

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**050803Orig1s000**

**OTHER REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 18, 2010

To: Susan Walker, MD, Director  
**Division of Dermatology and Dental Products (DDDP)**

Through: Mary Willy, PhD, Deputy Director  
**Division of Risk management (DRISK)**  
Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk management (DRISK)**

From: Steve L. Morin, RN, BSN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): VELTIN™ (clindamycin phosphate and tretinoin) Gel,  
1.2%/0.025%

Application Type/Number: NDA 50-803

Applicant/sponsor: Stiefel Laboratories, Inc.

OSE RCM #: 2010-1158

## 1 INTRODUCTION AND BACKGROUND

Connetics Corporation submitted an original 505 (b) (2) New Drug Application, NDA 50-803, for VELTIN™ (clindamycin phosphate and tretinoin) Gel, 1.2%/0.025% on August 23, 2004 . The Agency took a Not Approvable Action on June 10, 2005. The Agency was notified on January 9, 2007 of the transfer of ownership of this application to Stiefel Laboratories, Inc. The Applicant submitted a Class 2 Resubmission of their NDA on October 16, 2009.

VELTIN Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older. ZIANA™ (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel, NDA 50-802, was approved on November 7, 2006, and is the Referenced Listed Drug. DRISK used the currently approved PPI for ZIANA™ (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel as a comparator. We also referenced the recent DRISK review of the ACANYA Gel (clindamycin phosphate 1.25 and benzoyl peroxide 2.5%) PPI, completed May 2010.

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for VELTIN™ (clindamycin phosphate and tretinoin) Gel, 1.2%/0.025%. Please let us know if DDDP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## 2 MATERIAL REVIEWED

- Draft VELTIN™ (clindamycin phosphate and tretinoin) Gel, 1.2%/0.025% Prescribing Information (PI) submitted on June 1, 2010 and revised by DDDP and provided to DRISK on June 8, 2010
- Draft VELTIN™ (clindamycin phosphate and tretinoin) Gel, 1.2%/0.025% Patient Package Insert (PPI) submitted June 1, 2010 and revised by DDDP and provided to DRISK on June 8, 2010

## 3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured consistency with the currently approved ZIANA™ (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel PPI and May 2010 completed DRISK review of the ACANYA Gel (clindamycin phosphate 1.25 and benzoyl peroxide 2.5%) PPI, to the extent possible
- ensured consistency with current DRISK patient labeling standards

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

10 Pages of Draft Labeling have been  
Withheld in Full Immediately Following  
this Page as B4 (CCI/TS)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-50803

-----  
ORIG-1

-----  
STIEFEL A GSK CO Veltin

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

/s/  
-----

STEVE L MORIN  
06/18/2010

MARY E WILLY  
06/19/2010  
I concur

## ***MEMORANDUM***

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

---

**Date:** June 9, 2010

**To:** Cristina Attinello, MPH, DDDP  
Gary Chiang, MD, DDDP  
David Kettl, MD, DDDP

**From:** Andrew Haffer, PharmD, DDMAC Professional Reviewer  
Shefali Doshi, MD, DDMAC DTC Reviewer

**Re:** NDA 050803  
DDMAC Review of VELTIN™ (clindamycin phosphate and tretinoin) Gel

DDMAC has reviewed the draft PI labeling for VELTIN™ (clindamycin phosphate and tretinoin) Gel. DDMAC's comments are based on the proposed draft labeling provided to DDMAC from Cristina Attinello via email on June 7, 2010.

DDMAC's comments are provided directly in the PDF document attached (see below).

If you have any questions about DDMAC's comments on the FPI please contact Andy Haffer. If you have questions about DDMAC's comments on the PPI please contact Shefali Doshi.

10 Pages of Draft Labeling have  
been Withheld in Full Immediately  
Following this Page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50803	ORIG-1	STIEFEL A GSK CO	Veltin

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

/s/

ANDREW S HAFFER  
06/09/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 17, 2010

To: Susan Walker, MD, Director  
Division of Dermatology and Dental Products

Through: Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, PharmD, Acting Team Leader  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Veltin (Clindamycin Phosphate and Trentinoin) Gel  
1.2% /0.025%

Application Type/Number: NDA 050803

Applicant: Stiefel Laboratories, Inc.

OSE RCM #: 2009-2215-1

**\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\***

## **1 INTRODUCTION**

This review responds to a request from Division of Dermatology and Dental Products to evaluate the proposed revised container labels, carton labeling, and insert labeling for vulnerabilities that could lead to medication errors.

## **2 METHODS AND MATERIALS**

Using Failure Mode and Effects Analysis (FMEA)<sup>1</sup> DMEPA evaluates the proposed container labels (Appendix A) and carton labeling (see Appendix B) submitted by the Applicant on March 12, 2010. We also evaluated the recommendations pertaining to the label and labeling presented in OSE review #2009-2215, dated March 5, 2010, to see if the DMEPA recommendations had been incorporated into the labels and labeling.

## **3 DISCUSSION**

The Division of Medication Error Prevention and Analysis reviewed the revised container labels, carton, and insert labeling and find the revisions acceptable. DMEPA did not note any further areas of needed improvement at this time.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

We have no further comments or recommendations on the container labels, carton, or insert labeling at this time. We are willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Janet Anderson, OSE project manager, at 301-796-0675.

## **5 REFERENCES**

1. Oleszczuk, Z. OSE Review #2009-2215: Label and Labeling Review for Veltin. March 5, 2010.

2 Pages Draft Labeling have been Withheld in Full Immediately Following this Page as B4 (CCI/TS)

---

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50803	ORIG-1	STIEFEL A GSK CO	Veltin

---

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

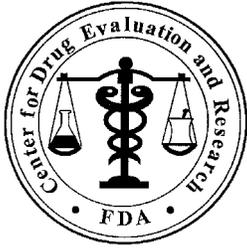
---

/s/

---

FELICIA DUFFY on behalf of ZACHARY A OLESZCZUK  
05/28/2010

DENISE P TOYER  
05/28/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: March 5, 2010

To: Susan Walker, MD, Director  
Division of Dermatology and Dental Products

Through: Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, PharmD, Acting Team Leader  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Veltin (Clindamycin Phosphate and Trentinoin) Gel  
1.2% /0.025%

Application Type/Number: NDA 050803

Applicant: Stiefel Laboratories, Inc.

OSE RCM #: 2009-2215

# **1 BACKGROUND**

## **1.1 INTRODUCTION**

This review is written in response to a request from the Division of Dermatology and Dental Products (DDDP) for assessment of the container labels, carton labeling, insert labeling, and patient package insert labeling for Veltin (Clindamycin Phosphate and Trentinoin) Gel for their vulnerability to medication errors.

## **1.2 PRODUCT INFORMATION**

Veltin (Clindamycin Phosphate and Trentinoin) Gel is indicated for topical treatment of acne vulgaris in patients 12 years of age or older. The recommended dose is to apply once daily in the evening lightly covering the entire affected area. Veltin is available as a single strength topical gel of 1.2% clindamycin phosphate and 0.025% tretinoin. Veltin will be supplied in 30 gram aluminum tubes.

# **2 METHODS AND MATERIALS**

## **2.1 LABELS AND LABELING**

DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted container labels (see Appendix A), carton labeling (see Appendix B), package insert labeling (no image) and patient package insert (no image) on November 10, 2009.

# **3 CONCLUSION AND RECOMMENDATIONS**

Our evaluation of the labels and labeling noted areas where the presentation of information can be improved to be consistent with other marketed topical gels. Section 3.1, Comments to the Division, contains our recommendations for the package insert labeling for discussion during the labeling meetings. Section 3.2, Comments to the Applicant contain our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Janet Anderson, OSE Regulatory Project manager, at 301-796-0675.

## **3.1 COMMENTS TO THE DIVISION**

### **3.1.1 General Comments**

The product strength is embedded in the established name and the active ingredients are separated with a hyphen (clindamycin 1%-tretinoin 0.025%) throughout the labels and labeling. The strength should not be imbedded in the established name and multiple active ingredients should separated with the word 'and'. The following presentation of the established name and strength should be used in running text:

(clindamycin phosphate and tretinoin) 1.2%/0.025%

The following presentation should be used when appropriate in absence of running text:

(clindamycin phosphate and tretinoin)  
1.2%/0.025%

### 3.1.2 Dosage Form and Strength

The presentation of strength in Section 3, *Dosage Form and Strengths*, is inconsistent with other marketed topical gels. The strength and dosage form should be presented as the following to be consistent with other marketed topical gels:

Each gram of Veltin Gel contains 10 mg (1%) of clindamycin as clindamycin phosphate and 0.25 mg (0.025%) tretinoin in an aqueous based gel.

### 3.2 COMMENTS TO THE APPLICANT

1. The product strength is embedded in the established name and the active ingredients are separated with a hyphen (clindamycin 1%-tretinoin 0.025%) throughout the labels and labeling. The strength should not be imbedded in the established name and multiple active ingredients should be separated with the word 'and'. The following presentation of the established name and strength should be used in running text:

(clindamycin phosphate and tretinoin) 1.2%/0.025%

The following presentation should be used on the container labels and carton labeling when appropriate in absence of running text:

(clindamycin phosphate and tretinoin)  
1.2%/0.025%

2. The net quantity (**30 grams**) and "Rx only" statement are detracting from the prominence of the proprietary name on the principal display panel of the contain label and carton labeling. Decrease the prominence of net quantity on the container labels and carton labeling by revising the statement so that it is not in bold text. Decrease the prominence of the "Rx only" statement by revising the color of the text to black.

2 Pages Draft Labeling have been  
Withheld in Full Immediately Following  
this Page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50803	ORIG-1	STIEFEL A GSK CO	Veltin

---

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

---

/s/

---

ZACHARY A OLESZCZUK  
03/05/2010

DENISE P TOYER  
03/05/2010

## FDA Facsimile Memorandum

**Date:** March 4, 2005  
**To:** Katy Morton  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%)

Ms. Morton,

The Chemistry Reviewer has the following comments regarding the labeling for your NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

### **Chemistry Reviewer's Comments on Labeling:**

#### **Labeling** (Section 1.3.2, page 1 of 1):

a. Established name - The word "gel" should not be part of the established name because the product with its established name is not USP monographed. We recommend to have the word "gel" in the proprietary name. The dosage form should not appear in both of the proprietary name and the established name.

c. Drug product - The dosage form should be "gel" (b) (4)

k. How Supplied - (b) (4)

#### **Packaging Insert** (Section 1.3.2.1, page 1 of 7):

The molecular formula of clindamycin phosphate has a typo. It should be a letter "O" in the formula instead of a numeric "0".

The chemical name of tretinoin should not have a hyphen between "non" and "atetraenoic".

#### **Carton/Container Label** (Section 1.3.2.2):

The fill size (30 g (b) (4)) should be present in all of the labels consistently. Currently, (b) (4) for the 30 g size, it is the tube label does not have it but the carton label has.

The word "gel" should have the same font size as the word "Velac" because it is a part of the proprietary name.

Respectfully,

Margo Owens  
Project Manager

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

/s/

-----  
Margo Owens  
3/4/05 03:22:28 PM  
CSO  
Faxed to applicant 3/4/05.

# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

## CLINICAL INSPECTION SUMMARY

DATE: February 28, 2005

TO: Margo Owens, Regulatory Project Manager  
Bindi Nikhar, M.D., Medical Officer, Clinical Reviewer  
Division of Dermatologic and Dental Drug Products, HFD-540

THROUGH: Ni A. Khin, M.D., Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations, HFD-46

FROM: Debi Tran, Pharm.D.  
Consumer Safety Officer  
Good Clinical Practice Branch I  
Division of Scientific Investigations, HFD-46

SUBJECT: Evaluation of Domestic Inspections

NDA: 50-803

SPONSOR: Connetics Corporation (Connetics)

DRUG: Velac<sup>®</sup> (clindamycin 1% - tretinoin 0.25%) Gel

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment for Acne Vulgaris

CONSULTATION REQUEST DATE: November 10, 2004

GOAL DATE TO PROVIDE  
INSPECTION SUMMARY: March 31, 2005

DIVISION GOAL DATE: April 15, 2005

PDUFA GOAL DATE: June 25, 2005

## I. BACKGROUND:

Velac<sup>®</sup> Gel is a combination product of clindamycin and tretinoin. Clindamycin is a lincosamide antibiotic, and Tretinoin is a vitamin A derivative. The individual components of Velac Gel are indicated for use in the treatment of acne vulgaris.

The following protocols were audited:

Protocol VLC.C.305: “A Phase III, Multicenter, Randomized, Double-Blind, Active- and Vehicle-Controlled Study of the Safety and Efficacy of Velac<sup>®</sup> Gel for the Treatment of Acne Vulgaris”

Protocol VLC.C.304: “A Phase III, Multicenter, Randomized, Double-Blind, Active- and Vehicle-Controlled Study of the Safety and Efficacy of Velac<sup>®</sup> Gel for the Treatment of Acne Vulgaris”

The pivotal studies were conducted in male and female subjects 12 years of age or older with acne vulgaris. Subjects must have facial acne vulgaris and may also have acne on other parts of the body (neck, chest and/or back). The primary endpoints of the study protocol are to evaluate the percent change in lesion counts (total, inflammatory, non-inflammatory) from baseline to Week 12 (end of treatment) and the proportion of subjects who have an Investigator’s Static Global Assessment (IGA) score of 0 or 1 at Week 12.

Sites # 103 and 124 were selected for inspection because they yielded robust efficacy results for Velac over its comparators, Clindamycin and Tretinoin, which had a significant impact on the overall pooled efficacy analysis. When site # 103 is deleted from the statistical analysis, Velac is no longer significantly greater than Clindamycin with respect to inflammatory lesion counts and IGA scores. When site # 124 is deleted from the statistical analysis, Velac is no longer significantly greater than Clindamycin with respect to inflammatory lesion counts.

## II. RESULTS (by site):

Name (site)	City, State	Protocol	Insp. Date	EIR Recd.	Classn.	GCP file#
Bonnie Elewski, MD Site # 103	Birmingham, Alabama	V.L.C.305	1/24-25/2005	2/3/2005	VAI	11402
Diane Thiboutot, MD Site # 124	Hershey, Pennsylvania	V.L.C.304	1/12-14/2005	1/31/2005	NAI	11413

### A. Protocol # VLC.C.305

Bonnie Elewski, Birmingham, Alabama: Acceptable

- a. What was inspected: There were 31 subjects randomized at this site. The investigator reviewed all 31 of the subjects’ source documents (lab results, progress notes and photographs), case report forms, informed consents, institutional review board approvals, drug accountability records, and correspondences with the sponsor.
- b. Limitations of inspection: None
- c. General observations/commentary: This inspection was classified as Voluntary Action Indicated (VAI) with no response required. The protocol deviations observed are:
  - (1) One of the inclusion criteria is that subjects must have a minimum of 20, but not more than 150 facial non-inflammatory lesions (open and closed comedones), excluding nasal lesions.

Subject # 5741 did not meet inclusion criteria because the subject only had 12 non-inflammatory lesions at baseline. The sponsor granted approval to continue enrollment of this subject in the study. Subject was randomized to the Clindamycin Gel treatment arm and completed the study. This protocol deviation was noted in the data-listing submitted to FDA.

- (2) The protocol requires that a medical history, review of systems, and physical exam be performed for each subject during Visit 1 (Week 0/Day 1 [Baseline]). No physical exam was conducted for Subject # 5745 during this visit; however, the subject was enrolled in the study. Subject was randomized to the Tretinoin Gel treatment arm and completed the study.
- (3) The protocol requires that the study coordinator weigh and dispense one tube of study drug at Visit 1/Week 0, Visit 3/Week4, and Visit 4/Week 8. In addition, on Visits # 3 and 4, previously dispensed study drug container are collected and weighed prior to dispensing of new study drug container. A March 6, 2004, written correspondence from the sponsor to the site states that “many” subjects received only one tube of the study drug. This protocol deviation was noted by the sponsor when the site returned all study drugs upon completion of the trial.

#### B. Protocol # VLC.C.304

Diane Thiboutot, Hershey, Pennsylvania: Acceptable

- a. What was inspected: There were 33 subjects randomized at this site. The investigator reviewed 21 subjects’ records, source documents (lab results, progress notes and photographs), case report forms, informed consents, institutional review board approvals, drug accountability records, and correspondences with the sponsor.
- b. Limitations of inspection: None
- c. General observations/commentary: There was one protocol deviation observed. The protocol requires that subjects must have a minimum of 17, but not more than 40 facial inflammatory lesions (papules plus pustules) including nasal lesions. Subject # 3668 did not meet inclusion criteria. The subject was enrolled in the study despite having 44 inflammatory lesions, and the protocol deviation was not discovered until after Visit # 3. The sponsor was notified of the deviation and granted a protocol exception to continue enrollment of this subject in the study. Subject was randomized to the Clindamycin Gel treatment arm and completed the study. However, this protocol deviation was **not** listed in the data-listing submitted to the Agency.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There were two subjects that did not meet one of the inclusion/exclusion criteria (lesion count) as previously discussed. Overall, the data submitted in support of this NDA appear to be acceptable.

*{See appended electronic signature page}*

Debi Tran, Pharm.D.  
Consumer Safety Officer  
Good Clinical Practice Branch I  
Division of Scientific Investigations, HFD-46

CONCURRENCE:

Supervisory comments

*{See appended electronic signature page}*

Ni A. Khin, M.D.

Branch Chief

Good Clinical Practice Branch I, HFD-46

Division of Scientific Investigations

Office of Medical Policy

Center for Drug Evaluation and Research

7520 Standish Place, Room 125

Rockville, MD 20855

DISTRIBUTION:

NDA 50-803

HFD-540/Nikhar/Owens (through DFS)

HFD-45/Division File

HFD-45/Reading File

HFD-45/Program Management Staff (electronic copy)

HFD-46/Khin/Tran

HFD-46/GCPB1 File# 11402, 11413

r/d: DNT: 2/25/05

reviewed:NK: 2/28/05

f/t: DNT: 2/28/05

o:\DNT\Velac Gel CIS NDA 50803

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

/s/

-----  
Debi Tran  
2/28/05 03:15:04 PM  
DDMAC REVIEWER

Ni Aye Khin  
2/28/05 03:35:44 PM  
MEDICAL OFFICER

## DSI CONSULT: Request for Clinical Inspections

**Date:** November 10, 2004

**To:** Roy Blay, GCPB Reviewer/HFD-47

**From:** Margo Owens, Regulatory Project Manager/HFD-540

**Subject:** **Request for Clinical Inspections (Revised)**  
(b) (4)  
Connetics Corporation  
Velac (clindamycin, 1% - tretinoin, 0.025%) Gel

### Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Treatment of acne vulgaris	VLC.C.305	Site 103 Boni Elewski, M.D. University of Alabama at Birmingham Department of Dermatology The Kirklin Clinic 2000 6th Ave. South Birmingham, AL 35233	1136
Treatment of acne vulgaris	VLC.C.304	Site 124 Diane Thiboutot, M.D. MS Hershey Medical Center Department of Dermatology 500 University Drive UPC 2, Room 4300 Hershey, PA 17033	33

**Rationale:**

Success of the trial occurs when Velac is superior to all comparators in 2 of 3 lesion counts (as measured by percent reduction) AND in IGA. When all sites are included in the efficacy analysis, Velac is significantly greater ( $p < .05$ ) on all 3 lesion counts and IGA to ALL comparators. However, when site 103 is deleted Velac is NO longer significantly greater than Clindamycin for inflammatory lesions AND IGA ( $p=.0614$  and  $.0756$  respectively). As a result, Velac would NOT have met study objectives. Site 103 only has 31 total subjects, so it's ability to change efficacy results as much as it did suggests a reason for further inspection.

The reasoning is similar for Site 103. As with Study VLC.C.305, Velac is statistically superior ( $p < .05$ ) to all comparators for every endpoint with the exception of comparing Velac to Clindamycin for inflammatory lesion counts which had a p-value of  $.0503$ . When site 124 is deleted, this p-value becomes  $.1991$ . However, statistical significance remains for total lesion counts, non-inflammatory lesions, and IGA for this comparison. So, even with this site excluded the study met all objectives as it did with its inclusion.

**Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **March 2005**. We intend to issue an action letter on this application by (action goal date) **June 25, 2005**.

Should you require any additional information, please contact Margo Owens.

Concurrence: (if necessary)

Markham Luke, M.D., Ph.D., Clinical Team Leader, Dermatology  
Bindi Nikhar, M.D., Clinical Reviewer  
Mohamed Alesh, M.D., Biostatistics Team Leader  
Matthew Soukup, Ph.D., Biostatistics Reviewer

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

/s/

-----  
Margo Owens

11/10/04 11:42:59 AM

## **DSI CONSULT: Request for Clinical Inspections**

**Date:** October 19, 2004

**To:** Roy Blay, GCPB Reviewer/HFD-47

**From:** Margo Owens, Regulatory Project Manager, HFD-540

**Subject:** **Request for Clinical Inspections**  
(b) (4)  
Connetics Corporation  
Velac (clindamycin, 1% - tretinoin, 0.025%) Gel

### **Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

<b>Indication</b>	<b>Protocol #</b>	<b>Site (Name and Address)</b>	<b>Number of Subjects</b>
Treatment of acne vulgaris	VLC.C.304	Site 109 Hector Wiltz, M.D. FXM Reserch Corporation 11760 Bird Road, Suite 451 Miami, FL 33175	
Treatment of acne vulgaris	VLC.C.304	Site 113 Amy Paller, M.D. Children's Memorial Hospital Division of Dermatology 2300 Children's Plaza #107 Chicago, IL 60614	

Treatment of acne vulgaris	VLC.C.305	Site 103 Boni Elewski, M.D. University of Alabama at Birmingham Department of Dermatology The Kirklin Clinic 2000 6th Ave. South Birmingham, AL 35233	
----------------------------	-----------	---	--

**Rationale:**

These sites have data that may be inconsistent with the other sites in the study.

**Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **March 2005**. We intend to issue an action letter on this application by (action goal date) **June 25, 2005**.

Should you require any additional information, please contact Margo Owens.

Concurrence: (if necessary)

Markham Luke, M.D., Ph.D., Medical Team Leader  
Bindi Nikhar, M.D., Medical Reviewer

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

/s/

-----  
Margo Owens  
10/19/04 12:11:33 PM