may be dangerously confused with sound-alike or look-alike drug names. For instance, at the 1998 NIH conference referenced earlier, Dr. Woodcock focused on significant errors – those which could "be traced to 441 cases resulting in patient hospitalizations, 235 cases where the patient's life is threatened, 206 cases where patients undergo medical intervention and 65 cases where patients experience permanent disability." Similarly, David Feigal, M.D., then Medical Deputy Director for the Center for Biologics Evaluation and Research (CBER), discussed restrictions on potential errors that have the "highest risk consequences." Such risks are completely absent in the unlikely event of confusion between the names "Clindoxyl" and "Clindagel." We note also, that the Division itself has apparently already recognized that the names of substantially similar products with low toxicity profiles which are indicated for non-life-threatening dermal indications need not be completely without overlap. Thus, drugs containing benzoyl peroxide (with and without additional active ingredients) with the names "Benzac AC", "Benzagel", "Benzamycin", and "BenzaClin", among others, are all currently available in the US.

Finally, during the May 28 conference call, the Division indicated that there may be some concern from Galderma Laboratories, L.P. (Galderma), the company marketing Clindagel. We are pleased to inform the Division that, in a June 3, 2002 letter (attached), Humberto C. Antunes, President of Galderma, affirmed his belief that the trademarks "Clindagel" and "Clindoxyl" are "substantially different phonetically," and that they could "coexist in the pharmaceutical market place."

Doxil and Levoxyl

Stiefel sees no real potential for confusion between the names "Clindoxyl" and "Doxil" or "Levoxyl." This view is substantiated by OPDRA's June 2000 initial review of "Clindoxyl" for sound-alike and look-alike confusion. While both products were already being marketed at that

time, neither "Doxil", nor "Levoxyl" were identified as names that could hinder approval of Clindoxyl. It is important to note that the techniques used in brandname reviews being conducted at that time by OPDRA (as described by Jerry Phillips, then Director of OPDRA (and now of DMETS) in a July 2001 *Pharmaceutical Executive* article) are essentially the same as those being used today by DMETS. Nonetheless, our detailed analysis of the potential for confusion with "Doxil" and "Levoxyl" is presented below.

Visibly, the words "Clindoxyl" and "Doxil" look nothing alike, having different spellings, and a different number of letters (length). The risk of confusion is presumably the similarity in sound between "Doxil" and the last two syllables of "Clindoxyl." However, the audible confusion of the two words is improbable since Doxil only bears a likeness to the end of the word "Clindoxyl"—the pronunciation of the words is simply different, "Doxil" with two syllables and "Clindoxyl" with three.

In addition to these phonetic considerations, we note that the two drugs have substantially different indications and dosage forms – features so different, in fact, that the mis-prescribing is highly unlikely. Clindoxyl is a gel prescribed to treat acne and is administered by the patient on a once daily basis. Doxil, on the other hand, is available in single dose vials and is indicated for treatment of ovarian cancer and AIDS-related Kaposi sarcoma. As such, it is administered by a physician in an in-patient healthcare setting. The drug is not likely to be found in consumer pharmacies where patients would go to purchase Clindoxyl.

"Clindoxyl" and "Levoxyl" are also clearly distinguishable. The appearance of the two words, when written, and the sound of the last syllable may be confusing insofar as they have the same ending— 'oxyl.' But the appearance and sound of the first syllables of the two words is entirely different. First, 'Clin-dox-yl' starts with five letters that neither look nor sound anything like the first three letters of 'Lev-ox-yl.' Second, "Levoxyl" is pronounced 'LE-vox-yl,' with inflection on the first syllable and a long 'e' vowel as in "tree." In contrast, "Clindoxyl" is

pronounced 'Clin-DOX-yl,' with inflection on the middle syllable and a short 'i' vowel as in "lint." Finally, even if the 'C' could be confused with the letter 'L' due to illegible handwriting, 'lin' could hardly be mistaken for 'ev,' and the 'd' in the middle of "Clindoxyl" does not have any corresponding letter in "Levoxyl." The vertical, linear shape of 'l' and the dot on the 'i' would appear nothing like the single, rounded 'e.'

Conclusion

The many differences among Clindoxyl, and Doxil and Levoxyl in dosage form, usage, sound and appearance affirm the reasonableness of OPDRA's initial approval of the name "Clindoxyl." The substantial phonetic difference between Clindoxyl and Clindagel recognized by the President of Galderma, the contrasting appearance of the two names, the fact that there is little risk of harm to the patient attributable to label confusion, and the likeness in composition of the two acne medicines all support approval of the trade name "Clindoxyl." For these reasons we ask for the Division to approve the product with the trade name "Clindoxyl" or "ClindOxyl." Failing all other options, Stiefel is also prepared to accept the name Duac. We note, however, that Stiefel does not have trademark protection for this name and would therefore greatly prefer the name "Clindoxyl."

Please do not hesitate to telephone us with any questions regarding this submission.

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Vice President

WAC/mjc
Attachment

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Stiefel Laboratories, Inc.	June 14, 2002
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(305) 443-3800	(305) 443-3467
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code telephone & FAX number)* IF APPLICABLE
255 Alhambra Circle, Suite 1000 Coral Gables, FL 33134	Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-741

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Clindamycin Phosphate and Benzoyl Peroxide	Clindoxyl™ Gel

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate) and benzoyl

CODE NAME *(If any)* Not Applicable

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Gel	Clindamycin phosphate equiv to 1% clindamycin and 5% benzoyl peroxide	Topical

(PROPOSED) INDICATION(S) FOR USE: Inflammatory Lesions of Acne vulgaris

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Not Applicable Holder of Approved Application Not Applicable

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Response to FDA's May 28, 2002 telephone request for additional information regarding the proposed product tradename

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all *manufacturing*, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready

See attached.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See attached.

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50(k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	William A. Carr, Jr. Vice President	6/14/2002

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Route 145 Oak Hill, New York 12460	(518) 239-6901

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
'bert H. Humphrey Building, Room 531-H
) Independence Avenue, S.W.
/ashington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

FORM FDA 356h (7/97)

STIEFEL LABORATORIES, INC.

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

DRUG SUBSTANCE(S):

CLINDAMYCIN PHOSPHATE:

MANUFACTURER(S):

NAME:

ADDRESS:

TELEPHONE:
FACSIMILE:

CONTACT:

CLINDAMYCIN PHOSPHATE:

MANUFACTURER(S):

NAME:

ADDRESS:

TELEPHONE:
FACSIMILE:

CONTACT:

BENZOYL PEROXIDE:
MANUFACTURER(S):

NAME: ———

Mfg Address: ———

Mailing Address: ———

———

———

TELEPHONE: ———
FACSIMILE:

CONTACT: ———

DRUG PRODUCT: Clindoxyl™ Gel
(clindamycin phosphate equivalent to
1% clindamycin and 5% benzoyl peroxide)

NDA 50-741

MANUFACTURER:

NAME: Stiefel Laboratories, Inc.

ADDRESS: Corporate Headquarters:
255 Alhambra Circle, Suite 1000
Coral Gables, FL 33134

TELEPHONE: 305-443-3800
FACSIMILE: 305-443-3467

MANUFACTURING: Route 145
Oak Hill, NY 12460

TESTING/STABILITY: Route 145
Oak Hill, New York 12460

*Testing/Stability testing is performed by A.C. Stiefel Research Institute, Inc. – a wholly owned subsidiary o f Stiefel Laboratories, Inc.

CONTACT: William A. Carr, Jr.
Vice President

TELEPHONE: 518-239-6901
FACSIMILE: 518-239-8402

CENTRAL FILE NUMBER(S):
Stiefel Laboratories, Inc.: 1314819
A.C. Stiefel Research Institute, Inc.: 1316245

We here confirm that all sites referenced above are, and will remain, ready for inspection by FDA.

STIEFEL LABORATORIES, INC.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Drug Substance:

Clindamycin Phosphate:

Contatiner/Closure System:

APPEARS THIS WAY
ON ORIGINAL

GALDERMA
USA

GALDERMA
LABORATORIES, L.P.

Humberto C. Antunes
President

14501 N. Freeway
Fort Worth,
TEXAS
76177

Tel: (817) 961-5000
Fax: (817) 961-3035

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

HCA/grp

Cc: Brenda Horn
Laurent Venetz

RECEIVED
JUN - 3 2002

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.

2

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 [redacted] 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Stiefel Laboratories, Inc.
255 Alhambra Circle
Suite 1000
Coral Gables, FL 33134

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

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

3. TELEPHONE NUMBER *(Include Area Code)*
518-239-6901

4. PRODUCT NAME
Clindoxyl™ Gel

DOES THIS APPLICATION CONTAIN CLINICAL DATA? [X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
2991

7. LICENSE NUMBER/NDA NUMBER
20722

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- [ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92
- [ ] THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*
- [ ] AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

- [ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- [ ] A CRUDE ALLERGENIC EXTRACT PRODUCT
- [ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
- [ ] AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? [ ] YES [X] NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President Regulatory Affairs and Quality Assurance	3 May 1996

FORM FDA 3397 (12/93)

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application c supplement submitted to the Agency on or after January 1, 1994. The Prescription Drug User Fee Act of 1992, Publi Law 102-571, authorizes the collection of the information requested on this form to implement the Act. Failure to complete this form may result in delay in processing of the submission.

ITEM NOS. **INSTRUCTIONS**

1 - 3 Self-explanatory.

4 **PRODUCT NAME** - Include the generic name and the trade name, as applicable.

5 If clinical data are required for approval, then the application should be identified as containing clinical data. Please refer to the FDA policy regarding clinical data, Interim Guidance, Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under The Human Prescription Drug Use Fee Act of 1992, July 12, 1993. Copies may be obtained from: Food and Drug Administration; Office of Small Business, Scientific and Trade Affairs; 5600 Fishers Lane, HF-50; Rockville, MD 20857. Please include two (2) pre-addressed mailing labels with your request.

6 **USER FEE I.D. NUMBER - PLEASE MAKE SURE THIS NUMBER AND THE NUMBER ON THE APPLICATION PAYMENT CHECK ARE THE SAME. FOR APPLICATIONS SUBJECT TO USER FEE PAYMENT,** please supply the following identifying information:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individu identification number may be obtained by calling the Center for Drug Evaluation and Research Central Document Room, at (301) 443-8269.

FOR BIOLOGIC PRODUCTS - The first 4 characters are the U.S. License Number, including leading zeros; the second characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 594-2906.

EXAMPLE: For U.S. License Number 4, product code ZZ01, with a document submission date of 8/3/93, the number would be: 0004ZZ0103AUG93.

7 **LICENSE NUMBER/NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank.

FOR DRUG PRODUCTS - Indicate the NDA number, if known, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 443-0035.

EXAMPLE: For NDA99999, the number would be: N099999.

8 **EXCLUSIONS** - Check the appropriate box if this application is NOT covered by user fees because it is excluded from the definition of "human drug application" as defined in Section 735(1) and (2) of the Prescription Drug User Fee Act.

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any sa or ester of an active ingredient); or NOT a new indication for use.

9 **WAIVER** - Complete this section only if the application has qualified for the small business exception or a waiver has been granted for user fees for this application. A copy of the official FDA notification that the waiver has been granted must be provided with this submission.

Research in Dermatology

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

May 5, 1997

Food and Drug Administration
Division of Dermatologic and
Dental Drug Products
9201 Corporate Blvd.
2nd Floor North, HFD-540
Rockville, MD 20850

RE: **DEBARMENT STATEMENT**
NDA 50-741

Dear Sir/Madam

We certify that Stiefel Laboratories, Inc., and Stiefel Research Institute, Inc., have not and will not use in any capacity the service of a person debarred under subsection (a) or (b) [Section 306(a) or (b)] of the Federal Food, Drug and Cosmetic Act, in support of this - or any other - New Drug Application.

Further, we certify that neither Stiefel Laboratories, Inc., or Stiefel Research Institute, Inc., nor any other affiliated persons have been convicted under 306(a) or (b).

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Vice President

WAC:mjt

**APPEARS THIS WAY
ON ORIGINAL**

Research in Dermatology

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

May 3, 1996

Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Sir:

In accordance with the provisions of 21 CFR §314.53 (c)(1) and (c)(2) we are providing patent information on our product Clindoxyl™ Gel.

Please be advised that Clindoxyl™ Gel is the subject of U.S. Patent 5,466,446 issued on November 14, 1995 with an expiration date of February 16, 2014.

Subject patent is a composition and a method of use patent.

The patent owner is Stiefel Laboratories, Inc. Coral Gables, FL, the sponsor of the Application.

In addition to the above information we submit the following original declaration:

The undersigned declares that Patent No. 5,466,446 covers the composition and method of use of Clindoxyl™ Gel. This product is the subject of this application for which approval is being sought.

Sincerely,
STIEFEL LABORATORIES, INC.

William A. Carr, Jr.
Vice President
Regulatory Affairs and
Quality Assurance

WAC:cgw

EXCLUSIVITY SUMMARY for NDA # 50-741 SUPPL # __

Trade Name DUAC Topical Gel **Generic Name** (clindamycin, 1% - benzoyl peroxide, 5%)

Applicant Name Stiefel Laboratories, Inc. **HFD- 540**

Approval Date August , 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/_x__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_x__/

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

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

      YES /_x__/ NO /___/

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

      _____

      _____

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

      _____

      _____

d) Did the applicant request exclusivity? . .

YES /_x__/NO /___/

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

3

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

YES /___/ NO /x___/

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # _____ Drug Name _____

NOTE:
BenzaCLin is applied twice daily while DUAC is once in the evening.
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_x__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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

YES /_x__/ NO /___/

Clindamycin Phosphate Gel 1% 4 generic products

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

NDA # 50-782 Clindamycin Phosphate Topical Gel USP

NDA # ANDAs 65-067,65-048, 64-106

NDA # _____ _____

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

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

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

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

YES /_x__/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /x___/NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

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

YES /___/ NO /x__/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /x___/

If yes, explain: _____

_____

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

Investigation #1, Study # 150

Investigation #2, Study # 151

Investigation #3, Study # 158

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

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

Investigation #1	YES /___/	NO /_x__/
Investigation #2	YES /___/	NO /_x__/
Investigation #3	YES /___/	NO /_x__/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /x___/

Investigation #2 YES /___/ NO /_x__/

Investigation #3 YES /___/ NO /__x_/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #_1_, Study # 150

Investigation #_2_, Study # 151

Investigation #_3_, Study # 158

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor

of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1 Study #1 150

IND # _____ YES /_x__/ NO /___/ Explain: _____

_____

_____

Investigation #2 Study #2 151

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #3 Study #3 158

IND # _____ YES /___/ NO /___/ Explain: _____

_____

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

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

YES /___/ NO /_x__/

If yes, explain: _____

_____

_____

_____ _____
Signature of Preparer Date
Title: Victoria Lutwak, Project Manager

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA

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

/s/

Jonathan Wilkin
8/26/02 06:32:34 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : NDA 50-714 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: February 26, 2002 **Action Date:** August 26, 2002

HFD -540 **Trade and generic names/dosage form:** DUAC (clindamycin, 1 % - benzoyl peroxide, 5%) Topical Gel

Applicant: Stiefel Laboratories, Inc **Therapeutic Class:** Anti-bacterial agent

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Topical treatment of inflammatory acne vulgaris

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ ☑ **No: Please check all that apply:** ____**Partial Waiver** ☑ **Deferred** ____**Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies: Age 13-30 years

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments: Labeled for pediatric use for 12 years and above.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

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

/s/

Victoria Lutwak
8/26/02 01:41:48 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

..JA/BLA # 50-741 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

(CLINDAMYCIN PHOSPHATE/Benzoyl Peroxide)

HFD-540 Trade and generic names/dosage form: CLINDOXYL GEL Action: AP AP NA

Applicant Stiefel Labs. Therapeutic Class 35

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application Treatment of acne vulgaris

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,
__ (2) Protocols were submitted and approved.
__ (3) Protocols were submitted and are under review.
__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. Waiver for pediatric studies under age 12 granted. See attached memo/review.

__5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical review (e.g., medical review, medical officer, team leader)

/S/ Project Manager 8/22/00

Signature of Preparer and Title Date

/S/ 9/5/00

cc: Orig NDA/BLA # 50-741
HFD-540/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 50-741 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: CLINDOXYL GEL. (CLINDAMYCIN PHOSPHATE/BENZOYL PEROXIDE) Action: AP AE NA

Applicant STIEFEL LABS Therapeutic Class ANTI-BACTERIAL AGENT

Indication(s) previously approved _____

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application ACNE VULGARIS

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

X 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/ 5/8/97

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 50-741
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

/S/ 5/14/97

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

Listed are all the investigators under Studies 156, 158, and 157.

Pediatric information and waiver request

The sponsor requests a waiver of the requirement for pediatric studies for ages up to 12 years. They state that the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in this age group, and is not likely to be used in a substantial number of patients.

A subset analysis of the results in patients aged 12-16 years in Studies 156 and 158 is provided. Approximately 50% of the patients were in the 12-16 year age group, with the remainder aged 17-31 years. The results in the 12-16 year age group were either comparable or were superior to the results in the whole study population. The local tolerance was also comparable to that in the larger population.

Reviewer's evaluation: The financial disclosure statement is adequate to meet the requirements for Studies 156, 158, and 157.

It is felt that a waiver of the requirements for pediatric studies for the age groups of up to 12 years should be granted.

/S/ M.D.

Phyllis A. Huene, M.D.

7/31/00

Cc: Orig NDA 50-741
HFD-540 Division files
HFD-540\Wilkin
HFD-540\Walker SW 8/3/00
HFD-540\Huene
HFD-540/Freidlin
HFD-540\Cintron
HFD-540\Vidra
HFD-540\Jacobs 8/15/00
n50741.aml

✓Not in DFS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 26 1996

Michael T. Jarratt, M.D.
PRD Pharmaco International, Inc.
4009 Bannister Lane
Austin, Texas 78722

Dear Dr. Jarratt:

On October 31,1996, Mr.Lance D. Johnson, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (protocol 9401) of the investigational drug, Clindoxyl Gel, performed for Steifel Labs:" A Two Center , Double-Blind Clinical Comparison of the Safety and Efficacy of Clindoxyl Gel, and Vehicle Gel in the Once Daily Treatment of Acne Vulgaris for 11 Weeks". This inspection is a part of FDA's Bioresearch Monitoring Program which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you adhered to pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Johnson during the inspection.

Sincerely yours,

/S/

Bette Barton,Ph.D.,M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

bcc:
HFA-224
HFD-340/R/F
HFD-344/C/R/S
HFR-SW100
HFR-SW150
HFC-230
HFC-132
HFD-/540/Div. Dir./Doc. Rm.: IND _____
NDA 50-741

CFN: 1628466

CIB: 5061

Field Classification: NAI

H.Q. Classification:
_x_ 1) NAI
___ 2) VAI - no response requested
___ 3) VAI - response requested
___ - follow-up indicated
___ 4) OAI

Reason for Change in Classification, if applicable:

r/d:L.O.Martynec(MO) October 19, 1996
reviewed:BLB:11/21/96
finaled:slk:11/21/96

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 31

Christopher J. Huerter, M.D.
Department of Dermatology,
Creighton University School of Medicine
601 North 30th Street
Omaha, Nebraska 68131

Dear Dr. Huerter:

On October 1,2, 4- 8, 1996, Mrs. Jane E. Nelson, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of the clinical study (protocol # 9405) of Clindoxyl Gel in treatment of Acne Vulgaris sponsored by Stiefel Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we conclude that you adhered to all pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations.

We appreciate the cooperation shown Investigator Nelson during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

cc:
HFA-224
HFD-344
HFD-340 r/f
HFD-342
HFR-SW350
HFR-SW300
HFD-540 Review Division Div. Dir./Doc. Rm.: NDA #50-741
MO/Susan Walker/CSO Kevin White
HFC-230
HFC-132

r/d:JACarreras:12/31/96
typed:slk:12/31/96

CFN:1915582

Field classification: NAI

Headquarters classification:
_X___1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 18 1997

Dan K. Chalker, M.D.
Augusta Cosmetic Center
1433 Stovall St.
Augusta Georgia 30904

Dear Dr. Chalker:

On January 13-15, 1997, Mr. Robert P. Neligan, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of the clinical study (protocol # 9401) of the investigational drug Clindoxyl Gel, performed for Stiefel Laboratories, Inc. This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and of the documents submitted with that report, we conclude that you adhered to all pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations.

We appreciate the cooperation shown Investigator Neilgan during the inspection.

Sincerely yours,

/s/

Bette L. Barton, Ph.D., M.D.
Chief Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

CFN: 1062461

Field classification: NAI

Headquarters classification:
_X___1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

If Headquarters Classification is different classification explain why:

cc:
HFA-224
HFD-344
HFD-340 r/f
HFR-SE150
HFR-SE100
HFD-540
HFD-540 Review Division Div. Dir./Doc. Rm.: NDA#20-492
MO - S. Walker CSO - K. White

HFC-230
HFC-132

r/d:JACarreras:2/10/97
finaled:slk:2/11/97

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

90 pages